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The Importance of Randomized Clinical Trials and Evidence-Based Medicine: A Clinician's Perspective

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Summary: Clinical evaluation of therapies for patient care has evolved during the twentieth century from a variety of scientific methods. As a result of medical, political, and economic changes that occurred in the 1990s, randomized clinical trials and evidence-based methods are presently in the forefront of the physician's thinking in the decision-making process for therapeutic interventions. A new standard of patient care has emerged during this process. This report provides a clinician's viewpoint of the importance and interpretation of evidence-based methods and suggests a strategy when such evidence does not exist.

Key words: randomized clinical trials, evidence-based medicine, physician decision-making, clinical trials and meta-analyses, standard of care

Introduction

Unequivocally during the 1990s, most clinicians in diverse health care environments have encountered the term "evidence-based medicine."[1] This catchword of evidence-based medicine and its counterpart, randomized clinical trials (RCTs), have become ubiquitous to discussions of health care policy (government and private) and the delivery of health care services. One must wonder what events led to the pervasiveness and dominance of such a development? Why do younger physicians seem to regard evidence-based medicine as routine knowledge, while many older clinicians frequently are puzzled by the emphasis placed on such investigations? Indeed, clinical studies attest to the fact that physicians under 40 years of age more frequently are familiar with and practice evidence-based medicine, whereas older physicians were trained in an era that was not evidence-based and frequently have limited exposure or access to education concerning evidence-based medicine.[2] This report explores recent medical history that resulted in a focus on RCTs, provides a clinician's viewpoint of the importance and interpretation of evidence-based methods, and suggests a strategy for the current "gray" zones of clinical practice when evidence does not exist.

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Historical Evolution of Clinical Scientific Methods

The modern era of reporting medical data to clinicians evolved from early personal clinical experiences of individual physicians and often took the form of textbooks. Early in this century, classic texts (e.g., those of William Osler and Sir Thomas Lewis) sought to guide physicians in the diagnosis of and therapy for a variety of clinical disorders.[3, 4] Similarly, medical journals of case reports and case series evolved to describe original observations on diagnosis and therapy (e.g., Prinzmetal's angina and Dressler's syndrome).[5, 6] With this evolution of scientific reporting came an appreciation that comparison of outcomes of treated patients with a control group was an important feature in evaluating therapies. Subsequently, early medical reports assessed the effectiveness of a therapy against a historical control, while later studies evolved to use concurrent controls.[7] During this time, the field of biostatistics emerged, providing analysis methods with adjustment for significant differences that might exist between treatment and control groups.[8] Nevertheless, it became clear in the late 1940s that one of the best methods of removing biologic and measurement variability, as well as observer and selection bias, was the process of blinded randomization (i.e., the allocation of patients by chance);[9, 10] thus, there subsequently emerged the double-blind, placebo-controlled randomized trial[11] (Fig. 1). The process of randomization ensured equal distribution of confounding factors (known and unknown) to both the treatment and placebo groups with simultaneous follow-up of outcomes and evolved as the strongest clinical scientific design. Whereas many early clinical trials may have focused their therapeutic outcomes on surrogate end points, clearly, in the 1990s, mortality and morbidity are the most important primary and secondary objectives of modern RCTs.[12] Ideally, an RCT (resources permitting) should seek to enclose a population with a specific disease, of all ages, both genders, with comorbidities, from diverse environments (mul-

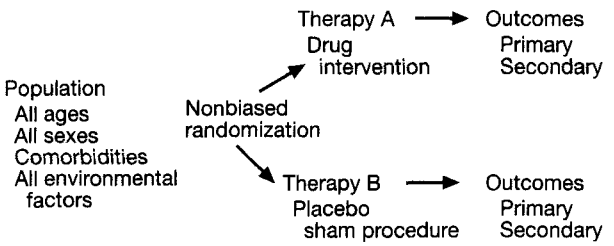

FIG. 1 Randomized placebo-controlled clinical trial design.

tiregion or multicountry), to be randomized in a blinded manner to a therapy versus placebo with simultaneous follow-up of outcomes. The RCT examines the effect of such therapy upon the occurrence of mortality and morbidity, as well as other aspects of disease (e.g., quality of life) (Fig. 1).

The Scientific, Political, and Economic Spotlight That Focused Attention upon Randomized Clinical Trials

It is surprising that the early hypertension RCTs, upon reflection, did not generate more enthusiasm for the reduced cerebrovascular and cardiovascular event outcomes evidenced by diuretic and beta-blocker therapy.[13] These data became widely known by clinicians and gave genesis to guidelines for hypertension.[14–16] Nevertheless, a realization that the RCT design, per se, established the definitive mortality and morbidity benefit of antihypertensive therapy was not generally appreciated by practicing clinicians. Similarly, the inception of the early megatrials in cardiovascular medicine (e.g., beta-blocker, thrombolytic, and ACE-inhibitor therapy) that defined patient mortality and morbidity benefit did not necessarily permeate the "outcomes" consciousness of many practicing clinicians.[17–19] Clinicians often clearly failed to implement beneficial therapies demonstrated by RCTs as evidenced by consistent underutilization of beta-blocker and/or ACE-inhibitor therapy in appropriate postinfarction patients.[20–23] These attitudes, however, were dramatically changed by the Cardiac Arrhythmia Suppression Trial (CAST).[24]

Pharmaceutical data indicates that in 1987 the antiarrhythmic drug market in the United States had grown to several hundred million dollars.[25] Both scientific query and academic concern regarding the efficacy of antiarrhythmic therapy in suppressing ventricular arrhythmias for the prevention of sudden death brought about a critical test of this therapy in the randomized, placebo-controlled clinical trial CAST.[24] The hypothesis that ventricular arrhythmia suppression decreased sudden death had its origin in the early lidocaine experience that decreased mortality in the coronary care unit.[26] Subsequently, extension of ventricular arrhythmia suppression out-of-hospital in patients with ischemic heart disease by means of oral antiarrhythmic therapy became an acceptable clinical therapy that was practiced worldwide.[27] CAST enrolled patients post myocardial infarction who had frequent and complex ventricular arrhythmias and who demonstrated ventricular arrhythmia suppression with encainide, flecainide, or moricizine, and subsequently randomized such patients to antiarrhythmic therapy versus placebo. The early announcement of CAST results in 1989[24] and the subsequent definitive publication in 1991,[28] indicating that patients enrolled in CAST who were treated with antiarrhythmic therapy had a three-fold increased mortality rate compared with that of placebo-treated patients, was indeed a shocking revelation to clinicians. These findings, widely discussed in scientific circles, subsequently focused on the error in clinical judgment that emanated from treating surrogate end points without knowing true clinical outcome (Fig. 2).[12, 29] The error of treating surrogate end points (i.e., the ventricular arrhythmias) highlighted an awareness of other therapies for which outcomes were questionable. Indeed, some therapies for hypertension, congestive heart failure, and other cardiovascular conditions had been deemed efficacious based upon the alleviation of surrogate symptoms or signs of disease (e.g., edema, cardiomegaly, etc.), and had scant evidence of morbidity or mortality benefit (efficacy) or, for that matter, established safety (*Primum non nocere*).

Concurrently, during the CAST era, there emerged in the United States important political and societal changes destined to affect the health care system. A new president and political administration sought health care economic reform and a wider based health care system. The latter events focused attention upon the "managed care concept" and spawned both private sector and government forces, beginning a process of consolidation, reorganization, and exploration to reap the benefits of an integrated managed care delivery of health care services.[30, 31] In 1989, the Agency for Health Care Policy was created to promote the quality of health care, reduce its cost, and broaden access to essential services[32] (Fig. 2). These events focused attention on RCTs and evidence-based medicine. Sometime during the early 1990s, the United States Food and Drug Administration (FDA) insidiously began to shift its policy (not always consistently) toward demanding that evidence-based outcomes data be provided for new pharmaceuti-

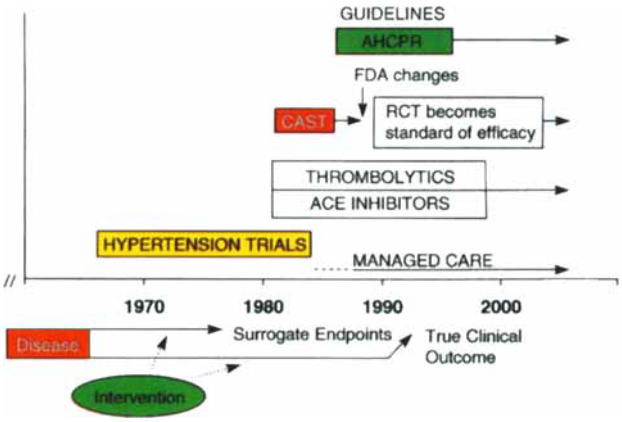

FIG. 2 Evolution of the importance of randomized clinical trials. RCT = randomized clinical trials, AHCPR = Agency for Health Care Policy, FDA = Food and Drug Administration, CAST = Cardiac Arrhythmia Suppression Trial, ACE = angiotensin-converting enzyme.

cal agents to assure their efficacy and safety (Fig. 2). Such was the case for the early RCT of the lipid-lowering statins (simvastatin and pravastatin) to attest to their safety and efficacy, since earlier fears and doubts had suggested that cholesterol lowering could result in early cancer or violent mortality in treated populations.[33–35] Nevertheless, these government regulatory policies seem to have not been applied consistently. Currently, the FDA varies between demanding evidence-based morbidity and mortality outcomes data for the approval of some products (e.g., simvastatin and pravastatin), whereas other lipid-lowering agents seem to have received approval on the basis of surrogate end point data to lower serum cholesterol (e.g., atorvastatin and cerivastatin).

Standard of Care

Imagine the apprehension and anxiety that churned the scientific community (and policy makers) upon the realization from CAST that many clinical decisions regarding patient therapy were based on surrogate end points rather than on outcomes data. This enlightenment and a concern for patient safety brought about widespread introspection in the medical community and a renewed focus on the risk versus benefit of all therapies. One prominent example was the Joint National Committee (JNC)-IV guidelines for hypertension that, in addition to diuretics and beta-blocker therapy (based on randomized clinical trials), had recommended other agents (ACE inhibitors and calcium-channel blockers) without outcome evidence as first-line therapy for hypertension.[14] Revision of the guidelines led to a reversal of the earlier recommendations and a return to low-dose diuretics and beta-blocker therapy as first-line initial therapy of hypertension (JNC-V and VI guidelines).[15, 16] Moreover, within the scientific community arose a proliferation of interest in RCTs to test both old and new therapies with regard to clinical outcomes to ensure both safety and efficacy.

This introspective process clearly began to focus the individual clinician's attention on the question of his standard of care in evaluating the benefits of a therapy. Was his standard of care, as had so often been true in the past, focused upon the alleviation of symptoms and signs of disease? (Fig. 3). This decision-making process by physicians (probably extending to ancient times) has guided clinicians to relieve the symptoms and signs of a disorder, and has been reinforced by the appreciation and gratitude of symptomatically improved patients toward "a good physician." Physicians receiving such appreciation assumed that those patients had an improved clinical outcome of morbidity and mortality. Undoubtedly many patients' symptomatic, functional, and quality of life outcomes have been improved. On the other hand, as demonstrated by some heart failure RCTs, physicians could deliver symptomatic improvement to patients while disappointingly increasing their mortality and morbidity.[36–38] Clearly, as the end of the century nears, the physician's focus on therapeutic approaches should make those therapies demonstrated to improve survival and decrease morbidity, and at least do no harm, a first priority (Fig. 3). Although clinicians have always

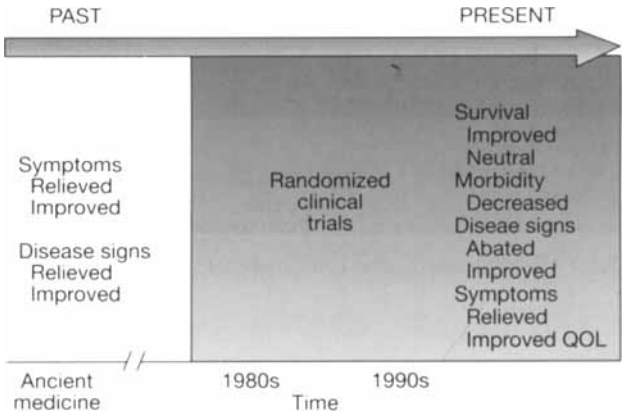

FIG. 3 Physician's standard of care. QOL = quality of life.

endeavored to alleviate patients' symptoms and improve functional outcomes resulting in a better quality of life, these latter attributes cannot be achieved at a detriment to survival. Unequivocally, emerging knowledge of patient care outcomes has focused attention on society's allocation of limited and costly health care resources, and has spurred health care organizations to follow efficient and proven pathways of therapy that most commonly are based on RCTs.[29–31] Upon reflection, the era of individual physician autonomy in making clinical decisions without considering RCT evidence (when it exists) is drawing to an end.[29] Although the individual physician's personal experience continues to be a valuable, irreplaceable asset in the decision-making process for the care of patients, RCT information should provide the foundation of that decision-making for specific therapeutic interventions. Whereas clinical guidelines seek to encompass pathophysiologic principles, observational studies, clinical experience, and consensus expert opinion, they are clearly anchored by the results of RCTs when such data exist.

Clinicians, however, should remember that optimum treatment of disease (by evidence-based medicine) is not the same as optimum caring for the patient. One must also consider important individual patient factors, such as patient preference, costs, competing health priorities, and the magnitude of the benefit to the individual patient.[39]

The Clinician's Approach to Evaluating Evidence-Based Medicine

It is not surprising that clinicians trained before the 1990s received limited education concerning randomized clinical trials and meta-analyses. What guidelines should they use to evaluate and critique the merits of a clinical trial? What are they to believe? Does a meta-analysis provide a more objective and quantitative summary of the evidence than RCTs or traditional reviews and expert consensus opinion? How do they identify a valid meta-analysis? Randomized clinical trials and meta-analyses provide a continuum of evidence that is mutually complementary and therefore should be viewed from that perspective (Fig. 4).

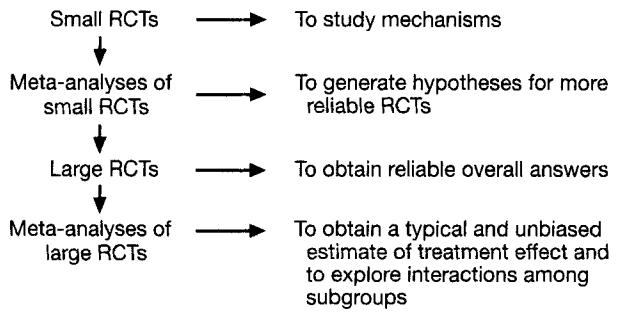

FIG. 4 Complementary roles of randomized clinical trials and meta-analyses. RCTs = randomized clinical trials. Source: Ref. No. 50.

Randomized Clinical Trials

Califf and Woodlief called attention to the differences between the "mechanistic" and the "pragmatic" randomized trial.[40] Mechanistic trials seek to explain a hypothesized mechanism of benefit and most often study a relatively small number of patients with multiple measurements and voluminous data collection according to a strict protocol. Such trials usually have lengthy consent forms and exclude specific patient subsets (by age, comorbidity, etc.) to demonstrate that a pathophysiologic mechanism is operative in resulting in specific clinical outcomes.[40] This detailed and precise data gathering usually is expensive per patient and costly overall. In contrast, the practical or "pragmatic" trial seeks only to determine whether a therapeutic agent results in improved mortality or morbidity.[40] It examines a large population of patients with only minimal inclusion or exclusion criteria and collects minimal data. Large RCTs may also be costly because of the size of the population (e.g., megatrials); but by not excluding or controlling multiple clinical factors, this design more readily reflects actual clinical practice in the real world, providing reliable overall answers.[40] This approach led to the first large-scale, randomized megatrial, the International Survival of Infarct Study (ISIS-I), that examined the effects of beta-blocker therapy in acute myocardial infarction.[17] ISIS-I investigators hypothesized that the cardiovascular benefits of beta-blocker therapy in acute myocardial infarction could result in an improved survival of 25%, and calculated that a sample size of 10,000 patients would be necessary to give an assurance of a p value < 0.01.[17] In reality, beta-blocker therapy resulted in approximately a 15% benefit, and it was necessary to enter more than 16,000 patients to demonstrate that effect.[17] It is interesting to note that over the past two decades the efficacy of several cardiovascular agents in patients with ischemic heart disease have all generally ranged in the area of 10 to 30% (e.g., beta blockers, aspirin, thrombolytic agents, ACE inhibitors, etc.).[41] That caveat should lead to caution in accepting the results of some cardiovascular RCTs that purport benefit in excess of this range.[42–44] Often the size and characteristics of the population, or the duration or conduct of the trial (preselection of patients, unblinding, etc.) may spuriously contribute to "out of range" outcomes.[42–44] When an RCT is adequately designed, the sample size of the population is based on realistic event rates in the control group, has expectations of plausible treatment effects (usually 10–30% reductions), and plans appropriate statistical power (minimum of 95% Type I and 80% Type II error).[11,45] For chronic cardiovascular diseases, a population of several thousand studied over a sufficient duration (3 to 7 years) is usually necessary for an RCT to establish significant therapeutic outcomes confidently.[33–35,45] Notwithstanding the practical merit of the megatrials, those that also help define mechanisms of action (often in substudies), as CAST defined the fallacy of suppressing ventricular arrhythmias, surely must be regarded as being the most valuable to medical understanding.

Equivalence Trials

Another emerging aspect of the RCT has focused on the ethical issue of withholding therapies of proven benefit in some populations (e.g., ACE inhibitors in patients with congestive heart failure) to conduct placebo-controlled trials. "Equivalence trials," which test new therapeutic agents against those of proven value, have evolved to address this concern.[46] Although the study design of equivalence trials is still evolving and is subject to controversial interpretation,[46–48] it nonetheless permits examination of untested therapeutic agents against those with established value without a placebo control.

Meta-Analysis Data

Meta-analyses, both retrospective and prospective, seek to provide inferential data of a specific therapy from a number of pooled investigations.[49–51] Past meta-analyses have generally been retrospective and therefore subject to the limitations of any form of retrospective research. Such analyses are fraught with difficulties in interpretation and demand rigorous literature review by both clinicians and biostatisticians before establishing valid inclusion of any individual clinical trial in the meta-analysis.[49] A current trend in meta-analysis is to encourage prospective meta-analysis by collaborative groups (e.g., the Cochrane Collaboration group) that defines a written prospective meta-analysis protocol.[50,52] The protocol identifies the trials to be included (prior to knowledge of results), defines key end points and secondary subgroups, and standardizes methodology. Such an approach permits advance power calculations. The concept of "optimum information size" perhaps should be applied to all meta-analyses and requires a sample size at least as large as that of a single, well-designed, and optimally powered randomized clinical trial.[50] This avoids a meta-analysis of small RCTs, which are more likely to be affected by publication bias (unpublished results of negative trials) than are the larger trials.[53–55] The "publication lag" of negative RCTs has also been documented and signals a warning that spuriously larger treatment effects are often defined in early meta-analyses.[56] This is particularly important in rapidly evolving fields in which newly emerging therapies may quickly become outdated. Cumulative meta-analysis should be used to evaluate the overall importance of late-appearing or negative trials.[57] Clinicians should realize

that when meta-analyses are composed of limited populations or early results of the evidence, false conclusions may be drawn.[56,58–60] Indeed, some meta-analyses have been shown to have only slight to good correlation (positive predictive accuracy 68%; negative predictive accuracy 67%) compared with their definitive RCTs.[61] Even with appropriate considerations, discrepancies between meta-analyses and large RCTs will result from the variability of treatment responses in different persons, protocols, and populations.[62] Advanced techniques of meta-analysis (meta-regression and hierarchial Bayes) explore specific sources of heterogeneity to discover why meta-analyses and their corresponding large RCTs do not always agree.[51] However, in contrast to RCTs, evidence that meta-analyses per se have improved health outcomes in patients is lacking.[63] In summary, meta-analyses are both complementary and adjunctive to RCTs in the evolutionary process of evaluating therapeutic interventions[41,50] (Fig. 4). Meta-analysis is a method of scientific investigation that aims to quantify evidence and to explore bias and diversity systematically; it is not a shortcut or "statistical alchemy" to make life easier or to avoid large RCTs.[51,62]

Limitations of Randomized Clinical Trials and Clinical Guidelines

Some limitations of RCTs seem to have been appreciated only in retrospect and most commonly have resulted from (1) advances in medical care during the conduct of the trial that decreased primary end point events, resulting in an underpowered study; or (2) failure to account for rapid advances in a therapy (e.g., interventional coronary stents and devices). For example, some therapies in interventional cardiology are tested, thought to be beneficial according to early data, adopted in the community and, before an "optimum information" database exists, are replaced by yet another technology. These limitations are currently being appreciated and proactive solutions to their prevention are contemplated; yet virtually no substantive data in this regard exist.

Moreover, the problem of resolving areas of conflict from various authoritative guidelines (e.g., the recommendations of the National Cholesterol Education Program vs. the American College of Physicians Guidelines on cholesterol lowering) must be addressed on the basis of community data and benefit rather than academic theory or zeal. Many issues and pitfalls will continue to surface as RCTs move from the academic environment of the mechanistic trials to the community theater of the pragmatic megatrials. Recognizing and solving such problems is in harmony with today's changing health care environment, which demands practical cost-effective quality outcomes for the public welfare.

The Clinician's Evaluation

Clinicians should remember these diverse factors, particularly when barraged by marketplace influences that often support the validity of their product with "a clinical trial" or "a meta-analysis." An appraisal of the population (size, gender, ages, and comorbidity), consideration of the disease entity (case fatality rate and annual mortality), duration of the trial, and bearing in mind the 95% confidence limit will usually indicate whether such data should be regarded with low or high confidence. Small clinical trials of short duration may claim implausibly large effects on mortality, and those results are unreliable even when accompanied by apparent statistical significance.[42–44] A similar critique of a meta-analysis should be conducted, bearing in mind that statistical power cannot compensate for early results, heterogeneity, or methodologic flaws, and that the data should be at least as comprehensive as those generated from a well-designed clinical trial.[50,56] In addition, clinicians should not be dissuaded from seeking evidence-based outcomes of efficacy and safety for new therapies by such commercial clichés as "it's a class effect" or "it's ethically wrong to perform more RCTs against placebo." Class effects do not necessarily result in equivalent outcomes, as discovered with beta blockers that have intrinsic sympathomimetic activity,[64,65] and equivalence trials sometimes result in surprising medical discoveries and potential patient benefits.[66]

Strategies for the "Gray" Zones of Clinical Practice

Daily, clinicians make decisions within a range of uncertainty on behalf of individual patients (Fig. 5).[29] Guided by RCTs and expert consensus guidelines, physicians have an opportunity to utilize proven and necessary therapies in the care of their patients. Whether such data apply to an individual patient must be determined by the patient's physician. Similarly, clinicians are cautioned to avoid the inappropriate use of unproven therapies encountered either through premature scientific disclosure, commercial influence, or personal attitudes, and to seek substantive data before employing such therapies.[29] Given the current emphasis in medicine on cost-effective outcomes, it would seem that large RCT results should provide the greatest influence on the physician's decision-making process. What if substantive, evidenced-based outcome data do not exist for a specific medical condition—how should the practicing clinician proceed?

While definitive data on the subject are lacking, one can suggest several approaches. First, if there is an ongoing randomized clinical trial on the subject, the physician should attempt to follow or actively participate in the trial. Such participation imparts a level of knowledge of developments in the field. Second, it has been argued that when definitive evidence does not exist, knowledgeable, thoughtful, traditional review of original clinical studies provides the closest standard of reference for summarizing disparate evidence in medicine.[49,63,67] For the busy clinician, this is most expeditiously achieved by reviewing published clinical practice

FIG. 5 Physicians' practice patterns.

guidelines on the subject. Practice guidelines emanate from a variety of sources (e.g., the Agency for Health Care Policy and Research, professional societies, and health maintenance organizations), and in the present age of technology can be accessed via the internet through the U.S. National Library of Medicine Medline database (www.nlm.nih.gov) or through web pages of various professional societies. Moreover, educational CD-ROM periodicals (e.g., UpToDate), computer-assisted decision software,[68] and internet clinical trial forums (e.g., Cardio-Vascular Clinical Trials at www.biomednet.com and Center Watch at www.centerwatch.com) are all sources of guidelines and RCT information.

Finally, within this context, the physician, in many instances, should share his knowledge and the uncertainty of definitive outcome data for specific therapies with the patients for whom they are prescribed. The patient thus is aware of the undefined outcomes of therapy, evaluates his own trust and dependence on the physician that due diligence in finding the best therapy has been exerted, and can be proactive in his own behalf in defining outcomes. Many patients are gratified to receive such insight into their prescribed therapy and consequently often accept participation in appropriate RCTs.

Conclusions

Certainly, as we approach the end of the millennium, a physician's choice of therapeutic interventions should be biased to utilize those interventions that primarily improve mortality and morbidity (or are neutral), and secondarily treat symptoms and signs of disease. A new standard of care has evolved in the 1990s and lamentably remains unemphasized to many clinicians around the world. Emerging evidence suggests that the managed care approach may be more rapid and successful in implementing evidence-based therapies, since it often requests the physician to justify therapeutic decisions diverging from clinical guidelines.[69] Nevertheless, every clinician must now place into decision-making view not only surrogate end points but also evidence-based outcomes. Undoubtedly, the process is not an "all or none" phenomenon.[70] Nevertheless, consideration of recent medical history suggests that most often the scales of judgment should be weighted toward evidence-based medicine when such data exist.

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