Computer-Based Drug-Utilization Review — Risk, Benefit, or Boondoggle?

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Accessibility
HORMONE-REPLACEMENT THERAPY — BREAST VERSUS HEART VERSUS BONE

THANKS to many public health advances, in the developed countries the average woman will be postmenopausal for about one third of her life. As a consequence, she and her physician will ultimately need to make a decision about postmenopausal estrogen-replacement therapy. This treatment has been used for several decades, but there is a surprising lack of consensus about when and how to use it. The initial goal of estrogen-replacement therapy was to alleviate menopausal symptoms. More recently, the possibility has emerged that estrogen can reduce morbidity and mortality from ischemic heart disease and osteoporosis. However, women and their physicians must balance these apparent benefits against the possibility that estrogen therapy might increase the incidence of cancer of the breast and uterus or mortality from these diseases.¹

The situation has been further muddled by the increasing use of hormone-replacement therapy — that is, estrogen and a progestin in combination. This practice reflects unequivocal evidence linking unopposed estrogen therapy to endometrial hyperplasia and cancer, pathologic changes that are prevented by the cyclic or continuous administration of a progestin. Indeed, this risk of estrogen therapy was confirmed in the recent report of the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a three-year randomized trial of placebo, unopposed estrogen, or three estrogen-progestin regimens in 875 postmenopausal women.² This study found that the risk of adenomatous or atypical endometrial hyperplasia was about 1 percent among women randomly assigned to placebo or to any of the estrogen-progestin combinations, whereas it was 34 percent among women assigned to treatment with estrogen alone. Endometrial cancer was not an end point of the trial, but evidence from other sources shows an increase of up to sixfold in the incidence of endometrial cancer among women receiving estrogen-replacement therapy;³ the concurrent use of a progestin markedly reduces this risk. Thus, the use of estrogen and a progestin combined is increasing among postmenopausal women with an intact uterus who decide to begin replacement therapy.

What about hormones and the breast? Epidemiologic studies and studies in animals strongly implicate estrogen in the development of breast cancer. Recent meta-analyses of data on estrogen-replacement therapy and the risk of breast cancer suggest that there is little risk associated with past use or short-term use of estrogen, but it has been estimated that the risk of breast cancer after 10 years of estrogen therapy is increased by 13 to 30 percent.⁴ Information about combined hormone-replacement therapy and the risk of breast cancer has been harder to obtain, since many studies were conducted before such therapy became commonplace. The effects of estrogen-progestin therapy on the uterus and the breast may differ considerably. During the menstrual cycle, the mitotic activity of endometrial cells peaks during the early follicular phase (a time of increased estradiol production) and decreases during the luteal phase (a time when both estrogen and progesterone are produced). In contrast, most proliferative activity in the breast occurs during the luteal phase. Thus, estrogen plus progestin might increase the risk of breast cancer more than estrogen alone.⁵ Indeed, a study by Bergkvist et al.⁶ suggested just that — an increased risk with combined estrogen and progestin therapy, especially prolonged therapy. However, the types of estrogen-replacement therapy used in that study differed from those used in the United States, where most women receive conjugated equine estrogen.

In this issue of the Journal, Colditz et al.⁷ describe the effects of adding progestin to estrogen therapy in a U.S. population, the Nurses’ Health Study cohort. The report is based on 1935 cases of invasive breast cancer identified among postmenopausal women in the parent study during 725,350 person-years of follow-up. Most women took conjugated equine estrogen, and the study spanned the decade of the 1980s, when combined hormone-replacement therapy became substantially more common. The analysis showed that the relative risk of breast cancer was 1.32 for women who were currently receiving estrogen alone and 1.41 for women receiving estrogen plus a progestin. Thus, the addition of progestin to estrogen had no significant effect on the risk of breast cancer. The risk among past users or current users who had been taking hormones for less than five years was similar to that among postmenopausal women who had never taken hormones. However, the relative risk was 1.71 among women 60 to 64 years of age who had been receiving hormonal therapy for at least five years. The finding that the risk of death due to breast cancer paralleled the incidence suggests that these breast cancers were clinically important.

Given the disparate effects of estrogen and progestin on the breast and the uterus, what do we know about the effects of estrogen and estrogen—progestin therapy on other clinical outcomes? Ischemic heart disease is the most common cause of death among postmenopausal women in this country. Numerous observational studies suggest a 50 percent reduction in the risk of heart disease among postmenopausal women who receive estrogen-replacement therapy.⁸,⁹ Concern that progestin might weaken the protective effects of estrogen has been alleviated by the PEPI trial, which showed that estrogen-replacement therapy or combined hormone-replacement therapy improved the lipoprotein profile and lowered fibrinogen levels without appreciable effects on blood pressure or post-challenge insulin levels. However, estrogen had a more favorable effect on high-density lipoprotein cholesterol than any form of combined therapy, a noteworthy finding since this form of cholesterol is important in protecting women from atherosclerosis. The effect of these changes on the incidence of cardiac events is not known, because the study was designed to focus only on intermediate end points.⁸

The relative effectiveness of estrogen and estrogen—
CHIPPING AWAY AT MARBLE-BONE DISEASE

OSTEOPETROSIS (marble-bone disease) results from diminished skeletal resorption.1 We are certain of this pathogenesis because histologic studies of bone show that primary spongiosa — the scaffolded synthesized by chondrocytes in growth plates for subsequent deposition of osseous tissue — is not removed by osteoclasts during skeletal remodeling (turnover). Instead, this form of cartilage becomes encased as “islands” within trabecular bone and persists away from sites of endochondral bone formation. Bone formation continues normally, and the bones become increasingly dense.1

When skeletal resorption is profoundly impaired, the neural foramina do not widen, the medullary space is choked with bone, and skeletal remodeling is slowed. Consequently, severely affected patients suffer cranial-nerve entrapment, bone marrow failure, and recurrent fractures.1

Two types of osteopetrosis are generally known — an infantile (“malignant”) form and an adult (“benign”) form that are inherited as autosomal recessive and autosomal dominant traits, respectively.2 Untreated, the infantile type is usually fatal during the first decade of life; patients die of infection, hemorrhage, or profound anemia.1

Palliative therapy for osteopetrosis includes the administration of a glucocorticoid to improve the hematologic consequences of extramedullary hematopoiesis.3 More specific treatment, however, focuses on increasing skeletal breakdown. Since osteoclasts mediate bone resorption, these multinucleated cells are the appropriate target of experimental regimens. Indeed, histopathologic study of the bones of patients with infantile osteopetrosis usually shows an abundance of osteoclasts.1 Nevertheless, some straightforward approaches to stimulating osteoclasts have not been very successful — for example, injection or increased secretion (caused by the ingestion of a calcium-deficient diet) of parathyroid hormone.1,3

Fortunately, there are a variety of animal models of

References

osteoepetrosis. In 1972, Donald G. Walker made the important discovery that grey-lethal mice are cured by temporary parabiosis to normal littermates. Thus, a circulating cell or factor can permanently correct this disorder. Subsequently, he showed that the intravenous administration of cell suspensions prepared from the bone marrow or spleens of unaffected littermates had the same effect. His work revealed that osteoclasts in this murine model of osteopetrosis are derived from a cell of hematopoietic origin that circulates.

In 1977, bone marrow transplantation improved a number of manifestations of osteopetrosis in an infant girl. Subsequently, this treatment has reversed the complications of the disease in a convincing number of severely affected patients. There is evidence from the success of this treatment that osteoclasts in humans are derived from bone marrow precursor cells. Nevertheless, allogeneic marrow transplantation has risks for the recipient and is technologically demanding and expensive. Furthermore, HLA-matched donors are important for a successful outcome. In a study of 69 patients, primarily in Europe, 79 percent of those who received marrow from HLA-identical sibling donors were alive with osteoclast function five years after transplantation, but the outcome was much poorer with less favorable HLA matches.

Where do we look for new treatments of osteopetrosis? Laboratory studies make it clear that osteoclast development is complex and that skeletal resorption is highly regulated. Mononuclear cells of monocyte-macrophage lineage in the marrow or the blood attach to osseous tissue and fuse to become multinucleated osteoclasts. These cells are then influenced by a complex milieu of systemic and local factors to secrete the hydrochloric acid and proteases that dissolve bone.

In this issue of the Journal, Key and coworkers report that long-term therapy with recombinant interferon gamma-1b is beneficial in patients with infantile osteopetrosis. The rationale for this therapy was the observation that circulating leukocytes in these patients had a decreased ability to oxidize nitroblue tetrazolium. After interferon gamma was found to correct this defect in patients with chronic granulomatous disease, Key and colleagues undertook pilot studies with this agent in patients with osteopetrosis. The observation that circulating leukocytes in these patients had a decreased ability to oxidize nitroblue tetrazolium.
SOUNDING BOARD

COMPUTER-BASED DRUG-UTILIZATION REVIEW — RISK, BENEFIT, OR BOONDOGGLE?

On October 28, 1990, with little debate, Congress passed the Omnibus Budget Reconciliation Act, requiring the states to provide claims-based drug-utilization review to approximately 34 million Medicaid enrollees.1,2 The provisions of the program were borrowed from the ill-fated Medicare Catastrophic Coverage Act of 1988, repealed in 1990; the stated goals were to reduce potentially inappropriate prescribing and dispensing of medications, enhance the counseling of patients, and reduce growth in expenditures for drugs.1 Drug-utilization review is a structured, ongoing program that interprets patterns of drug use in relation to predetermined criteria and attempts to prevent or minimize inappropriate prescribing.3-6 Thus, it resembles other programs reviewing the appropriateness of medical procedures, including surgery and hospital admissions. As in the case of drug-utilization review, there is substantial debate about the cost and effectiveness of such programs.3-8

Drug-utilization review may be conducted retrospectively or prospectively, and the 1990 act mandated both types. A prospective review is designed to enable pharmacists to detect potential problems with drug therapy before they dispense medications. Currently, most pharmacists in the United States provide such a review on site: they maintain histories of their customers’ prescriptions, often using computerized screening systems unique to their own pharmacies. It is estimated that by the end of 1995 about half the states will have prospective programs on line.9 These programs use standardized software to detect potential drug-therapy problems and have access to centralized information about a patient’s prescription history, regardless of where the patient purchased the medication. The 1990 act required that criteria be developed to identify problems in certain categories, including inappropriate dosage (e.g., an excessive daily dose of oxycodone with acetaminophen), overuse (early refills), undertuse (late refills), duration of therapy, duplication of therapy, indications or contraindications, and interactions between drugs (e.g., carbamazepine with lithium). These criteria had to be drawn from drug compendiums specified in the 1990 legislation or from the peer-reviewed literature. If the patient’s prescription violated the criteria, the pharmacist was required to determine (sometimes by calling the prescribing physician) whether to dispense it as written, to adjust the prescription, or to discontinue no prescription.

A retrospective drug-utilization review, which is conducted after medications are dispensed, usually checks claims data to identify potentially inappropriate prescriptions for individual patients. If the computer program finds that a physician’s prescription for a particular patient has violated the criteria for optimal drug use (e.g., the use of long-acting benzodiazepines for elderly patients), the case is reviewed by a panel of physicians and pharmacists. If the panel finds the prescription problematic, it sends an advisory letter asking the physician to change it.

All Medicaid programs nationwide are now engaged in either retrospective or prospective review of this type. At least half the retrospective programs are operated by private firms. In the private sector, the prescriptions of an estimated 75 percent of Americans with outpatient drug insurance are scrutinized.10 Given this degree of penetration in both the private and public sectors, it is important to consider several fundamental questions if these systems are to improve the quality and efficiency of care.

We focus here on the most widespread application of drug-utilization review: the use of administrative-claims data bases to alert physicians and pharmacists to problems with prescriptions for individual patients. The 1990 Omnibus Budget Reconciliation Act encourages states to develop educational programs that include face-to-face counseling for physicians with a demonstrated need for specific advice about drug prescriptions.11 Interventions of this type and other means of improving aggregate prescribing practices12 — feedback to groups of physicians on their adherence to therapeutic guidelines, recruitment of physicians who are local opinion leaders to educate their peers, and the like — are beyond the scope of this article.

We believe that some forms of computer-based drug-utilization review, however well-intentioned, have been implemented without satisfactory evidence of their efficacy and safety. Current programs focus on errors of commission, without examining problems of underuse; they also emphasize savings in the short-term (e.g., reductions in doses or refills of costly medications) rather than longer-term efforts to achieve systemic savings (e.g., reduced rates of hospitalization due to increased compliance with antihypertensive regimens). In the private sector, recent acquisitions by drug companies of firms that conduct drug-utilization reviews may pose conflicts of interest. We conclude with recommendations for improvement in the scientific foundation of drug-utilization review as well as in private and public policies.

LACK OF SUPPORTING DATA

Claims that drug-utilization review is cost effective because it reduces the incidence of drug-related illness and hospitalization tend to be inflated and based on unpublished, poorly controlled, or biased studies.13,14 Few evaluations of commercial programs have been published,15 because of the proprietary nature of the programs.16 Typically, retrospective studies have merely determined how often problematic drugs are discontinued, often months after physicians have received a peer-review letter.17 The studies measure success by the percentage of cases in which drug-therapy decisions are...
altered, but they do not explore other possible explanations (e.g., that physicians may have changed their prescribing behavior before the peer-review letter was sent). These weak research designs suffer from many biases, including regression to the mean, which tends to exaggerate the effects of the review program.

Few controlled studies have examined the direct effect of drug-utilization review on patients’ outcomes, such as the use of hospitals. A notable exception is a recent controlled study of the Medicaid program in California, which revealed that retrospective review in several counties brought no changes in costs for health care or prescription drugs. The negative results may have been due to the small percentage of prescriptions flagged by the computer that resulted in letters to physicians; to a lack of diagnostic information, so that the appropriateness of prescriptions could not be determined; or to inability to identify the prescribing physician for about one fourth of patients.

To Congress’s credit, the 1990 law authorized funding to evaluate counseling by pharmacists and prospective drug-utilization review; demonstration projects in Iowa and Washington, funded by the Health Care Financing Administration, will be completed by 1996. The Iowa project will test whether prospective drug-utilization review is cost effective and will examine outcomes, including the frequency with which potential drug-therapy problems (i.e., failure of the prescribing physician to adhere to computerized criteria) are detected, the percentage of such problems that lead to an intervention by the pharmacist, and changes in hospital admissions for drug-induced illness. The Washington project will test whether reimbursing pharmacists for their counseling services increases the detection of problems, raises the number of interventions by pharmacists, and reduces the costs of drug therapy.

**Questionable Screening Criteria**

The efficacy of computer-based drug-utilization review depends largely on the plausible assumption that greater adherence to the many published criteria regarding drug interactions, excessive dosages, and other potential drug-therapy problems will reduce the incidence of serious adverse effects, as drug-related hospitalizations. With a few exceptions, however, there is little evidence to support this assumption. Lack of validation of the screening criteria is one of the most serious deficiencies of utilization review, for both drugs and medical care. To the extent that physicians receive conflicting information about the same therapeutic problem from different companies, the review process will be no more helpful than much of the prescribing information they have received in the past (e.g., from multiple pharmaceutical companies). Recent analyses suggest that the review criteria obtained from five authoritative drug compendiums differ substantially in content and scope. For example, among 26 possible interactions between digoxin and other drugs, the five compendiums agreed with respect to the existence and severity of only 1 (that between digoxin and quinidine). Not all of the compendiums agreed about the interaction of digoxin with verapamil, amply demonstrated by studies published in peer-reviewed journals.

Concurrence between computer-derived alerts of potential problems with drug therapy and expert opinions has been as low as 10 percent, suggesting that many such alerts are false positives. In a concurrent system of physician feedback operated by a commercial utilization-review firm (evaluated by one of us in a controlled trial), clinicians thought that the vast majority of messages generated by the computer were invalid or not clinically important for particular patients. In the words of one physician, “The system provided too much detail about drug-therapy problems that we already know about or about drug-therapy problems that were clinically insignificant.” The warning messages focused on drugs that are commonly accepted as relatively safe in most situations (e.g., antiulcer drugs). Furthermore, the system provided warnings without giving information on the estimated frequency of specific serious side effects; thus, clinicians could not weigh these risks against the benefits or consider other therapeutic options.

The costs of such presumed false alarms were often substantial. Residents reported spending considerable time looking into the situations causing the alerts. In addition, the large number of clinically irrelevant messages reduced the credibility of the program, especially in the eyes of experienced physicians. At the completion of the study, less than a quarter of the clinicians said that the messages influenced their prescribing decisions. Nor did prescribing practices change. Thus, the challenges facing unvalidated systems of drug-utilization review are similar to the problems with experimental computer-assisted diagnosis that have been previously described — for example, questionable clinical relevance of diagnoses, inconsistent knowledge bases, and incomplete data on patients.

**Underuse of Drugs**

Because of limitations in the technology and data (e.g., incomplete or absent diagnoses) associated with drug-utilization review and because of cost-containment imperatives, there has been an emphasis on errors of commission, whereas problems associated with the underuse of effective medications have been virtually ignored. Omissions of needed drugs, for example, are inherently harder to identify than interactions between drugs. A recent analysis of drug-utilization review in three states indicated that less than 1 percent of potential drug-therapy problems identified by the computer were related to underuse. However, recent research indicates that some of the most debilitating, costly, and treatable illnesses are undertreated. The underuse of antihypertensive drugs (e.g., through noncompliance) has been associated with increases in hos-
hospital admissions. In several large studies in the United States, less than half the patients with serious depression received effective medication or at least short-term psychotherapy. At one teaching hospital, one third of patients with acute myocardial infarction who were eligible for treatment with beta-blocker drugs did not receive any of those drugs, contrary to the guidelines of the American College of Cardiology. As a result, the mortality rate among these patients was 20 to 40 percent higher than that among patients given a beta-blocker. Moreover, most programs of drug-utilization review do not address problems caused by patients’ behavior, including prescriptions for refills of essential drugs that have gone unfilled.

Recent studies suggest that common policies for containing drug costs can also result in the underuse of effective medications, adverse clinical outcomes, and increased expenditures. For example, a Medicaid policy that limited drug reimbursement to no more than three drugs reduced the extent to which frail elderly and chronically mentally ill patients in the community were treated with essential somatic and psychotropic medications. The policy also increased the rates of institutionalization in nursing homes, emergency mental health visits, and full-day or half-day hospitalizations in community mental health centers — all at costs far in excess of the drug savings. Placing the primary emphasis on errors of commission is therefore a major weakness of current efforts to review drug use.

Risks of Denying Prescribed Drugs

Computer-based drug-utilization review can have educational functions (e.g., by providing information on appropriate dosages), but denying patients specific drugs at the point of sale may present unintended risks. For example, a program that reimburses the costs of medications for the elderly in Pennsylvania recently used its system of prospective drug-utilization review to refuse to fill prescriptions for the benzodiazepine triazolam (Halcion) if a patient had received that drug for three consecutive months. Although some long-term benzodiazepine treatment leads to habituation and represents inappropriate prescribing, denying the drug may violate the patient’s privacy and cause the adverse effects of rapid withdrawal. Confronting the patient in the pharmacy in this manner is an insensitive and ineffective form of drug-abuse counseling.

Computer-based systems have also been used to deny refills of medications to patients who request them seven days or more before the anticipated refill date. Between January and October 1993, for example, 144,880 requests for early refills were denied in Maryland. A recent report indicated that five Medicaid programs that screened prescriptions for early refills have realized enormous savings from such denials. Early refills may signal possible fraud or abuse, particularly if the drug has street value, as narcotics do, but there may be alternative explanations. The physician may have asked the patient to increase the dose of a drug without having notified the pharmacist; thus, the patient will need more of the drug sooner. Also, the patient may have misunderstood the instructions or may be able to travel to the pharmacy only when transportation is available.

Scrutiny of reports on two states arouses concern that refills are often denied for essential medications. In Maryland, the most common early refills requested in 1993 involved inhaled drugs for asthma and emphysema, antulcer drugs, several antihypertensive agents, both oral and injectable antidiabetic drugs, and medications prescribed for panic attacks. Several of these drugs are given for extended periods to treat life-threatening illnesses, and most have no potential for fraud or abuse. Similar refills were requested in Tennessee. In both states, over 75 percent of requests for early refills were denied. It is not known whether the prescriptions were eventually filled, whether the patients ever received these essential medications, or how much the state policies reduced patients’ compliance and precipitated adverse health outcomes.

In contrast to such across-the-board administrative restrictions, substantial savings may be achieved by discouraging the use of certain expensive drugs for which there are inexpensive, equally effective, and safe alternatives. Elsewhere in this issue of the Journal, Smalley and colleagues report the results of a well-designed, longitudinal study of the effects of a policy in the Tennessee Medicaid program that required prior authorization for the use of nongeneric nonsteroidal anti-inflammatory drugs (NSAIDs). This prior-authorization policy achieved a 53 percent reduction in expenditures for NSAIDs, primarily through the substitution of generic agents. As a result, there was an estimated savings of $12.8 million over a two-year period without concomitant increases in expenditures for other drugs or outpatient services.

Such carefully targeted strategies, which encourage the selection of cost-effective agents within a therapeutic category, may have implications for drug-utilization review. However, some caution is warranted. We do not know, for example, what proportion of the reported 26 percent reduction in overall use of NSAIDs by enrollees represented appropriate use by patients with painful and debilitating arthritis or another chronic condition. Nor do we know the amount of time required for physicians or pharmacists to seek prior authorization — the so-called hassle factor — that may divert their attention from more important tasks. Injudicious use of a prior-authorization policy to cover medications other than NSAIDs can be a barrier to essential care. In a study of Medicaid patients in West Virginia, the use of cimetidine among those with a diagnosis of peptic ulcer declined by 94 percent after the imposition of a prior-authorization requirement — at a time when there were no effective therapeutic alternatives.

Although the design of this study precluded a
valid assessment of the health and economic consequences of reduced access to histamine H₂ antagonists (e.g., increased hospitalizations), cases such as this underscore the need to monitor carefully the effects of drug-related policies on systemwide costs, quality, and outcomes of care.

**Conflicts of Interest**

Few would disagree that the primary goal of drug-utilization review — disseminating impartial information on drugs in order to increase the safety and cost effectiveness of treatment — should be educational. To achieve this goal, the data arising from such reviews must come from a source that is credible, authoritative, and accountable to physicians and the public.¹¹ This requires financial independence from pharmaceutical companies and other entities with vested interests in the sale of specific drugs. Recently, drug manufacturers have acquired several large pharmacy-management companies that conduct drug-utilization reviews and manage claims, formularies, and pharmacy purchases on behalf of health insurers that cover an estimated 90 million people.¹² Conflicts between the promotion of specific products and the dissemination of impartial and objective information about drugs are serious matters that merit further examination and debate.

**Conclusions**

Although computer-based drug-utilization review has been mandated for nationwide use in the public sector and is popular in the private sector, there are no valid scientific data to support its claimed benefit. Moreover, regulatory applications of this policy may reduce appropriate use of medications and pose risks to health and patient confidentiality. In general, the validity of the criteria used to detect problems with drug therapy is unknown. The data and experience reviewed in this article support several recommendations.

First, continued investment in existing programs of computer-based drug-utilization review should be predicated on reasonable evidence that such interventions are safe and effective (and ideally, cost effective), on the basis of experimental or quasi-experimental studies.¹³ Such research should examine the effects of various methods of review on both appropriate and inappropriate use of medications, cost, and health outcomes, especially among vulnerable populations (e.g., the unintended consequences of denied requests for early prescription refills). Studies should be conducted of the advertising claims made by companies engaged in drug-utilization review (e.g., claims of reduced hospital admissions) to inform public and private payers better about the services they purchase and to improve the detection of underuse of essential medications.

Second, a national consensus of experts is needed to identify the most salient problems with drug therapy from a systematic review of the scientific literature. Such a process should identify clinically important problems, doing so with acceptable levels of sensitivity and specificity and providing models for adaptation by programs at the state level. Furthermore, there is a critical need for pharmacoepidemiologic studies of the clinical and economic relevance of these criteria and their relation to patient outcomes.

Finally, all programs of drug-utilization review should disclose the source of specific therapeutic recommendations, as well as potential conflicts of interest, using the same disclosure principles that have been developed for product-specific evaluations of cost effectiveness.¹⁴ Disclosure is essential when drug-utilization review conducted by a pharmaceutical company involves drugs whose sale benefits the parent company.

The scientific base for drug-utilization review is in its infancy. Yet the stakes for patients, clinicians, and the marketplace are high. About three quarters of all visits to a physician end with a drug prescription.¹⁵ Used appropriately, medications represent some of the most cost-effective, health-promoting advances in medicine. Efforts to use computers to improve drug therapy in the private and public sectors must be made with attention to clinical, research, and policy issues so as to ensure that the benefits of the review outweigh the risks.

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