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SPECIAL ARTICLE

Equipoise Lost: Ethics, Costs, and the Regulation of Cancer Clinical Research

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A B S T R A C T

Cancer is the leading cause of death in Americans younger than 85 years of age and kills one American every 56 seconds. Advances in understanding of cancer biology have given us the potential to develop new, effective targeted therapies. However, progress is slowed by suboptimal/outdated clinical trial design paradigms and by regulatory complexity and rigidity. For instance, simulations suggest that restricting randomized trials to patients expressing drug target, instead of using unselected patient populations, could substantially reduce patient numbers required to demonstrate efficacy. High response rates that are achievable when patients and drugs are matched on the basis of molecular profiles may also make some randomized trials unnecessary or unjustifiable. Moreover, increasing the regulatory rigidity of clinical trials (regulatory fundamentalism) augments trial complexity and costs while slowing progress without demonstrating meaningful safety benefits. Time from drug discovery to marketing increased from 8 years in 1960 to 12 to 15 years currently. Toxic death rates on phase I trials have decreased from 0.8% in 1979 to 0.5% by 2002, but the estimated cost per life-year gained by tighter regulations is $2,700,000 (far higher than costs of other health measures), and simulations suggest that regulatory delays in development of effective therapies result in tens to hundreds of thousands of life-years lost, whereas stringent regulations save extremely few. Dysregulation is also a major disincentive to patient and clinician participation in clinical research. In summary, current approaches squander research resources and discourage research participation, and the marked imbalance between potential life-years lost versus saved renders the regulatory burden potentially unethical. We outline suggested solutions.

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PART 1: THE PROBLEM

Depending on the context in which it is used, the term "equipoise" has different meanings. At its simplest, it means "balance; equilibrium,"[1] although in clinical research, it is also used to describe a state of uncertainty that provides the ethical justification for proceeding with a randomized trial.[2] In this article, we offer evidence that, for lethal diseases, equipoise, or balance, has been lost and that the harms done by current clinical research regulation substantially outweigh the benefits. We have both the ability and the responsibility to restore this balance.

Background

Lifetime risk for development of cancer is approximately 44% for American men and 37% for women.[3] Cancer will kill 23% of all Americans.[3] Indeed, it is the leading cause of potential years of life lost and is the top killer of Americans younger than 85 years of age.[3] Despite treatment advances, metastatic cancer generally remains a death sentence. The toll taken by this disease lends urgency to this problem.

We have made great advances in our understanding of cancer biology, and these advances have the potential to markedly improve therapy efficacy. However, clinical research is fundamental to translating this ever-increasing biologic insight into new therapies, and insufficient attention has been paid to clinical research administrative processes. We agree with others that these processes need to be reformed and that "the dam holding back clinical trials" is one of the greatest impediments to progress.[4]

Clinical research is governed by regulations, laws, agencies, and so on, which are intended to protect patients from harm, exploitation, and invasion of privacy and to protect the public purse from misappropriations. Many groups are explicitly charged with protecting patients (and/or public funds) from damage and with preventing exploitation in clinical research, such as that perpetrated by the Tuskegee experiment.[5] Other bodies have only an indirect (but nevertheless important) impact on clinical research. Examples of those having a direct or indirect impact in the United States include institutional review boards (IRBs) and compliance offices, the US Food and Drug Administration (FDA),

the Office of Human Research Protections, the National Cancer Institute (NCI) and its Cancer Therapy Evaluation Program (CTEP), the Center for Medicare and Medicaid Services and its Clinical Laboratory Improvement Amendments (CLIA), the US Department of Health and Human Services and its Health Insurance Portability and Accountability Act (HIPAA), the Department of Veterans Affairs, the Internal Revenue Service, the Office of the Inspector General, the US Patent and Trademark Office, and the Joint Commission. The situation is made even more complex by the fact that international pharmaceutical sponsors may now for many studies attempt to run trials and collect data in a manner that will satisfy regulatory bodies around the world and not just the panoply of US regulators.

The intentions behind the regulations are good and appropriate. However, the pendulum has swung too far. Although the individual impact of new regulations on clinical cancer research may appear relatively small, the combined effect is large. This problem cannot be solved by just changing one or two regulations or agencies because the overall situation is dependent on the collective effect of hundreds of individual regulations and processes. Both the US FDA[6,7] and European regulators[8] have launched initiatives to try to improve efficiency, but these efforts are insufficient.[8,9] In the war on cancer, progress has been impeded by the regulatory bar having been placed too high and the efficacy bar having been placed too low.[10]

To achieve clinical trials equipoise, one seeks a favorable balance between potential benefits versus harms of proposed interventions. Because resources are not unlimited, cost effectiveness also merits attention. In addition, patient's wishes must be carefully considered—no easy task because people have diverse outlooks. Importantly, there has been no concerted effort to scrutinize the cost in lives (or dollars) of the regulations to assess whether they fulfill or thwart their purpose.

The Regulatory Traffic Jam

Clinical trials are analogous to cars speeding down the research highway in the quest for a cure. An accident happens, so the speed limit is reduced. Ultimately, research cars capable of traveling 120 mph are permitted a top speed of only 5 mph. The low speed limit reduces accidents, but safety and process have been granted higher priority than has speed in reaching our destination. This not only increases the time required to test each new idea, but it also decreases the number of ideas that can be tested, because if traffic slows, cars bunch up and there is no room for other cars on the highway. Cars in traffic jams are also more likely to malfunction. Similarly, clinical trials are more likely to fail to reach their accrual goals if it takes a long time to activate them,[11] and failed studies are very costly. First, the study activation process is expensive,[12] and activation costs are lost if the study is not completed. Second, researcher time is wasted. Third, patient resources are wasted. Many failed studies accrue at least some patients before being prematurely closed.[11,12] For example, from 2000 to 2007, 40% of all CTEP-sponsored trials failed to achieve minimum accrual objectives, despite accrual of 8,723 patients, and delayed study activation was identified as a major culprit behind accrual failure.[11] The data from patients on such studies is often of limited value, and the patient's entry on the failed study makes them unavailable for entry on other important trials.

Furthermore, research costs are driven sharply upwards by the increasing burden of regulatory compliance.[8] High costs mean that fewer ideas can be tested, and high research costs contribute to eventual high retail prices. The United States already spends more than 16% of its gross domestic product on health care (compared with $\leq$ 11% for almost all other countries),[13] yet in 2008, it ranked only 30th in life expectancy.[14]

In an attempt to improve the situation on our hypothetical highway, additional funding is allocated to buy costly new research Ferraris capable of reaching 200 mph, but despite their potential speed, they are permitted to go only 5 mph; there is consternation that increased research investment has not increased cure rates. Funding is very important, but this problem is not going to be fixed by increased funding alone.

Regulations are essential. By analogy, the German Autobahn has traffic fatality rates lower than those on many other European roads despite sections with unlimited speed limits, but it does require that slower cars keep to the right and generally does not allow passing on the right.[15] Hence, with well-thought out rules, high speed is possible without sacrificing safety. We need a cancer research equivalent.

Are Current Research Regulations Cost-Effective?

Clinical research regulation has become increasingly complex, stringent, and costly over time.[8,9,16-19] Although research regulations serve many purposes, the usual major justification is patient safety. To assess the impact on patient safety of increasing regulations, we calculated changes in toxic death rates between older versus newer phase I cancer clinical trials. In 460 studies involving all 11,935 patients placed on NCI phase I trials between 1991 and 2002, there were 58 toxic deaths (0.5%).[20] We reviewed all 227 phase I studies involving 6,426 patients published in PubMed-searchable journals between 1979 and 1990 and found 52 toxic deaths (0.8%) (R. Kurzrock, unpublished data), and another review of phase I trials published between 1972 and 1987 (6,639 patients, 211 trials) demonstrated toxic deaths in 31 patients (0.5%),[21] a proportion that is identical to the later 1991 to 2002 cohort. Hence, depending on which older studies are assessed, more stringent recent regulations seem to have reduced the toxic death rate by no more than 0.3%, although advances in supportive care (eg, new antibiotics) might have accounted for much of any improvement, and there is little evidence that regulatory changes actually contributed in a meaningful way to any possible reduction in the toxic death rate. Overall, the gains (if any) have been miniscule, and there is little room for any further improvement.

Regulatory complexity drives data management and research nurse costs. In 2000 to 2002, approximately two full-time employees were required for a site to conduct trials of moderate intensity that accrued 20 enrollees.[22,23] Study complexity and personnel costs have increased further since 2002. Staffing requirements have increased as protocols have evolved over the last two decades from guidelines outlining the intent of the study to legal-type documents that mandate adherence to the protocol's precise wording. Furthermore, the size of protocols has increased and they are now in some cases more than 200 pages long. Hence routine clinical decisions may now require careful rereading of a lengthy protocol to ensure that the clinical decision fully complies with protocol wording. Also, protocols typically stipulate numerous medical procedures. In a recent review of phase I trials at our institution, there were a mean of 3.16 physical examinations, 5.63 vital sign measurements, 4.36 ECGs, 18.08 nonpharmacology blood draws, and 15.14 pharmacology blood draws just within the first 28 days.[24] In addition, there are indirect/overhead costs, nonstandard-of-care procedures such as scans or biopsies, tumor measurements, and

so forth. Other clinical research expenditures include those related to monitoring by the study sponsor and the cost of providing the drug. Taken together, the combined costs now average $26,000 per patient entered onto a clinical trial.[25] This amount does not include impact of clinical trials on budgets of the FDA (now $2.7 billion per annum[26]) and other relevant US regulators. Clinical trials costs are increasing rapidly, and the rate of increase is itself increasing, from an inflation-adjusted annual rate of increase of 7.3% from 1970 to 1980 to an inflation-adjusted annual rate of increase of 12.2% from 1980 to 1990.[18] If it is conservatively estimated that 30% of the above per-patient costs (or approximately $8,000 per patient) are due to the increasingly complex regulatory environment, and if it is liberally estimated that the toxic death rate decreased by 0.3% and that all of that decrease in toxic deaths is due to enhanced safety engendered by more stringent regulations, and that patients with cancer on phase I trials have a life expectancy of 12 months, then the cost per life-year saved by the regulations is approximately $2.7 million. Although the current stringent regulations may have other benefits in addition to saving lives, safety is generally the major reason given by regulators in justifying them. The consensus among oncologists is that $100,000 per life-year gained is good value,[27] and if we compare this estimated $2.7 million per life-year saved by regulatory stringency to the cost of other prevention measures and therapies,[28-34] it is extremely high (Table 1). Only two of the selected comparator interventions (hemodialysis for renal failure at 1.4% to 3.9% and bevacizumab in advanced non–small-cell lung cancer [NSCLC] at 14%) exceeded 1% of the estimated cost per life-year gained by current regulations.

How Do Current Regulations Determine Who Drives the Agenda?

High regulatory costs mean that we can afford to test fewer clinical research ideas, and the ultimate costs of therapies that are successfully developed are very high, at an estimated $800,000,000 to $2,000,000,000 per new drug approved.[36] These high costs also mandate that large pharmaceutical companies drive the research agenda, because only they have the required capital. The pharmaceutical industry is a crucial source of innovation, but there are disadvantages to concentrating control of clinical research in the hands of a relatively small number of players. These include difficulties in developing agents that cannot be patented, in combining experimental therapies from different companies, in developing treatments for rare diseases, and in exploring higher-risk strategies. Although the NCI can partially mitigate this, its effectiveness is decreased by funding limitations and by the fact that it relies on contracts with pharmaceutical companies for access to drugs and extra funding. Furthermore, although large pharmaceutical companies have indeed played a major role in therapy advances, academic researchers and small biotechnology companies also make important discoveries. However, hurdles for developing drugs seem impassable for many investigators, and investigator-initiated studies can take years to activate or may be abandoned because of the difficulty in identifying sources of funds to pay the high costs of study regulatory requirements.

Because current regulations also deem the sponsor accountable for study conduct, the sponsor may hold substantial sway over which individual patients may or may not go on a trial and over dose adjustment decisions in the trial as a whole or in individual patients. The principal investigator (PI) and/or treating physician, although theoretically responsible for the trial and/or managing the patient, may in fact have limited real authority with respect to some key study aspects and, more importantly, over decisions regarding patient care that could deviate from the protocol. Hence the anomaly exists that, based on ubiquitous conflict of interest rules, individual investigators/physicians with more than a few thousand dollars worth of interest in an agent are not allowed to be involved in patient care decisions for that compound, whereas representatives working directly for corporations that have invested millions of dollars in compounds are given responsibility for ensuring that patient-related decisions comply with the protocol.

Table 1. Costs per Year of Life Gained by Selected Interventions

Procedure	Cost/Life-Year Saved*
Clinical trials regulations	$2,700,000
Hemodialysis[29]	$43,000-$104,000
Statins for heart disease (moderate- to high-risk patients)[30]	$19,000-$25,000
Colorectal cancer screening by colonoscopy[32]	$14,000
Adjuvant trastuzumab breast cancer[31]	$20,000
Bevacizumab advanced non–small-cell lung cancer[33]	$380,000
Paclitaxel/cisplatin for advanced ovarian cancer[34]	$26,000

*Converted to 2009 US dollars using an online inflation calculator.[35]

The Regulatory Burden and Its Impact on the Pace of Research

It now takes 12 to 15 years from drug discovery until marketing,[36,37] compared with an average of 8 years in the 1960s.[37] For oncology drugs, development time includes up to 6 years for FDA-mandated preclinical toxicology, pharmacology, and efficacy assessments; for preparation of clinical trials documents; and for approval and activation of early clinical trials.[38] Once early clinical data are available, it now takes a median of 370 to 481 further distinct processes and 26 to 27 months to take a cooperative group phase II or III trial from initial concept to activation.[39,40] This includes the time and processes required for initial concept development and then a median of 296 processes and 20 months from the time the concept is submitted to CTEP until study activation.[41] For studies not sponsored by a cooperative group, some activation steps can take even longer.[42] An average of 14.8 separate phase I, II, and III single-agent and combination clinical trials are required to get a drug approved,[43] and some of these studies are done sequentially, with similar delays built into each sequential step. From activation of initial clinical trials, it now takes a median of 7.8 years until submission of a New Drug Application to the FDA and a median of 1.3 years from New Drug Application submission to FDA approval.[38] Overall, we estimate that processes required for compliance with regulations directly or indirectly account for at least 5 years of the 12- to 15-year drug approval process.

One indirect impact of the regulatory burden is that it decreases both the number of patients and the number of physicians who are willing or able to participate in clinical research. Currently fewer than 5% of adult patients with cancer participate in clinical trials,[44] and the regulatory burden may play a major role in this,[45] for example, by reducing the number of available studies, excessively restricting eligibility, mandating study schedules that are impractical for patients, or delaying study activation so long that the question being asked is no

longer of much interest. At the same time, there has been a sustained decline in numbers of clinical researchers.[46] Although a variety of financial reasons have been proposed for this decline in clinician investigators,[46] blame has also been attributed to the "traumatic," "nightmarish" regulatory burden of activating and running a trial.[45] Not only do investigators become discouraged and disillusioned as they try to steer their way through the regulatory mud and fog, but bright young academic flames are also dampened or snuffed by the chill of seeing peers and mentors being threatened and censured by IRBs, institutional compliance offices, and regulatory agencies.

Equipoise Lost: Slowing Clinical Research Costs Lives

Regulatory delays in clinical research cost lives.[47] As noted above, toxic death rates have either not decreased at all from the 1970s[21] or have decreased at most from 0.8% on older phase I trials (R. Kurzrock, unpublished data) to 0.5% on more recent trials,[20] suggesting that newer regulations have reduced toxic death rates by no more than 0.3%, if at all. It takes a median of 5,435 patients on phase I to III studies for a new molecular entity to be approved by the FDA.[48] If we assume that the average life expectancy of patients with advanced cancer going on study is less than 1 year, then these regulations would save no more than 16.3 life-years over the course of drug development (5,435 patients entered on trials of the drug $\times$ 0.3% reduction in toxic death rate for those entered on studies $\times$ 1 year of lost life for each patient dying prematurely because of toxicity).

Let us further assume that the new treatment increases the overall cure rate of lung cancer by 1% through advances in adjuvant therapy, that the patients who are not cured have their life expectancy increased by an average of 3 months, but that the cumulative effect of the regulations delay the advance by 5 years or more, in keeping with how much longer it takes to get a drug approved now than was the case in the 1960s.[36,37] In this scenario, the regulations would result in 282,529 life-years lost in the United States and 1,931,250 worldwide. We calculated this as follows: It is estimated that there will be 219,440 new lung cancer cases in the United States this year[3] and more than 1.5 million worldwide,[49] and the 5-year relative survival rate for lung cancer is currently 16% in the United States.[3] If it were conservatively estimated that cured patients have a life expectancy of just 5 years, then the 5-year delay in the advance would mean 54,860 life-years lost in the United States attributable to patients who could have been cured but were not (1% $\times$ 219,440 patients $\times$ 5-year life expectancy for cured patients, or 10,972 life-years lost for each of the 5 years of the delay). If the cure rate has been increased to 17% from 16% as a result of the therapy, then the proportion of the population eligible for noncurative palliative therapy would decrease from 84% to 83%, and if their survival were increased by a median of 3 months (0.25 years) by the new therapy, the life-years lost among palliated patients as a result of the 5-year delay would be 227,669 (83% $\times$ 219,440 patients/year $\times$ 0.25 life-years lost per patient, or 45,533.8 life-years lost overall for each of the 5 years of the delay). The worldwide rate was calculated by dividing the number of new patients with lung cancer worldwide by the number in the United States (1,500,000/219,440 = 6.84) and multiplying this times the US life-years lost.

Even in the highly unlikely event that the steady increase in regulations slows research by only 1 year, then the life-years lost would be approximately 56,506 in the United States and 400,000 worldwide. For each month of regulatory delay, 4,709 life-years would be lost in the United States and 32,189 worldwide. The losses also remain large even if the palliative therapy only prolonged median survival of uncured patients by 1 month instead of 3 months (2,179 life-years lost in the United States and 14,895 worldwide for each month of regulatory delay). The size of the problem becomes much larger if one expands the potential impact of the new therapy to other tumor types, if one considers all the potentially useful agents that never even make it into clinical testing because of the regulatory burden, and if one aims for much more substantial therapeutic advances than the illustrative ones described above. The current regulatory situation is unacceptable and seems to be unethical.

Evolutionary Forces Driving Regulatory Fundamentalism: A Hypothesis on the Pathophysiology of Dysregulation

We propose the following as the reason for the current dysregulation. Well-qualified people generate reasonable, well-intentioned laws, rules, and regulations. Real abuses do in fact occur,[5,50] and rules and regulations are essential. Appropriate judgment is then used in enforcing these regulations. An unfortunate event such as the Vioxx scandal then generates public fear and anger.[50] This in turn leads to congressional hearings, statements, and laws that are intended to better protect patients. When patients have poor outcomes or have been misled, regulators and others may be interrogated and censured by congressional committees and may be vilified by the press. "Regulatory fundamentalists," who followed the exact letter of the regulations, are able to defend themselves by claiming to be faultless because they fully complied with and enforced all regulations. "Regulatory rationalists," who instead exercised judgment in aiming to fulfill the intent of the regulations while attempting to facilitate progress, are much less able to defend themselves.[51] This leads to enrichment of regulatory bodies with fundamentalists and fosters a fundamentalist reinterpretation of the regulations. Institutions, investigators, companies, and regulatory bodies then feel threatened and try to protect themselves from the uncertainty of both current and future fundamentalist reinterpretations of the regulations by taking steps that magnify the impact of the reinterpretations at the local level. This leads to greatly increased compliance rigidity, and this in turn leads to a massive regulatory traffic jam, with increased costs and delays and with decreased innovation and progress.

The new regulations and laws that are intended to prevent recurrence of a problem represent a broad solution for a specific problem and therefore have broad consequences beyond the specific scenario that represented the initial problem. Furthermore, there is no counterbalance, in that the downstream effects of the new regulations are not assessed adequately and often cannot be predicted.

Dysregulation Modulators

The situation is worsened if the regulators do not understand or accept the ultimate research goal. Government regulators and local institutional IRBs are largely charged with ensuring safety and enforcing compliance, not with facilitating progress. In fulfilling their mission, they gain little or nothing from speed, and in practice, speed is more likely to hurt them than to help.[17] The situation is also worsened if the regulators lack adequate resources or knowledge, if they derive secondary gain from identifying and prosecuting "bad guys," or if they are overly suspicious of clinical research, and it is compounded by the fact that there are genuine abuses that must be addressed. Furthermore, individuals concerned about the process have told us that they

Table 2. Examples of Current Problems With Clinical Research

Factors contributing to regulatory complexity/stringency:
Current culture fosters "regulatory fundamentalism"
Too many regulatory bodies with overlapping/conflicting responsibilities
Trials attempt to simultaneously satisfy regulatory requirements for several countries
Consequences of regulatory complexity/stringency/delays:
Life-years potentially lost ≫ life-years potentially saved by regulations
Increased research costs/health care costs
High costs mean decreased number of ideas that we can afford to test (decreasing the ideas that can be tested further slows progress and costs more lives)
Precludes assessment of many promising new approaches
Decreased probability a trial will be completed successfully
Squandered research resources
Limits research that can be done without pharmaceutical company support
Decreased number of patients willing/able to participate
Inhibits clinician participation
Drives away young investigators
Inadvertently coercive/mutes opposition
Problematic components of the regulatory process:
Too many study review steps/not enough value added
Preclinical toxicology: time-consuming/expensive/not validated/adds little value
SAE reporting: cumbersome/expensive/ineffective
Consent form revision processes delay study accrual
Multiple documentations of same consent process: add expense, not value
Re-consenting process: adds expense, not value
Protocol as a legal document makes study conduct inappropriately rigid
Detailed reporting of minor toxicities adds expense but little value
Requirement to report exact start/stop dates of toxicities adds expense but little value
HIPAA rules complicate long-term follow-up of study patients
Requirement for CLIA certification of tests that will be used to assign patients on study:
Slows progress
Escalates costs
Markedly decreases number of molecular markers that can be assessed
Other problems:
Phase III trials that don't select patients by presence of drug target/efficacy markers:
Markedly increase required patient numbers
Markedly increase study costs
May discard agents that are highly effective in small subpopulations
May lead to broad application of therapies to subpopulations that cannot benefit
More likely to detect a very small advance affecting a high proportion of patients
Less likely to detect a very large advance affecting a small proportion of patients
Pick the most common target as winner, not the best drug
Large randomized trials permit/encourage detection of very small gains
Overall survival is affected by subsequent therapy, comorbidity, and supportive care
Complexities of health care payment systems add unnecessary delays and costs

Abbreviations: SAE, serious adverse event; HIPAA, Health Insurance Portability and Accountability Act; CLIA, Clinical Laboratory Improvement Amendments.

feel that speaking up is useless, or alternatively that they fear that speaking up might generate a targeted audit of their research. Targeted audits may be cause for concern because the marked complexity of current protocols and research regulations mean that it is virtually impossible to get all aspects of a study perfect, and any audit would inevitably reveal some flaw in study conduct, no matter how careful the investigator. Ayn Rand wrote, "The only power that any government has is to crack down on criminals. . . . When there aren't enough criminals, one *makes* them. One declares so many things to be a crime that it becomes impossible for men to live without breaking laws."[52] Clearly, current regulations and regulators are well meaning, but an unintended consequence of regulatory complexity is the "criminalization" of clinical research, and regulatory complexity is intrinsically coercive because some who might speak up feel vulnerable.

PART II: SOLUTIONS

In the preceding paragraphs and in Table 2, we outline the problem. We collectively have both the ability and the responsibility to solve this problem. In the following paragraphs and in Table 3, we outline just a few possible steps.

Acceptable Levels of Risk

The level of acceptable risk should be substantially higher for clinical research in uniformly fatal, incurable diseases, such as metastatic incurable epithelial malignancies, than for benign or potentially curable conditions. Many patients with terminal cancer would gladly welcome higher risks in return for access to an experimental or potentially effective therapy.[19,53] Although regulators presume that they are protecting a vulnerable population by not permitting certain risks, patients are heterogeneous and may instead feel that they understand the risks and are being denied access to potential therapy. Indeed, the demographic and health status characteristics of participants in highly experimental phase I oncology trials are not those of a conventional vulnerable population.[54] This suggests that it may be inappropriate to assume that, as a group, they are an exploitable population requiring special protections, with a compromised ability to make informed, voluntary decisions.[54] The key emphasis should be on ensuring that patients are fully informed of the risks, rather than assuming for them what risks they should be allowed to take.

Regulatory Stringency

The regulatory burden should also be matched to the population under study, with simpler oversight for clinical research in uniformly fatal diseases than in benign or potentially curable ones. Every piece of information that must be collected and every step that must be taken from drug discovery to final approval (eg, the 296 to 481 steps needed to activate trials by NCI-CTEP and/or cooperative groups[39-41]) is a speed bump slowing the pace of progress while increasing costs and decreasing the number of ideas that can be tested. For many of these pieces of information and steps, there is little value added.[41,42] Although a higher degree of toxicity is already accepted for therapies aimed at lethal versus nonlethal diseases, a major factor in the inappropriate slowing of cancer clinical research is that the mechanisms and structures used to regulate it are nevertheless largely the same as the mechanisms used to regulate investigations of analgesics, dermatologic preparations, and so on. At the same time, because several different regulatory bodies are involved, each with a different set of regulations but overlapping responsibilities, none of them can unilaterally fix the overall problem. The regulatory situation has grown increasingly more burdensome in recent years,[8,9,16-19] despite the

Table 3. A Few Examples of Solutions

Reform regulatory oversight of trials in lethal diseases:
Form a single new regulatory body for research in lethal diseases
New body supersedes and replaces role of all others for lethal diseases
Stresses speed, simplicity, minimization of regulatory costs
Accept higher level of risk than for benign and nonlethal diseases
Reform preclinical requirements and study activation processes:
Preclinical toxicology: require only LD10 in rodents
Preclinical pharmacology: require only cytochrome p450 interactions
Study review:
Restrict review to no more than two bodies or agencies
Stress speed and efficiency
Centralize IRB review
Change SAE reporting and re-consent processes:
Make SAE reports available online to patients/physicians/IRBs
Do not require each PI to submit each SAE to each IRB
In particular, don't require SAE reporting to IRB if all local patients are off therapy
Simplify re-consent process (eg, dictated documentation note, not new signed form)
Do not require study delay while consent form is modified and reapproved
Study conduct:
Permit PI to do protocol override/appropriate modifications without IRB/FDA approval
Simplify health care payment systems
Permit long-term follow-up of study patients whether or not the study remains "open"
For patients off therapy, do not require signed re-consent for new observed toxicities
Do not require CLIA certification of all tests that will be used to guide study:
Only require post hoc CLIA validation of tests that actually seemed to be helpful
Conduct small studies aiming for large gains, not large studies aiming for small gains
Look for agents active versus tumors with a particular target, rather than looking for the most effective drug in unselected patient populations
Documentation requirements:
Stop the requirement for rapid reporting of all deviations/violations to IRB and sponsor
Require reporting at the end of the study based on what was actually done; what was actually done is more important than what was initially planned
Markedly simplify toxicity reporting
Retract the patient-specific reporting requirements of the FDA Amendment Act 2007
Patient selection:
From earliest phase I/II trials, assess molecular markers that correlate with response
As a second choice, define markers correlating with progression-free survival
Markers correlating with overall survival may be less useful as a result of the impact of:
Subsequent therapy
Comorbidities
Restrict phase III trials primarily to patients with these favorable molecular markers
As appropriate, later studies can further assess the drug in other patient groups

Abbreviations: LD10, lethal dose in 10% of mice; IRB, institutional review board; SAE, serious adverse event; PI, principal investigator; FDA, US Food and Drug Administration; CLIA, Clinical Laboratory Improvement Amendments.

FDA,[6,7] CTEP, and others launching laudable initiatives to try to address the problem. The situation could be improved if clinical research in lethal diseases were overseen by a new separate, distinct regulatory body with a specific set of rules and regulations that replaced and superseded those currently overseen by a host of agencies and groups and that put a much higher premium on speed, simplicity, and minimization of regulatory costs and eradicated processes that add little value.

Examples of Opportunities to Facilitate Cancer Clinical Research

Although it has been well documented that different regulators and institutions may interpret the same regulation in substantially different ways,[55] next we list just a few examples of possible changes that might be considered in addressing common ways in which regulations are currently enforced.

Preclinical toxicology and pharmacology. The extensive preclinical toxicology assessments required by regulators have not been validated,[17] and routine use of nonrodent species in preclinical toxicology studies before initial clinical trials with cancer therapeutics is not necessary.[56,57] Using one tenth of the lethal dose in 10% of mice is a rapid, safe mechanism to choose the starting dose in phase I oncology clinical trials.[56,57] We also should more carefully assess whether much value is added by extensive preclinical pharmacology studies other than definition of interactions of agents with the cytochrome p450 system (to help predict drug interactions).

Study review. Extensive FDA, NCI, and IRB review may delay study activation by 1 to 2 years or longer.[39-41] The problem is compounded when multi-institutional studies require review by multiple different IRBs, when reviewers at one organization disagree with reviewers at another, when different reviewers even within one organization set inconsistent standards, and when later study amendments also require review by each of these organizations. This is inefficient, time-consuming, costly, and of questionable value. For example, Humphreys et al[58] reported that 16.8% of the total costs of an observational protocol were devoted to IRB interactions, with exchanges of more than 15,000 pages of material, but with minimal or no impact on human subject protection or on study procedures. Because our data suggest that regulatory delays are neither cost-effective nor ethical, we propose that review of each individual trial should be limited to no more than two regulatory agencies or committees, including centralized IRB review for multi-institutional trials. Limiting and centralizing reviews would be expected to save both time and money.[59-61]

Serious adverse event reports and the re-consent process. A single adverse event may generate several serious adverse event (SAE) reports, and each copy received from the study sponsor requires that a separate document be prepared, submitted, reviewed, corrected, formatted, and resubmitted to the IRB. Furthermore, previously unreported SAEs require that the consent be updated and approved by all regulatory agencies/bodies involved, and then each patient must be re-consented. The marked excess of time and resources devoted to dealing with outside SAE reports is counterproductive, because the few potentially important events are buried in an avalanche of unimportant ones, minor variations on ones that are already well-known, or ones that are more likely to be due to the underlying cancer or to comorbidities than to the therapy. As noted above, the combined costs of documentation and of complying with regulations, including regulations regarding SAE reporting, are also so high that they largely preclude clinical research without substantial funding and markedly reduce the number of ideas that can be tested. In addition, the process of re-consenting patients on study with every consent revision has become onerous and ineffective. Patients presented with numerous

revisions of the many pages of consent become inured to signing documents. In our experience, it has been extremely uncommon for patients to decide to discontinue participation in a study because of the re-consent process. Physicians should inform patients of major new toxicities of their experimental therapies just as they are currently expected to inform them of newly noted major toxicities of their standard therapies. Furthermore, some agencies now require that the study be put on hold until the consent is updated and reapproved. The additive effect of holding the study for each consent modification may add months to drug development time. Instead of the current system, we agree with Emmanuel et al[62] that all involved in a clinical trial (patients, investigators, and so on) should have access to a centralized, frequently updated, online summary of drug toxicity, with reports of individual events available to those who want additional details.

Protocol deviations, violations, and amendments. Until recently, protocols were regarded as a guide for study conduct, and PIs had substantial latitude to permit deviations from protocol, as deemed appropriate. However, protocols are now regarded as legal documents that must be followed exactly, in the spirit of regulatory fundamentalism, and decisions about the permissibility of deviations have become the purview of the study sponsor whose financial conflict of interest may be extreme. We are unaware of any evidence that this has improved study conduct or outcome, and there are many reasons this approach may be unwise.[10]

Protocol deviations are defined as any failure to adhere to the approved protocol. Some institutions consider that deviations without prior IRB approval are violations. A major violation is one that may affect subject safety, study integrity, or a subject's willingness to participate, whereas minor violations do not affect these parameters. Although the differences between major and minor violations may seem clear-cut, they are not, because major violations include items such as enrollment of a subject who does not fully meet all of the usual 20 to 30 eligibility criteria or incorrect timing or omission of any one of the multiple study procedures mandated. Such strict protocol adherence often does not make sense. For example, enrolling patients with a platelet count of 99×10^9/L when eligibility criteria state that patients must have a platelet count of $\geq 100 \times 10^9$/L, though clinically insignificant, is now a major violation, whereas in the past it would have been acceptable with approval of the study PI. Further, protocols may now consist of 100 to 200 pages, and because the letter of the protocol, rather than the intent, must be followed, increased research staffing is required to ensure compliance, hence increasing costs. In addition, some protocol violations occur because patients' ability to maintain their job or family responsibilities are compromised by the study calendar, and hence patients may prefer to change the days of treatment or testing. Because violations are a poor reflection on study staff, and because all deviations and violations require that study staff fill out paperwork documenting these events and their corrective action plan for the IRB, reluctant patients may be strongly encouraged to undergo tests necessary for the protocol at the precise times required by the protocol, even though making changes to accommodate patient convenience would not compromise their medical condition or study integrity. Finally, at times, when medical judgment and the protocol document are at odds for an individual patient, the physician may have little choice but to adhere to the protocol or remove the patient from study, when in fact the best choice might be to deviate from the precise protocol requirements. Overall, permitting flexibility and medical judgment would allow broader generalizations, better predict how well the therapy will work when translated into medical practice, reduce complexity and costs, improve patient care on clinical trials, and promote more rapid accrual without compromising patient safety or requiring major increases in sample size.[63] The requirement for strict adherence to the protocol also adds costs and slows progress by requiring formal protocol amendments before instituting appropriate changes and by increasing the time and complexity of the initial protocol development as those writing it attempt to foresee regulatory problems that will be created by minor nuances in protocol wording. The definition of protocol violation should be changed to an event where the patient was harmed and/or the integrity of the data was affected because the protocol was not followed. Those involved in clinical research should be encouraged to use good clinical judgment and common sense and to then report what was actually done. It is true that, under this system, individual PIs may from time to time make bad decisions, but there is no evidence that PIs are any more likely to make bad decisions than are regulators, IRBs or industry sponsors.

Documentation processes. Photographer Ansel Adams is said to have noted, "There is nothing worse than a sharp image of a fuzzy concept." Current regulatory practices now demand excessively detailed documentation of imprecise events. It is just not all that important if it was day 5 versus day 6 that the patient's grade 1 fatigue improved, particularly when the patient then dies on day 40 of uncontrolled cancer. By requiring expenditure of substantial resources on trivia, progress is slowed and costs escalate. Although increased precision may in some instances be a good thing, whether it is worth it depends on the cost versus what is gained. In a research laboratory, some experiments require measuring to the nearest nanogram, whereas others require measuring only to the nearest gram. The researcher would not measure to the nearest nanogram if measurement to the nearest gram sufficed. The current fundamentalist clinical research approach assumes that there is always value in measuring to the nearest nanogram, but this is generally not the case if this costs a lot more. There are few (if any) instances in which the detailed documentation for start and stop dates of grade 1 to 2 toxicity has proven important in deciding whether or not a drug is of value in a given disease. We should not be squandering limited resources in this manner. If one wants to spend a lot of money on increased precision in clinical research, this would be better spent on more frequent computed tomography scans (to more accurately assess progression-free survival), on tumor volumetric assessments, and on assessments of tumor molecular markers, rather than on trying to precisely document imprecise clinical events that are often irrelevant. The information actually needed includes a relatively limited number of baseline patient characteristics, tumor characteristics, therapy doses and dates, the percent change in tumor size with the therapy being tested, time to progression, reason for going off therapy, nature of subsequent therapy and response to it, overall survival, cause of death, and grade 3 to 5 toxicity.

The documentation situation is about to get worse. With the FDA Amendment Act 2007, investigators will be required by late 2010 to submit detailed patient-specific data to the FDA for every patient on study. This will require increased expenditures by investigators (using money that could better be spent testing other new ideas), and if real-time submission is eventually required, it would mean that the pace of accrual can be no faster than the pace with which clinical data can be collected and shunted to the FDA. Furthermore, these data will

either not be looked at (and therefore the effort will be wasted), or the requirement for FDA review could slow the pace of the study, or else this will require a marked increase in expenditure to augment FDA staffing to assess the data coming in. Furthermore, the question arises regarding what the FDA personnel will be required to do with the data once in hand. Analogous to the way in which the role of study sponsors has evolved over the past several years, will the FDA eventually be expected to play a growing hands-on role in running trials and in deciding management of individual patients? Such a development would not be in the best interest of patients, and it would not help speed progress.

Patient care costs for patients on study. Substantial time and resources are expended on trying to ensure that study nonstandard-of-care procedures are not charged to Medicare, the patient, or their insurance. Research costs and complexity would be reduced if health care payment systems were simplified.

Long-term follow-up of study patients. HIPAA rules are interpreted by some IRBs (including ours) to mean that study data can be collected on a patient only as long as they are still on study and the study is open. On the basis of IRB interpretation of other rules from the Office of Human Research Protection, to keep the study open, one must continue to receive and process the mountain of adverse event reports for the agent, even if it is years since the last patient received the drug, and the patient has to be re-consented for new findings even if they have long since stopped the therapy. This adds costs and bureaucracy, but not value. The current alternative is to close the study once all patients are off therapy, but one then loses potentially important information on longer-term survival, late toxicity, and the effect of subsequent therapies. Some of the preceding suggestions regarding handling of SAE reports and the re-consent process would help, as would recently suggested revisions to HIPAA.[64] In addition, long-term follow-up of patients who have been on study should be permitted (provided the patient has not withdrawn consent) regardless of whether or not the study is still officially open.

CLIA certification of laboratory tests. The use of tumor molecular characterization to guide investigation of new therapies has the potential to revolutionize cancer treatment.[10] However, Center for Medicare and Medicaid Services regulations require that a laboratory test be done in a CLIA-certified laboratory if it will be used to guide assignment of therapy to a patient, even if the therapy is investigational, and this slows progress. It is much more expensive to do tests in a CLIA-certified laboratory than in a research laboratory because of the high costs associated with attaining and maintaining CLIA certification, and the process of setting up each new test in a CLIA-certified laboratory is also time-consuming. The higher expense and time requirements greatly reduce the number of molecular signatures that can be tested. Laboratory tests that are not CLIA-certified should be allowable for assignment of patients to an investigational therapy, provided that the patient is informed that the test is a research test and thus not fully validated. For the minority of molecular signatures that are eventually found to be useful, it is reasonable to require eventual CLIA validation (by prospective trials or alternatively by post hoc assessment of a subset of samples from completed studies).

The Importance of Defining Drug Molecular Targets

Making study efficacy end points more rational would save lives and money. The bar with respect to efficacy end points needed for registration studies is generally too low because the mandated improvement in survival compared with standard therapy focuses on a *P* value of .05 rather than on a clinically relevant absolute improvement in survival in rationally selected patients. The stipulated end points and comparators used in current clinical research approaches often increase the probability of incorrect conclusions and limited gains. Several different mutations may give rise to common tumors, and each mutation may require distinct treatments.[65] Large, randomized trials can detect outcome differences of a few days to weeks and may set a low efficacy bar by using large patient numbers and statistical power to overcome the fact that only small subpopulations benefit from the therapy.[10] If studies fail to demonstrate statistical significance (eg, gefitinib in NSCLC[66]), agents that are highly useful, but only in a minority of patients, may be abandoned. If a drug that increased survival by as little as 6 months in 10% of patients with lung cancer but did nothing for the rest were abandoned, approximately 11,000 life-years would be lost each year in the United States alone and 75,000 worldwide. On the other hand, with $P < .05$ (eg, erlotinib in NSCLC[67]), expensive therapies may be widely applied, including to large subpopulations whose survival benefit (if any) is no more than days or weeks.

A drug hitting an uncommon target may be missed unless thousands of unselected patients are treated. To explore this further, we used survival times from a data set of 334 patients with NSCLC at The University of Texas M. D. Anderson Cancer Center and used GraphPad Prism 5 (GraphPad Software Inc, San Diego, CA) to simulate a therapy that quintupled survival in patients expressing a specific target that was present in every 10th patient and that had no effect in the 90% of the patients whose tumors did not express the target. We then compared the simulated survival in this treated population of 334 patients with the actual survival in the original population (a 668-patient simulated study), and found the difference to be statistically insignificant (hazard ratio = 0.85; $P = .16$; Fig 1). Hence the drug would have been discarded despite quintupling survival in 10% of the patients. At an estimated $26,000 per patient,[25] this study would have cost $17,000,000, but would have given the wrong answer. In a repeat analysis of a subpopulation of patients, all of whom had the putative drug target, *P* was less than .02 (hazard ratio = 0.13), with just eight patients per arm in this particular example (Fig 2), indicating potential marked gains in clinical trials efficiency by correctly identifying subpopulations affected. If it cost $10,000 per patient for fresh tumor biopsies and screening to detect the 10% of patients expressing the target, then the entire study in the selected subpopulation would have cost just $2,016,000 ($1,600,000 to screen 160 patients to find the 16 needed, then $416,000 to study these 16), and, unlike the study in unselected patients, it would have yielded the right answer. Furthermore, we would have garnered molecular information on the 90% of the patients who did not express the target of interest, and this could have permitted them to be shunted to other studies specifically appropriate for their tumor molecular characteristics, thereby spreading the screening costs across a number of other studies. In our example above, we could detect a survival advantage with $P < .05$ in a trial if enrollment were increased to 2,000 unselected patients. At $26,000 per patient, this study would have cost $52,000,000 and again would have now incorrectly indicated that the drug is effective, when in fact it only works in 10% of patients.

If the drug only doubled survival in the 10% of patients with the target, properly selecting the right patient population becomes even more important. In our example simulation, with a doubling of survival in every 10th patient, 5,328 patients would be required on the phase III study to detect efficacy in unselected patients (a

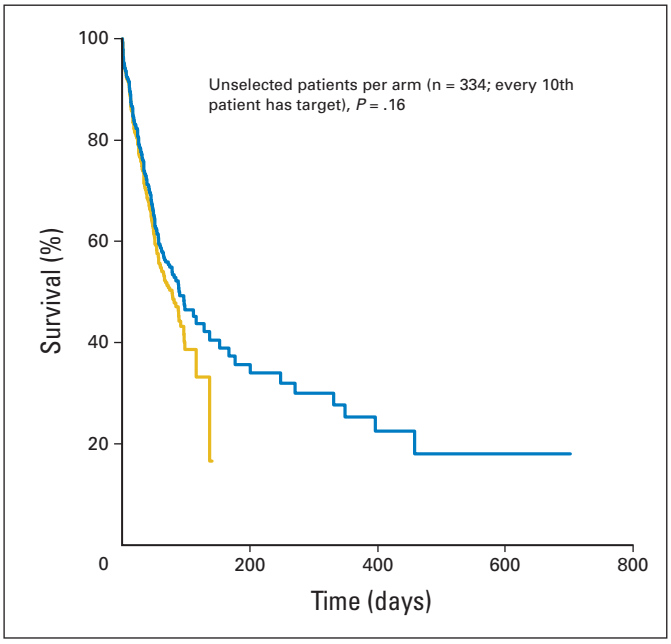

Fig 1. Simulation of a study involving 668 unselected patients in which a new therapy quintuples survival in patients with a relevant target and the target is present in the tumor of every 10th patient. Despite quintupling the survival of 10% of the patients, the drug would be judged to be ineffective and would be abandoned because the *P* value exceeded .05. This $17,000,000 study would have given the wrong answer.

$140,000,000 study) versus requiring 84 patients expressing the target (a $10,600,000 study, including $8,400,000 to screen 840 patients to find the 84 with the target). Finally, in our original 668-patient study, where quintupling survival of every 10th patient did not yield statistical significance, if we instead increased survival of all patients by just 30% (eg, from a median of 2.0 months to a median of 2.6 months, an absolute increase of just 18 days), a *P* value of .03 would have been achieved. Hence the randomization would have been more effective at demonstrating a small gain in a high proportion of patients than in detecting a large gain (eg, an increase in survival from 2 months to 10 months) in a small distinct subpopulation, whereas our perspective is that the latter is much more important than the former and that we have not been served well by the approach of looking for small gains.[10] Similarly, recent randomized discontinuation methodologies[68] are designed specifically to attempt to tease out very small gains, and we would question whether such limited improvements should be prioritized for resource allocation. Survival gains of just several days or weeks have been sufficient to win FDA approval for some new drugs, and this is unacceptable.[10] If randomized trials are used for registration, one should aim at least for a 6-month absolute increase or 50% relative increase in survival variables, because this will only be achieved if investigators first identify those most likely to benefit from the new therapy.

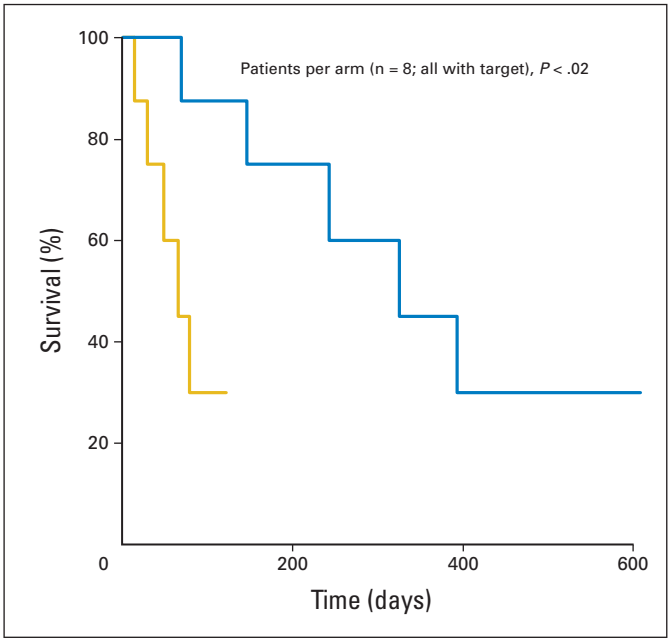

Fig 2. Simulation of a study involving 16 patients selected for a target, with the new therapy quintupling survival in patients with the target. Despite only 16 patients being entered, the study would have reached the correct answer, that the drug is effective in those with the proper target.

Randomized studies in unselected patients may pick the most common target, not the best drug. There are also other problems with standard randomized trials in unselected patients. If two therapies that hit different targets are compared, and one target is more common than the other, the study will suggest that the drug hitting the more common target is the better drug. This is the wrong conclusion. The right conclusion is that one drug is good against tumors with one target and the other drug is good against tumors with the other target, and one target is more common than the other. Unless this is recognized, studies will keep picking the drug that hits the more common target as the standard of care against which other drugs are compared, and no progress will be made, because agents that do a good job of hitting less common targets will repeatedly be discarded. Our conclusion is that even if molecular typing costs money, not doing so is ultimately far more expensive and gives the wrong answer.

Biomarkers of efficacy should be identified initially based on their correlation with tumor shrinkage, not survival variables. Our initial hypotheses regarding who will benefit from an agent are often wrong, and molecular profiles should be assessed in patients from earliest phase I trials on to permit the possibility of differentiating those who will versus will not benefit and to help rapidly narrow down populations to be tested in phase III trials. In these initial assessments, survival is often used as the end point because it is more precise and significant than other end points. However, advantages of using tumor shrinkage (or other measures of tumor-cell kill) may outweigh those for survival as an efficacy predictor, as follows: (1) In phase II studies of new targeted agents, the best predictor of eventual success in phase III studies was the ability to generate objective responses.[69] (2) One can directly assess in individual patients whether degree of tumor shrinkage is correlated with degree of expression of the predictive factor. (3) In survival analyses, it can be difficult to determine whether a factor is a predictive factor (associated with degree of benefit from the therapy) versus a prognostic factor (associated with rate of growth of the cancer and with patient survival in the absence of therapy),[70] whereas the confounding effect of prognostic factors is less of an issue with response. (4) Survival analyses are more likely than analyses of response or progression-free survival to be confounded by the effect of subsequent second-line therapies,[71] by comorbidity, and by supportive care measures. (5) Response assessment requires only a few weeks of patient follow-up, whereas survival analyses may require months or years of

follow-up. (6) Most patients are usually fully evaluable for response, whereas in survival analyses, many patients are censored and are hence less informative. (7) Of 31 anticancer agents approved by the FDA from 1973 to 2006 on the basis of response data (without randomization *v* placebo, supportive care, or standard therapy), all except gefitinib have retained their approval and have shown long-term evidence of safety and efficacy, suggesting that approval of anticancer drugs on the basis of robust response rates in nonrandomized trials is a sound, safe strategy.[72] More recent experience[73,74] with the one agent abandoned (gefitinib) strongly suggests that the initial response data provided a more accurate picture of the agent's true worth than did the subsequent randomized registration trial conducted in unselected patients. Redirection of the tens of millions of dollars required for large randomized trials in unselected patients would permit extensive tumor molecular profiling of every patient participating in phase I and II trials of a new agent. This in turn would have a reasonable possibility of defining the tumor molecular characteristics of patients who should be targeted for subsequent small, randomized trials. Indeed, in some cases, responders could probably be identified so reliably as to render a randomized trial pointless or even unjustifiable.

In conclusion, clinical research regulations were originally intended to protect patient safety, but the regulatory bar has now been placed too high. The extremely high costs per life-year gained and the markedly negative trade-off between life-years potentially lost versus life-years potentially gained by this flawed approach lead us to conclude that the current strategy seems to be unethical and squanders research resources. To change this, we must first set the efficacy bar higher and aim for true progress, not just a *P* value less than .05. From earliest phase I and II trials on, we must define the subpopulations deriving large benefit, then confirm this using small phase III studies aiming for large gains (not large phase III studies aiming for small gains) or by using phase II efficacy studies with robust response rates as an end point.[10] We also must change the culture of regulatory fundamentalism. In the war on cancer, the objective must be to make true progress against cancer, not to satisfy regulatory details that slow progress and hence cost lives. The problem is not one or two large impediments to progress, but rather the collective effect of hundreds[41] of small impediments. Regulations and processes governing clinical cancer research must be scrutinized, and those that do not add large demonstrable value must be discarded or changed. In the last few decades, immense strides have been made in our understanding of the biology of cancer and in diagnostic technology to identify molecular profiles. Furthermore, a multitude of novel, targeted drugs have entered or will soon enter clinical trials. We are potentially standing at the threshold of a new era in cancer therapy. It is estimated that in 2009 there will be 562,340 cancer deaths in the United States[3] (one every 56 seconds). Slowing progress in a regulatory traffic jam, abandoning good drugs that work in specific subsets of patients, and approving drugs in unselected populations whose survival benefit is measured in days to weeks can no longer be justified.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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