The Urgent Need for Clinical Research Reform to Permit Faster, Less Expensive Access to New Therapies for Lethal Diseases

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Abstract

High costs of complying with drug development regulations slow progress and contribute to high drug prices and, hence, mounting health care costs. If it is exorbitantly expensive to bring new therapies to approval, fewer agents can be developed with available resources, impeding the emergence of urgently needed treatments and escalating prices by limiting competition. Excessive regulation produces numerous speed bumps on the road to drug authorization. Although an explosion of knowledge could fuel rapid advances, progress has been slowed worldwide by inefficient regulatory and clinical research systems that limit access to therapies that prolong life and relieve suffering. We must replace current compliance-centered regulation (appropriate for nonlethal diseases like acne) with "progress-centered regulation" in lethal diseases, where the overarching objective must be rapid, inexpensive development of effective new therapies. We need to (i) reduce expensive, time-consuming preclinical toxicology and pharmacology assessments, which add little value; (ii) revamp the clinical trial approval process to make it fast and efficient; (iii) permit immediate multiple-site trial activation when an eligible patient is identified ("just-in-time" activation); (iv) reduce the requirement for excessive, low-value documentation; (v) replace this excessive documentation with sensible postmarketing surveillance; (vi) develop pragmatic investigator accreditation; (vii) where it is to the benefit of the patient, permit investigators latitude in deviating from protocols, without requiring approved amendments; (viii) confirm the value of predictive biomarkers before requiring the high costs of IDE/CLIA compliance; and (ix) approve agents based on high phase I–II response rates in defined subpopulations, rather than mandating expensive, time-consuming phase III trials. *Clin Cancer Res; 21(20); 4561–8. ©2015 AACR.*

See all articles in this *CCR Focus* section, "Innovations to Speed Drug Development."

Introduction

Due to lack of effective therapies, more than 660,000 North Americans die annually from cancer, and 8,200,000 die annually from cancer worldwide (1–3). Despite an explosion of knowledge that has spawned the potential for major therapy advances, flawed clinical research practices and dysfunctional clinical research regulatory approaches (operating at multiple institutional, corporate, governmental, and international levels) slow progress (4). Essential regulation helps ensure research participant safety, protects patient privacy and right to informed consent, and safeguards trial data integrity. The Helsinki Declaration (5) enshrines the principle of placing research participant protection ahead of scientific advancement. However, current regulatory approaches to cancer clinical research are inefficient and costly, and may even harm research participants because compliance to minute details of the protocol disallows decisions that may benefit patients (4). The move to closer oversight and tighter rules with respect to clinical research came initially from discovery of major patient abuses (6) that most of us would agree are unacceptable. However, applying general solutions to address specific issues has the potential to be detrimental to great numbers of patients, with needless suffering and shortening of patient life expectancy while approval of effective new therapies is delayed (7, 8). While protection of patients from unsafe medications and from unethical investigator conduct is of high importance, we feel that over-regulation has become a major problem. There is an urgent need to "right size" the regulatory requirements to balance the risk of abuse versus the dampening effect on progress. A combination of very targeted solutions and monitoring can avoid overuse of general rules that may or may not improve safety and ethical investigator conduct but definitely do cause delays, bureaucracy, and cost.

At the outset we need to be clear that the reasons we are failing in drug development are multifactorial. As examples, the simple fact that cancer is increasingly recognized as comprising a multiplicity of genetic subsets, and the fact that we have pursued many targets that were not properly and adequately validated, are not the topics of this treatise. These topics are covered elsewhere in this (9, 10) and earlier editions (11) of *CCR Focus*. Rather, we will focus on aspects of drug development that we as a community have much more control over. And, we are not arguing that solving

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these problems alone would lead to the cure of cancer; we argue that addressing these problems will enhance our ability to get on with the work. When we talk about regulatory burden, we are not laying the problem at the door of the FDA. Regulatory demands are built into every level of the system, and we have argued in the past that once implemented, a regulatory hurdle is rarely removed (4). The FDA has worked hard to develop new approaches that streamline and speed the drug approval process (12).

We all collectively share the blame for the current issues. When we see abuses, we expect them to be dealt with, but often we have not adequately weighed the consequences of the methods chosen to solve the very real problems that arise. Compounding this problem is the fact that several different participants add their own interpretation of regulatory requirements or render decisions or directives that affect clinical research either directly or indirectly. For example, in the United States this includes Institutional Review Boards (IRB), institutional contract offices, clinical trial sponsors, clinical research organizations (CRO), the FDA, the Office of Human Research Protection, National Cancer Institute, Clinical Laboratory Improvement Amendments (CLIA), Center for Medicare and Medicaid Services, Health Insurance Portability and Accountability Act (HIPAA), Internal Revenue Service, Office of the Inspector General, hospital accreditors, Patent Office, legislatures, and courts (4, 13). Our comments in this article on regulatory inefficiency are not directed at a single group or entity. Current issues have arisen due to complex interactions involving many different players.

The average cost to take a drug from discovery to approval (research spending divided by number of drugs approved) is very high. Across 100 companies recently surveyed, the median value for this average cost was $800,000,000 (14). While some question these figures (15), costs of complying with clinical research regulation have nevertheless risen much faster than inflation—a key factor driving high drug development costs (4, 16). Tighter regulation has improved safety minimally, with a reduction of only 0.3% (from 0.8% to 0.5%) in toxicity-related death rates among phase I trial participants (4). Although current low toxic death rates leave little room for further improvement (4), the regulatory burden continues to steadily increase. Although it is generally considered reasonable to pay $50 K to $250 K for therapies per life-year gained (17), the cost per life-year saved by tighter regulation is much higher than this: if one calculates the life-years saved by tighter regulation by taking the reduction in proportion of clinical trial patients dying from toxicity (0.3%) and multiplying this by the median anticipated life expectancy of a patient with previously treated advanced metastatic cancer (<12 months), and divides this into the estimated increase in average cost per patient of complying with tighter regulation [>$8,000 in 2006–2007 (4), but substantially higher now], then the cost per life-year saved by tighter regulation of cancer clinical research is millions of dollars (4). This suggests that cost-effectiveness of clinical research safety regulations could potentially be improved 10- to 100-fold by addressing inefficiencies if regulation were held to the same cost-effectiveness standard as clinical practice.

It is imperative that we address the costs of regulatory compliance since they contribute to drug costs, and drug costs in turn play a major role in driving health care costs. No company could thrive unless it could recoup the costs of bringing its drugs to market and also make a profit (18). If payers and patients become unable or unwilling to pay for these agents [and this is a major concern (19), with prices of some agents exceeding $120,000 per year], or if measures are created that force prices down without addressing development costs, this will compromise investment in cancer drug development. Furthermore, enormous drug development costs effectively minimize the number of competitor drugs since fewer companies can afford to develop new agents. The very high development costs also create an environment that is risk averse, and some authors feel that this translates directly into decreased innovation and more of a "me-too" drug development approach, with several companies developing agents targeting the same molecular aberration, rather than assessing newer potential targets (20). Overall, this is unhealthy because competition is often a major driver of both innovation and price reduction. Finally, money and infrastructure are limited commodities: high development costs for one drug reduce resources available to develop additional agents. Therefore, high clinical research costs directly slow progress by reducing the number of ideas that can be tested with available resources (18, 21). The choice is clear: reduce drug development costs or our health care systems will be bankrupted, progress halted, patient suffering increased, and lives shortened.

Regulatory processes create numerous speed bumps on the road to drug approval (4, 21). Hundreds of distinct processes and 2 years on average are required to bring a cooperative group trial from initial concept to activation. Many of the required steps add little to patient safety or research quality, and may even be detrimental (22–25). On a 25-mile-long highway with speed bumps every 0.1 miles, removing just a few bumps would have little impact. Similarly, addressing just some of the bumps on the research road yields limited benefit. We need re-engineering of the entire process. Research speed bumps slow progress and delay access of patients with fatal diseases to new therapies that could alleviate suffering and prolong lives. This problem is compounded by the innate inefficiencies of the cooperative groups, pharmaceutical companies, academic institutions, and investigators involved in study initiation and conduct.

Delays in approval of effective new agents are important since they translate into life-years lost. To illustrate this principle, we will take the example of metastatic colorectal cancer, in which a randomized phase III trial demonstrated an improvement in median survival of 4.7 months (0.39 years) with the addition of bevacizumab to standard therapy (26). Worldwide, approximately 693,900 patients die from colorectal cancer each year (3). A delay in access of these patients to bevacizumab would therefore translate into 270,621 life-years lost per year of delay (approximately one life-year for every 2 minutes of delay). While patients in some parts of the world might not have access to bevacizumab (even if it were approved) and while others might not be treated with it due to comorbidities, poor performance status, etc., even if only 10% of patients had the potential to receive the drug or even if the clinical trial overestimated the benefit of bevacizumab, there would still be more than 27,000 life-years lost per year of delay in approval. If only 1% of patients worldwide were able to access the drug after it was approved, this would still translate into 2,700 life-years lost per year of delay in access. When the cumulative impact is considered over all the useful drugs approved over the past few years, the numbers of life-years potentially lost due to approval delays become very large.

As noted previously, our calculations suggest that tighter safety regulation over the past several years has only reduced toxic death rates on clinical trials by about 0.3% (4). Although we do not have data on how many patients were needed on clinical trials of bevacizumab to bring it from discovery to market, the average

number of patients across a range of drugs is reportedly 5,435 patients per drug (27). If this were taken as an estimate of the number of patients on preapproval bevacizumab trials, and if the average life expectancy of clinical trial participants with advanced cancers were 2 years, then enhanced safety through tighter regulation would have saved 33 life-years over the course of drug approval ($0.3\% \times 5{,}435 \times 2$). Even if our safety estimates are off by a factor of 10 and 330 life-years were actually saved by tighter regulation, and if only 1% of patients with metastatic colorectal cancer were to receive bevacizumab following its approval, there would nevertheless be the potential for far more life-years to be lost due to regulation-induced delays in drug approval than would be saved by tight regulation. Overall, addressing inefficient clinical research systems and regulation is a matter of life and death for millions of patients.

Moreover, in many instances, the traditional paradigm of using large randomized phase III trials to assess drugs is irrational (28–30). Common cancers are generally a collection of uncommon orphan diseases that share common characteristics but that require agents targeting different aberrations (28, 31). Trials using unselected patients yield results that are the sum of responses of various subgroups to the therapy, including those with significant benefit, no response, or even enhanced tumor growth. Trials in unselected patients mislead by concealing these disparate outcomes (28, 29). Indeed, commonly observed low response rates in phase II–III studies using unselected patients make it an ethical challenge to continue exposing all patients to toxicity and drug costs when few benefit. Conversely, requiring large phase III trials that are restricted to small, defined subpopulations is enormously expensive and time consuing due to challenges in identifying eligible patients (28). In the era of precision medicine, we are discovering that individual cancers often have complex, unique genomic profiles, with no two identical, suggesting individualized therapy, rather than finding commonalities between patients, as the model for future cancer research (32, 33), and as discussed by Siu and colleagues elsewhere in this *CCR Focus*, next-generation sequencing of tumor genetic material will play a key role in this effort (9).

Regulation is so cumbersome that most FDA audits reveal at least some compliance issues (34). While there is no question that some serious breaches may be discovered in such audits, there is also a risk that credible, responsible investigators dedicated to research can be penalized, threatened, and denigrated by overzealous regulators, IRBs, and journalists. This, superimposed on the frustrations involved in activating and running trials (35), discourages young faculty members from pursuing a cancer research career, contributing to the 3.5% per year reduction in numbers of U.S. clinical investigators (36) that jeopardizes our future ability to do the research that is so essential to progress.

While the severity and nature of the problem vary somewhat across countries, inefficient regulation is a widespread problem that needs multinational solutions. Clinical research constraints engulfing the United States, Canada, Europe, and other geographical areas have arisen from a shift in thinking that has seen regulatory compliance replace actual progress in developing new therapies as the *de facto* primary objective of clinical research (37). For example, we have seen investigators forced to discard costly, precious data judged to be "insufficiently" compliant due to disagreement over issues such as whether patient consent was specific enough to permit a chart review, whereas data that have been judged to be "adequately" compliant for such matters are retained and even published, even if they are of little clinical utility. We do not at all disparage publication of high-impact negative data, which can actually save a lot of time, and we condemn true ethical breaches, but our point is that the focus should be on accelerating the delivery of new and accessible treatments for cancer patients rather than on obsessive compliance with rigid regulation that lacks a genuine ethical basis. Some think this is an unsolvable problem; we believe it can and must be addressed.

Solutions

Progress-centered regulation

Examples of solutions are outlined in Tables 1 (general issues), 2 (issues dealing with trial approval and activation), 3 (issues in study conduct), and 4 (economic issues). Regulatory approaches are currently constructed to facilitate regulation rather than research (38). This must change. Patients are suffering and dying prematurely due to lack of effective drugs. As there is now an emphasis on "patient-centered care," we must move to "progress-centered regulation." For lethal diseases, the overarching goal of regulation and of clinical research practices must be to facilitate the rapid, inexpensive approval of effective new therapies. Each regulatory process and clinical research practice that is essential to patient safety, data integrity, etc., must be continuously reassessed and redesigned to optimize compliance with this overarching goal. If regulatory oversight and clinical research practices are reframed in this context, solutions become possible.

Aim high and approve drugs based on phase I–II data

Historically, only 5% of agents entering clinical trials won approval (39). Articles in both this (10) and earlier (11) *CCR Focus* editions identify some of the reasons for this high failure rate. Large phase III trials using "unselected" patients are inefficient and misleading. The major impetus behind large trials is that they permit sufficient statistical power to detect small gains (4, 21, 29), and investigators, institutions, and cooperative groups benefit more academically from running "positive" versus "negative" trials. However, large trials take years to complete and are expensive, thereby delaying patient access to effective therapies and justifying high drug prices. Furthermore, even large trials may have insufficient statistical power to detect drug benefit if only a subpopulation has the drug's required target. A drug that is useful in a subpopulation will then be discarded (4, 29), and development costs for the failed drug will be recouped through higher prices for the small number of "successful" agents. Alternatively,

Table 1. General changes required for progress-centered regulation of clinical research in lethal diseases

Current state	Where we need to go
Safety/compliance-centered regulation	Progress-centered regulation for lethal diseases
Long and costly	Fast and inexpensive
Large studies, small gains	Small studies, large gains
Oversight	Oversight
Same agencies for all indications	Separate regulators for lethal versus nonlethal diseases
Regulatory gridlock since multiple regulators	Single regulator for research in lethal diseases
Contracts/intellectual property agreements: often time-consuming and complicated	Standardized, simple, rapid
Privacy laws excessively restrictive	Rationalize privacy laws

Table 2. Requirements for changes in study design and review for progress-centered regulation of clinical research in lethal diseases

Current state	Where we need to go
Extensive/costly preclinical toxicology	Only LD10 in rodents
Extensive/costly preclinical pharmacology	Only oral bioavailability and Cytochrome p450 interactions
Study review: obstructive, frustrating	Study review: fast, facilitating through redesign processes used by industry
Consent form: long, complex, multiple changes to wording	Short, simple, standardized, with patient access to additional online information
Study approval and activation: multiple individual institutions review/approval/activation	Single site approval Multiple site "just-in-time activation" if eligible patients seen
IDE/CLIA: Technical validation of a predictive test, then assess it	No IDE/CLIA: Assess predictive test, then perform technical validation if it is useful

large trials may have sufficient power to demonstrate a statistically significant benefit and to win drug approval despite only a small subgroup possessing the required target and truly benefitting. In this case, all patients with the general characteristics of the unselected group may subsequently be exposed to the costs and toxicity of being treated with the agent, despite few benefiting (4, 21, 29). A more effective, "patient-centered" approach is embodied by recent FDA "breakthrough drug approval" processes (40) and similar approaches discussed in more detail in this *CCR Focus* by Theoret and colleagues (12). In keeping with the principle of progress-centered regulation, early drug trials should focus on defining which (if any) distinct subpopulations benefit, with rapid approval based on high response rates in phase I–II trials in these defined subpopulations (28, 29). Pragmatic postmarketing surveillance would permit confirmation of drug utility (28). The FDA has made laudable strides, with two drugs [the ALK inhibitor ceritinib for lung cancer (41) and the antiPD1 immunotherapy pembrolizumab for melanoma (42)] recently approved after phase I.

Oversight

The same agencies usually oversee research in lethal diseases like aggressive cancers and in nonlethal diseases like acne. We suspect that this affects the role and orientation of regulators and the rules they set. In acne (and in highly curable cancers), the most important priority is safety. In lethal diseases, the priority must instead be progress toward finding effective therapies as quickly as possible. Separation of regulatory bodies for lethal versus nonlethal diseases would clarify the very different objectives for these different research processes (4). In some countries, several agencies have an impact on research. For example, as we noted previously, in the United States, the FDA, the Office of Human Research Protection, the National Cancer Institute, and multiple other players render decisions impacting clinical research (4, 13). Each group is fulfilling what it sees as its responsibility, but cumulatively this results in regulatory gridlock that paralyzes reform attempts. A better solution would provide a single path that only requires that we address a list of the relevant and necessary components of each of these, rather than multiple reviews by disparate individuals and bureaucracies.

Table 3. Requirements for changes in study conduct for progress-centered regulation of clinical research in lethal diseases

Current state	Where we need to go
Amendments: approval often delays trial	Amendments: minimal review and rapid approval for many specified types
Excessive documentation Little real value added One of the major drivers of cost	Greatly simplify documentation Pragmatic postmarketing surveillance Investigator accreditation and then CME Redesign of entire documentation process
Study conduct: rigid adherence to protocol	PI can verbally approve minor deviations to eligibility requirements Minor variations permitted in treatment and testing schedules

Anticancer agent preclinical toxicology and pharmacology

Expensive, time-consuming preclinical toxicology and pharmacology are of little practical value. Although toxicology may identify serious toxicities, it usually predicts toxicities that would have been monitored anyway, misses clinically important toxicities, and/or predicts toxicities that are ultimately unimportant (4, 21). It rarely identifies unanticipated toxicities that improve clinical trial conduct. While extensive preclinical toxicology is warranted for agents that are intended for nonlethal diseases or that will be tested in healthy volunteers, this is not the case with anticancer agents that will be tested initially in fully informed, consenting patients with advanced, incurable malignancies, where the lack of alternative therapies and the small but real potential for benefit outweigh the potential risk. The only toxicology needed in this setting is definition of the dose killing 10% of rodents (LD10; refs. 43, 44). Available data indicate that it is generally safe and appropriate to start human phase I trials at 10% of the LD10 (43, 44). There are exceptions for which more extensive preclinical toxicology is helpful (e.g., in designing analogues free of toxicity seen in human trials of the parent compound), but exceptions should not drive general practice. The only preclinical pharmacology that is generally useful is oral bioavailability and CYP450 interactions (to help predict drug interactions; refs. 4, 21).

Study design and approval

The hundreds of steps in designing and activating trials must be abbreviated (22–25). Approaches improving efficiency include use of "Master Protocols" in trial construction, "Master Contracts" for multiple sponsor–investigator agreements, a single IRB review to cover multiple institutions (45), adaptive trial designs (as discussed elsewhere in this *CCR Focus;* ref. 46), "basket" trials that accrue patients with multiple tumor types sharing a common mutation (47), "umbrella" trials that match patients with a specific molecular profile to a specific drug (47), phase I studies with tumor-specific expansion cohorts (48), phase II trials in which multiple drugs are sequentially assessed without requiring repeat trial approval, telescoped studies that segue from phase I to phase II–III without repeat trial approval, and expedited IRB review of most protocols unless they contain nonstandard elements. Companies such as Nike, Ford, Toyota, Kimberley-Clark, and Intel, to name just a few from different industries, have successfully designed and implemented practices that have made them better at producing the results they want (effectiveness) and doing so with the least waste of time, effort, and resources (efficiency). They have done so using proven business process

Table 4. Requirements for changes in economics of drug development and pricing for progress-centered regulation of clinical research in lethal diseases

Current state	Where we need to go
Price	Price
Whatever market will bear	Reduce cost of development
Justified by high drug development costs	Competition by fast analogue development
Investment economics driven by	Investment economics driven by
Prospect of charging very high price	Low costs of drug approval
Large market size (unselected patients)	Reduced risk
High costs/high risk of development	Rapid approval/longer patent life

redesign and re-engineering methods (49–53). Both government and academia should learn to apply these commonly used techniques to make study approval processes more effective and efficient.

Consent forms

Shorter, simplified, standardized consent forms (accompanied by online access to additional relevant information, as wished) would provide more "informed" consent than the lengthy forms currently utilized. It is irrational that participation in a study that may prolong one's life requires a more detailed consent process than almost any other sphere of human endeavour. Furthermore, IRBs may unnecessarily delay activation of a trial months for minor, largely irrelevant changes in consent form wording, spelling, and grammar. Patients await therapies that could relieve their suffering as consent form wording is perfected.

Study and consent form amendments

Trials often have accrual interrupted for weeks to months pending approval of amendments, with minimal ultimate changes to those amendments. For most types of amendments, apart from a short list of specified exceptions like changing eligibility from incurable patients to curable patients, accrual interruptions should be only a few days.

Contracts

Trial activation may be delayed months pending successful negotiation of contract wording. The "sticking points" usually involve issues of intellectual property, publication rights, and liability/indemnification. Broad standardized approaches to these issues would avoid recapitulating the same discussions for multiple studies at each center.

Just-in-time trial activation

Substantial time and cost are associated with trial activation. A site's trial activation costs are spread across all patients accrued. However, when $\leq$5% of patients with a malignancy express a required target, the time and resources required for trial activation are problematic. Centers may decline to participate, and it is expensive for sponsors to activate trials at a sufficient number of centers for adequate accrual. Hence, we need "just-in-time" trial activation for "accredited" members of a worldwide cooperative group: if multiplex screening identifies a consenting patient who meets eligibility requirements, investigators would take a brief online study-specific training session, thereby generating immediate trial activation at their site, with drug shipment within 24 hours (28). This approach could be supplemented by systems currently under development that permit automatic feeding of molecular screening data to central sites that would notify physicians when their patient was potentially a trial candidate.

Documentation

While the issues outlined above delay drug approval, the requirement for markedly excessive documentation that greatly exceeds requirements for the task at hand is in our experience a major driver of approval costs since it necessitates employment of multiple research personnel [research nurses, research assistants, monitors, contract research organizations (CRO), and others]. The involvement of a CRO in a study often exacerbates the documentation problem. Most CROs are not cancer specific and appear to have a fixed template for documentation that is rigid, generic, and that ultimately raises an extra hurdle of trying to find irrelevant data to fit into a generic set of forms. In our experience, CROs frequently also generate an enormous number of queries on the data, and each query must be answered. While pharmaceutical companies employ CROs to make their job easier, these CROs add substantially to the documentation burden, wasting both time and money. It remains unclear, however, if some CROs are a problem in and of themselves, or a natural response to the perceived mandates of regulatory agencies. Overall, the costly documentation requirements are of little value from the perspective of safety or progress (4, 28, 54). Indeed, the documentation volume may be potentially dangerous and counterproductive. In needing to comply with regulations informing investigators of adverse events, so much volume of minor or known adverse events is generated that if there were something truly new and dangerous it might well be buried by the noise.

Documentation requirements need to be completely redesigned. For example, there is currently expensive, detailed documentation of grade 1–2 toxicities for drugs that end up never being marketed. This should be replaced by greatly simplified, less detailed requirements. If the drug is approved, more details could be collected through sensible, pragmatic postmarketing surveillance (28). Rather than all investigators receiving from the sponsor the hundreds of toxicity reports on an agent that they currently must wade through (often when they have no active patients on study), there should be online access to these reports for investigators, regulators, and patients. Much of the data submitted to sponsors or regulators should be automatically transferred from electronic source documents (using software to be designed for this purpose), rather than the requirement for the detailed forms that currently must be completed. Rather than sites needing years of expensive storage of documents, there should be centralized electronic storage.

Investigator accreditation

To compensate for the proposed less restrictive approach to documentation and regulation, research sites (55) and individual investigators would require initial "accreditation" at the start of their clinical research career, with reaccreditation through ongoing continued medical education processes and periodic peer review. Indeed, many centers already require multiple mandatory training modules before faculty or staff can participate in clinical research, and this training encompasses the needed accreditation.

Study conduct

Principal investigators should be permitted to approve accrual on their trial of patients with minor deviations from protocol

eligibility criteria (e.g., minor renal dysfunction), and to make specified types of protocol modifications without formal IRB approval. While one might argue that the wording of the protocol should be sufficiently flexible to permit reasonable exceptions, this has generally not worked in our experience, since IRBs, regulators, and sponsors often severely limit the ability to be flexible by disallowing protocol wording that would permit flexibility. While there is undoubtedly some potential for abuse if eligibility criteria are more flexible, we believe the current situation to be worse.

Minor deviations from study schedules for treatment and testing should be at the discretion of qualified investigators. Currently, minor deviations are either not permitted, to the detriment of the patient (and often against the patient's wishes), or it is the protocol sponsor who decides if a deviation or violation is permitted (37). This highlights the rich paradox of sponsors, who have millions of dollars vested in an agent, making decisions for patients they have never seen, while the patient and physician/investigator have no recourse. Most physician-investigators cannot have any financial conflicts of interest, while the significant conflict of interest of the sponsor is ignored. Finally, reconsenting should not be required for patients who have already completed therapy on a trial. Long-term follow-up of patients on a trial should be allowed whether or not a trial is still officially "open."

Privacy

Privacy oversight (e.g., HIPAA; ref. 56) needs to be redesigned to bring it into alignment with the principle of progress-centered regulation while still protecting patients from detrimental use of their data.

Companion diagnostics

Based on test reproducibility issues (57), laboratory errors or data misrepresentation (58), among other issues, U.S. regulators mandated that if biomarker assessments were to be used to select patients for trials, they had to be CLIA-certified (59). More recently regulators have required Investigational Device (IDE) filing for such tests for "significant risk devices" (58), but they have defined a "significant risk device" to include anything (including a laboratory test) that is used to make a diagnosis or treatment decision (60). In practice, the requirement for IDE filing in individual studies has appeared to us to be confusing and inconsistent, with filing being required for some tests and studies but not for others. CLIA certification is also costly and time-consuming. Costs and time are amplified markedly for IDE filing, potentially adding years to study start-up time (58). These regulations are contrary to the principle of progress-centered regulation. Certification requirements discourage the use of biomarkers to guide studies, even as evidence accumulates that biomarker-based studies are more likely to be successful. This may partially explain why remarkably few (~9% in the last 3 years) clinical trials in lethal diseases such as pancreatic cancer have a biomarker stratification strategy (61), although we recognize that other factors also contribute to this low rate. Indeed, rapidly expanding biomarker regulations now may force one to invest heavily in the test before knowing if it is useful. The result is that many life-saving tests may never be investigated. With patient consent, we should first assess if a test is of value, and only then take on the costs of perfecting it, with pragmatic postmarketing surveillance (28) to monitor the predictive reliability of the test.

Pricing

Drug prices are affected by development costs and time required for approval. Faster, cheaper drug development should make lower drug pricing more economically feasible. Lower prices, in turn, would make it easier for payers to grant access to these agents, thereby providing companies with better long-term revenue through improved market penetration and through ongoing sales to patients whose lives had been prolonged by the agent. This would provide the essential economic incentive to develop effective new agents, even for small subgroups. At the same time, faster, cheaper drug development should facilitate development of competing medications that would help bring prices down. However, as pointed out recently (62), in the few cases where the FDA has accelerated early drug approval, pricing does not appear to have been affected. While it may take more than a couple of such cases to actually have this positive economic impact, we believe that even if the pharmaceutical industry did not respond in kind to changes that reduce their costs, reducing drug development costs would provide society, payers, clinicians, and scientists with a powerful business and fairness case that would demand a *quid quo pro* from industry.

Responsibility for Change

We all share responsibility for the international epidemic of dysfunctional regulation that increases health care costs and impedes development of and access to new therapies that could relieve suffering and prolong lives. To our patients, the need for reform is urgent. Too many are dying prematurely not only from lack of new drugs but also from lack of access to them. Failure to act constitutes collective negligence. As Churchill stated, "It's not enough that we do our best; sometimes we have to do what's required." Progress-centered regulation is imperative. We must make this happen.

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References

1. Canadian Cancer Statistics 2014 [PDF on the Internet]. Toronto (ON): Canadian Cancer Society; c2014 [cited 2015 Mar 20]. Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2014-EN.pdf.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
4. Stewart DJ, Whitney SN, Kurzrock R. Equipoise lost: ethics, costs, and the regulation of cancer clinical research. J Clin Oncol 2010;28:2925–35.
5. Rickham PP. Human experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. Br Med J 1964;2:177.
6. Pressel DM. Nuremberg and Tuskegee: lessons for contemporary American medicine. J Natl Med Assoc 2003;95:1216–25.
7. Freireich EJ. Who took the clinical out of clinical research?–Mouse versus man: Seventh David A Karnofsky Memorial Lecture–1976. Clin Cancer Res 1997;3:2711–22.
8. Christie DR, Gabriel GS, Dear K. Adverse effects of a multicentre system for ethics approval on the progress of a prospective multicentre trial of cancer treatment: how many patients die waiting? Int Med J 2007;37:680–6.
9. Siu LL, Conley BA, Boerner S, LoRusso PM. Next-generation sequencing to guide clinical trials. Clin Cancer Res 2015;21:4536–44.
10. Seruga B, Ocana A, Amir E, Tannock IF. Failures in phase III: causes and consequences. Clin Cancer Res 2015;21:4552–60.
11. Bates SE, Amiri-Kordestani L, Giaccone G. Drug development: portals of discovery. Clin Cancer Res 2012;18:23–32.
12. Theoret MR, Pai-Scherf LH, Chuk MK, Prowell TM, Balasubramaniam S, Kim T, et al. Expansion cohorts in first-in-human solid tumor oncology trials. Clin Cancer Res 2015;21:4545–51.
13. Kantarjian H, Stewart DJ, Zwelling L. Cancer research in the United States: dying by a thousand paper cuts. Cancer 2013;119:3742–5.
14. Herper M. How much does pharmaceutical innovation cost? A look at 100 companies [Internet]. Forbes 2013 [cited 2015 Mar 20]. Available from: http://www.forbes.com/sites/matthewherper/2013/08/11/the-cost-of-inventing-a-new-drug-98-companies-ranked/.
15. Light DW, Warburton R. Demthologizing the high cost of pharmaceutical research. BioSciences 2011;1745–08552:1–17.
16. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003;22:151–85.
17. Ubel PA, Berry SR, Nadler E, Bell CM, Kozminski MA, Palmer JA, et al. In a survey, marked inconsistency in how oncologists judged value of high-cost cancer drugs in relation to gains in survival. Health Aff (Millwood) 2012;31:709–17.
18. Stewart DJ, Bradford J-P. To benefit from new cancer drugs, reform the regulatory regime. Globe and Mail 2015 [cited 2015 Mar 20]. Available from: http://www.theglobeandmail.com/globe-debate/to-benefit-from-new-cancer-drugs-reform-the-regulatory-regime/article22696420/.
19. Rollet P, Lemoine A, Dunoyer M. Sustainable rare diseases business and drug access: no time for misconceptions. Orphanet J Rare Dis 2013;8:109.
20. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. JAMA Otolaryngol Head Neck Surg 2014;140:1225–36.
21. Stewart DJ, Kurzrock R. Cancer: the road to Amiens. J Clin Oncol 2009;27:328–33.
22. Dilts DM, Sandler A, Cheng S, Crites J, Ferranti L, Wu A, et al. Development of clinical trials in a cooperative group setting: the eastern cooperative oncology group. Clin Cancer Res 2008;14:3427–33.
23. Dilts DM, Sandler AB, Baker M, Cheng SK, George SL, Karas KS, et al. Processes to activate phase III clinical trials in a Cooperative Oncology Group: the Case of Cancer and Leukemia Group B. J Clin Oncol 2006;24:4553–7.
24. Dilts DM, Sandler AB, Cheng SK, Crites JS, Ferranti LB, Wu AY, et al. Steps and time to process clinical trials at the Cancer Therapy Evaluation Program. J Clin Oncol 2009;27:1761–6.
25. Dilts DM, Cheng SK, Crites JS, Sandler AB, Doroshow JH. Phase III clinical trial development: a process of chutes and ladders. Clin Cancer Res 2010;16:5381–9.
26. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
27. Reichert J. Clinical development of therapeutic medicines: a biopharmaceutical versus pharmaceutical product comparison. Drug Information J 2001;35:337–46.
28. Stewart DJ, Batist G. Redefining cancer: a new paradigm for better and faster treatment innovation. J Popul Ther Clin Pharmacol 2014;21:e56–65.
29. Stewart DJ, Kurzrock R. Fool's gold, lost treasures, and the randomized clinical trial. BMC Cancer 2013;13:193.
30. Kurzrock R, Stewart DJ. Equipoise abandoned? Randomization and clinical trials. Ann Oncol 2013;24:2471–4.
31. Braiteh F, Kurzrock R. Uncommon tumors and exceptional therapies: paradox or paradigm? Mol Cancer Ther 2007;6:1175–9.
32. Wheler J, Lee JJ, Kurzrock R. Unique molecular landscapes in cancer: implications for individualized, curated drug combinations. Cancer Res 2014;74:7181–4.
33. Wheler JJ, Parker BA, Lee JJ, Atkins JT, Janku F, Tsimberidou AM, et al. Unique molecular signatures as a hallmark of patients with metastatic breast cancer: implications for current treatment paradigms. Oncotarget 2014;5:2349–54.
34. Morgan-Linnell SK, Stewart DJ, Kurzrock R. U.S. Food and Drug Administration inspections of clinical investigators: overview of results from 1977 to 2009. Clin Cancer Res 2014;20:3364–70.
35. Vickers AJ. Do we want more cancer patients on clinical trials if so, what are the barriers to greater accrual. Trials 2008;9:31.
36. Institute of Medicine (US) Forum on Drug Discovery, Develpoment, and Translation. Transforming clinical research in the United States: challenges and opportunities: workshop summary. Washington (DC): National Academies Press; 2010.
37. Kurzrock R, Stewart DJ. Compliance in early-phase cancer clinical trials research. Oncologist 2013;18:308–13.
38. Freireich EJ. The investigational new drug application–who benefits? Nat Clin Pract Oncol 2006;3:62–3.
39. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004;3:711–5.
40. Horning SJ, Haber DA, Selig WK, Ivy SP, Roberts SA, Allen JD, et al. Developing standards for breakthrough therapy designation in oncology. Clin Cancer Res 2013;19:4297–304.
41. Chabner BA. Approval after phase I: ceritinib runs the three-minute mile. Oncologist 2014;19:577–8.
42. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109–17.
43. Newell DR, Burtles SS, Fox BW, Jodrell DI, Connors TA. Evaluation of rodent-only toxicology for early clinical trials with novel cancer therapeutics. Br J Cancer 1999;81:760–8.
44. Newell DR, Silvester J, McDowell C, Burtles SS. The Cancer Research UK experience of pre-clinical toxicology studies to support early clinical trials with novel cancer therapies. Eur J Cancer 2004;40:899–906.
45. Saginur R, Dent SF, Schwartz L, Heslegrave R, Stacey S, Manzo J. Ontario Cancer Research Ethics Board: lessons learned from developing a multicenter regional institutional review board. J Clin Oncol 2008;26:1479–82.
46. Bates SE, Berry DA, Balasubramaniam S, Bailey S, LoRusso PM, Rubin EH. Advancing clinical trials to streamline drug development. Clin Cancer Res 2015;21:4527–35.
47. Menis J, Hasan B, Besse B. New clinical research strategies in thoracic oncology: clinical trial design, adaptive, basket and umbrella trials, new end-points and new evaluations of response. Eur Respir Rev 2014;23:367–78.
48. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693–703.
49. Womack JP, Jones DT, Roos D. The machine that changed the world. New York: Free Press; 1990.
50. Six Sigma. From Wikipedia [about 9 screens] [cited 2015 Mar 20]. Available from: http://en.wikipedia.org/wiki/Six_Sigma.
51. Theory of Constraints. From Wikipedia [about 12 screens] [cited 2015 Mar 20]. Available from: http://en.wikipedia.org/wiki/Theory_of_constraints.

52. Business Process Management. From Wikipedia [about 9 screens] [cited 2015 Mar 20]. Available from: http://en.wikipedia.org/wiki/Business_process_management.
53. Hanna S. Top 10: lean manufacturing companies in the world. Global Manufacturing 2014 [cited 2015 May 13]. Available from: http://www.manufacturingglobal.com/top10/38/Top-10:-Lean-manufacturing-companies-in-the-world.
54. O'Leary E, Seow H, Julian J, Levine M, Pond GR. Data collection in cancer clinical trials: too much of a good thing? Clin Trials 2013;10:624–32.
55. Koski G, Tobin MF, Whalen M. The synergy of the whole: building a global system for clinical trials to accelerate medicines development. Clin Ther 2014;36:1356–70.
56. Wipke-Tevis DD, Pickett MA. Impact of the Health Insurance Portability and Accountability Act on participant recruitment and retention. West J Nurs Res 2008;30:39–53.
57. Gown AM. Current issues in ER and HER2 testing by IHC in breast cancer. Mod Pathol 2008;21 Suppl 2:S8-S15.
58. Kurzrock R, Kantarjian H, Stewart DJ. A cancer trial scandal and its regulatory backlash. Nat Biotechnol 2014;32:27–31.
59. Personalized medicine regulation: pathways for oversight of diagnostics [PDF on the Internet]. Washington (DC): Personalized Medicine Coalition; c2013 [cited 2015 Mar 20]. Available from: http://personalizedmedicinebulletin.wp.lexblogs.com/wp-content/uploads/sites/205/2013/02/Personalized_Medicine_Regulation-Pathways_for_Oversight_of_Dx.pdf.
60. Information sheet guidance for IRBs, clinical investigators, and sponsors. Significant risk and nonsignificant risk. Medical device studies [PDF on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2006 [cited 2015 May 13]. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf.
61. Heestand GM, Kurzrock R. Molecular landscape of pancreatic cancer: implications for current clinical trials. Oncotarget 2015;6:4553–61.
62. Bach P. Cancer: unpronounceable drugs, incomprehensible prices. Forbes 2014 [cited 2015 May 13]. Available from: http://www.forbes.com/sites/matthewherper/2014/08/13/cancer-unpronounceable-drugs-incomprehensible-prices/.