SOUNDING BOARD

Randomized Clinical Trials — Removing Unnecessary Obstacles

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Since their widespread introduction in the middle of the 20th century, randomized trials of sufficiently large size have provided reliable assessments of the safety and efficacy of treatments that have produced substantial improvements in health.[1] During the past decade, however, increasingly onerous regulation and related bureaucracy have made trials much more difficult and costly to conduct, slowing further improvements.[2,3] This adverse regulatory environment hinders important research and urgently needs to be changed for the benefit of patients and public health.

As one example of the current problems (Table 1), the requirement to obtain approval from many different bodies before starting a trial results in substantial delays and costs.[4] Even where centralized regulatory and ethics reviews have been adopted (e.g., in the United Kingdom), hurdles remain when permission is required from each study site, resulting in duplicated effort and delays. For multicenter trials, this can involve hundreds of separate approvals, take more than a year to complete, and cost hundreds of thousands of dollars.[5] The situation is exacerbated when trials involve more than one country, each requiring separate approval from multiple organizations. For example, in China, it typically takes up to a year to obtain regulatory approval. Such inefficiencies are increasingly recognized as damaging to medical progress, as noted in reports from the U.S. President's Council of Advisors on Science and Technology[6] and the Institute of Medicine.[7]

Previous randomized trials have shown that a number of widely used treatments are not effective or safe; for example, treatment with antiarrhythmic drugs after heart attacks causes cardiac arrests, and routine glucocorticoid use for head injury reduces survival.[8,9] Because of the large increases in cost and effort caused by the current regulatory system, many existing and new interventions are not being evaluated, and the trials that are conducted are smaller and less informative than they might otherwise be.[7,10] Trials comparing widely accepted treatments are also being inhibited because of the trend toward requiring excessively detailed informed consent and related litigation (as in the case of recent neonatal intensive care trials[11,12]). The negative effect these obstacles have on efforts to obtain reliable evidence regarding the safety and efficacy of treatments affects the care of people not just in developed countries but also in developing countries, where resources are more limited and the burden of disease is large.[13] Hence, there is an urgent need for major changes in procedures for the initiation, conduct, monitoring, and safety reporting of clinical trials, such that they are more proportionate to the likely hazards of the trials. Otherwise, researchers may be inhibited from conducting such trials at all, which will ultimately place patients at much greater risk.

Many regulators acknowledge the seriousness of these problems, but their attempts to resolve them have often further hampered research. For instance, the European Union 2001 Clinical Trials Directive (Directive 2001/20/EC)[14] was intended to facilitate the performance of trials across Europe and better protect the public. However, it is now widely accepted — including by the European Commission itself — that this directive, which was incorporated into legislation differently in different countries, failed to achieve either aim.[2,10] As a consequence, trials that involve European Union sites, including those conducted by U.S. investigators, have been impeded, and patient care has suffered. After public consultation, the European Commission issued a proposal in July 2012 to replace the Clinical Trials

Table 1. Problems with the Clinical Trial Environment and Possible Solutions.*

Problem	Solution
The approval process is complex, costly, heterogeneous, and time-consuming	Single submission point for clinical-trial authorization with defined timelines for approval
A one-size-fits-all approach is used, with regulation of low-risk trials of well-understood drugs that is similar to regulation of trials of completely new drugs, for which the risks are unknown	Adoption of risk-based approach, with less burdensome rules and shorter approval time for low-risk trials (e.g., a marketed drug with a good safety profile being tested for nonstandard uses)
Monitoring of trial conduct involves disproportionate focus on retrospective data verification	Adoption of risk-based approach to monitoring of clinical trials, with increased use of centralized monitoring
Monitoring of drug safety involves undue focus on individual case reports without consideration of adverse-event rates in control groups	Greater emphasis on regular review of emerging safety data by independent data and safety monitoring committees in the context of the efficacy results, with appropriate sharing of this information with regulatory authorities
The ICH-GCP guidelines are inflexible and frequently overinterpreted and place undue emphasis on relatively unimportant aspects of trials at the expense of key quality aspects	Propagation of risk-based approaches to streamlining clinical trials by the International Conference on Harmonization, by issuing appropriate interpretations of the ICH-GCP guidelines, a revised version of the ICH-GCP guidelines, or both; development of authoritative and informed "good clinical trial practice" guidelines by experts in clinical trials, with input from regulators

* ICH-GCP denotes International Conference on Harmonization Good Clinical Practice.

Directive with a regulation that would be uniform among all European Union countries.[10] This proposal does include some improvements, such as a single portal for authorizing trials conducted in the European Union, more flexibility for obtaining consent in emergency situations, and measures to decrease indemnity costs. It also proposes less burdensome rules and shorter approval times for trials described as "low-intervention" (i.e., trials testing marketed treatments used in accordance with their authorized uses or standard practice and involving additional procedures that pose no more than a minimal risk or burden to participants). This proportionate, risk-based approach will be appreciated by researchers who have been advocating it for many years.[15-18] However, the definition of low-intervention trials used by the European Union should be extended to trials in which established treatments with good safety profiles are tested for novel uses — for example, aspirin for cancer prevention (Table 1). The proposed regulation also does not address many of the other problems; its changes are directed chiefly toward expediting trial initiation (e.g., approval processes). In particular, there is still inappropriate emphasis on safety assessments that rely on reports of individual adverse events, as well as on inefficient approaches to the conduct and monitoring of trials that derive from the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines.

The intention of the ICH-GCP guidelines was to ensure the safety and rights of participants in trials and also to ensure the reliability of trial results so that the safety of future patients would be protected.[19] Despite these well-intended aims, the ICH-GCP guidelines have often been interpreted and implemented in ways that have been unnecessarily obstructive and have not yielded the intended outcomes.[20] Regulatory agencies have drafted guidance on the ICH-GCP guidelines, but these documents are often lengthy (some several hundred pages long), illustrating the difficulties in its interpretation. The ICH-GCP guidelines were developed jointly between the pharmaceutical industry and various regulatory authorities, without the involvement of academic experts in trial design and conduct. Perhaps as a consequence, it is not based on a clear understanding of the key principles that underlie trials involving randomization and control groups (in particular, their robustness for unbiased assessments of safety and efficacy).[1,20,21] Instead, the ICH-GCP guidelines often place undue emphasis on less important aspects of trials at the expense of critical aspects — for example, they focus to an inappropriate extent on ensuring the completeness and accuracy of each piece of data that is recorded, even though minor errors occurring with similar frequency in the treatment groups should not materially affect the findings.[20,21]

Approaches derived from the ICH-GCP guidelines for monitoring the conduct of trials often involve frequent site visits, even though they are costly and time consuming and evidence of their usefulness is lacking.[20-22] The emphasis at such visits, reinforced by the extensive list of documents classed by the ICH-GCP guidelines as "essential" for trial conduct, is typically on things that are easy to check — for example, curricula vitae and drug-storage records and temperature logs. However, it is now widely ac-

cepted that monitoring should focus on those aspects of trials that are of most relevance to the rights and safety of participants (e.g., the consent procedures and ascertainment of serious adverse events) and on the reliability of the study results (e.g., the integrity of the randomization process and completeness of follow-up).[20,21,23] Monitoring should be designed to detect important problems early in a trial so that they can be addressed, as opposed to discovering problems retrospectively by auditing, when there is no longer an opportunity to rectify them. Consequently, the use of centralized statistical monitoring as part of a risk-based approach to ensuring trial quality has been advocated by the Clinical Trials Transformation Initiative (www.ctti-clinicaltrials.org)[24] and endorsed by the Food and Drug Administration (FDA).[16] European regulators have also recently recommended risk-based quality management,[17,18] and the proposed European Union regulation allows the extent and nature of monitoring to be modified depending on the characteristics of the trial. However, because the current draft of the regulation refers to the ICH-GCP guidelines as a quality standard (despite their inherent problems), the successful implementation of a risk-based approach in Europe will require either a fundamental shift away from the current rigid interpretation of the guidelines or a substantial modification of the guidelines themselves.

A risk-based approach should also be applied to safety monitoring during trials. However, the ICH-GCP guidelines and related regulations currently require rapid reporting of all serious adverse events thought to be related to the study treatment and not previously documented with that treatment to all relevant regulatory authorities, ethics committees, and site investigators. In accordance with the regulatory requirements, these "suspected unexpected serious adverse reactions" are typically reported on a case-by-case basis (rather than as grouped reports with a meaningful denominator) only for the participants in the active-treatment group, rather than with the corresponding event rates for the control group. The use of this type of uncontrolled data can reasonably be expected to detect only large effects of drug exposure on rare outcomes, such as the Stevens–Johnson syndrome, hepatic failure, or angioedema.[1] Currently, however, regulatory authorities and all those involved in the conduct of clinical trials are being confronted by an overwhelming volume of reports on suspected unexpected serious adverse reactions[25] and, despite a substantial expenditure of money and effort, this approach to pharmacovigilance has rarely led to useful insights or improved safety.

By contrast, moderate adverse effects of treatment on common outcomes, such as an increase in cardiovascular events with coxib treatment,[26] may well be of much greater relevance to public health, but their reliable detection requires evidence from studies that are both randomized and controlled.[1] Consequently, a more effective strategy for safety monitoring in randomized, controlled trials would be based on the regular review of the emerging safety data that is customarily conducted by independent data and safety monitoring committees, with the study-treatment assignments revealed and considered in the context of the efficacy results. The degree to which such safety information is shared with regulatory authorities could be agreed on before the start of the trial and could depend on a number of factors, such as the amount of previous experience with the treatment being studied. The cogency of these concerns about the present approach to safety monitoring has been recognized by the FDA, which has issued revised guidance for reporting requirements.[25,27] In particular, to reduce current levels of overreporting of alleged serious drug reactions, the FDA seeks rapid reporting of such an event only when there is considered to be a reasonable possibility that it was caused by the study drug. The FDA guidance also distinguishes between the rare circumstances in which it is appropriate to submit individual case reports and the more common circumstances in which cases should be aggregated and compared with those in a control group. However, the European Commission guidance and the proposed regulation from the European Union have not yet made this important distinction.

In conclusion, some regulatory agencies have responded positively to the need for improvements in the regulatory environment for clinical trials. However, the effect of those responses may be limited by the complex system of regulation and related bureaucracy that applies to clinical trials at local, national, and international levels. Those responsible for the ICH-GCP guidelines have been resistant to engaging adequately

with the research community about the incorporation of risk-based approaches and other evidence-based revisions. Certain entities have benefited from the complexity of the current regulatory environment — not just contract research organizations and companies providing training in the ICH-GCP guidelines, but also regulatory groups in pharmaceutical companies and other institutions, which have seen their revenue and influence increase substantially — and they too may oppose streamlining. Ultimately, rather than the piecemeal changes that are currently being made to the regulations and bureaucracy governing clinical trials, comprehensive reform of the whole system is required. This should involve experts in clinical trials developing authoritative "good clinical trial practice" guidelines founded on the key principles that underpin the reliable assessment of the safety and efficacy of treatments. At the same time, processes that are of little proven value should be strongly discouraged.

With support from all the relevant stakeholders — including regulators, academics, those in industry, and patient representatives — and, crucially, a better understanding of these issues at the governmental level, such guidelines could provide a more appropriate basis for the development and interpretation of regulations for clinical trials. It is becoming increasingly clear that more extensive use of health records and informatics platforms,[28] along with more refined ethical approaches characterized by the expectation that participation in clinical trials is the norm rather than the exception,[29] could support a dramatic increase in the emergence of definitive evidence about treatments. Unless radical improvements are made to the regulatory environment, the potential of clinical trials to assess the safety and efficacy of new and existing treatments and, thereby, to produce substantial improvements in health care and public health will not be fulfilled.

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