CLINICAL TRIALS

A Virtual National Laboratory for Reengineering Clinical Translational Science

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Clinical research is burdened by inefficiencies and complexities, with a poor record of trial completion, none of which is desirable. The Clinical and Translational Science Award (CTSA) Consortium, including more than 60 clinical research institutions, supports a unified national effort to become, in effect, a virtual national laboratory designed to identify, implement, evaluate, and extend process improvements across all parts of clinical research, from conception to completion. If adequately supported by academic health centers, industry, and funding agencies, the Consortium could become a testbed for improvements that can dramatically reduce wasteful complexity, thus increasing the likelihood of clinical trial completion.

A SCIENTIFIC APPROACH TO CLINICAL RESEARCH MANAGEMENT

Translational research is the process of taking biomedical laboratory findings from preclinical product development to clinical trials, to widely adopted treatments in the community, and ultimately to improvements in human health. It encompasses all of the steps required to support the entire continuum of health product development, from discovery to standard clinical practice, as well as measures of effectiveness. The translational process has become sufficiently complex, slow, and frustrating that it constitutes a major challenge facing science and society in the early 21st century (*1*–*5*). Impaired translation of biomedical research threatens the pharmaceutical industry (*6*). Even if such reductions abate over time, major translational challenges remain. Pharmaceutical products ready for clinical testing have failure rates in excess of 80% and development costs of over $1.2 billion per drug. In addition, years of drawn-out scientific, regulatory, and institutional processes encumber clinical trials (*7*–*10*) [see Fig. 1 for steps to opening an oncology clinical trial (*11*)]. Until recently, no concerted effort to streamline performance in biomedical product (devices, drugs, surgical procedures, etc.) development in the United States has been undertaken, in marked contrast to the automotive and other industries, which reduced their production times by 41% in the decade from 1995 to 2004 (*12*).

Among the phases in the translational pipeline (*13*), clinical research is certainly crucial for testing potential products in humans because it provides evidence of product safety and effectiveness when delivered to the community. The management of clinical research, however, has become as complex and lengthy as the scientific discovery of potential products, greatly impairing the efficient evaluation and incorporation of emerging laboratory concepts into the clinical development of marketable products (*14*). Lack of sufficient institutional understanding and commitment to effective ways of streamlining clinical research management has impaired efforts to eliminate wasteful steps and improve efficiency. Among the many challenges to clinical research management are lengthy and variable protocol and contract processing pathways and completion times, duplicative institutional review board (IRB) examination of identical multisite clinical protocols, protracted study start-up, failure to enroll adequate numbers of participants in some clinical trials and delayed completion of others, and too many studies that lack sufficient participant accruals to permit statistically acceptable analysis. Based on historical drug development data, it has been estimated that clinical research measured from the time a protocol for clinical testing was first conceived until the time the product was licensed for use takes an average of 90.3 months and costs an average of $100.4 million (*15*). Reduction of complexity, elimination of wasteful steps, and timely, successful completion of trials will have measurable economic and patient value.

More recently reported observational studies attest to the severity of the persistent need for change. In oncology, the most-studied disease area, for example, the development of National Cancer Institute (NCI)–sponsored phase III protocols from initial submission to final approval required a median of 2.5 years (*16*), and between 22 and 38% of such trials eventually failed owing to patient accrual issues (*17*, *18*). Furthermore, long development times correlated with low accrual success (*19*), suggesting that these problems may be part of a more systemic failure. These findings have led to a call for reinvigoration of the national cancer clinical trials system (*18*).

Although the evidence clearly shows that improvement in clinical research management is both warranted and valuable, tested and validated methods have been completed primarily at single institutions. What has been lacking, then, is unified knowledge sharing and testing of ideas. The CTSA Consortium presents such an opportunity to provide a virtual national laboratory.

IMPROVING MANAGEMENT BY USING EVIDENCE

Improvement in clinical research efficiency at academic health centers (AHCs) across the United States became a top priority of the recipients of the Clinical and Translational Science Awards (CTSAs)—a program started by the National Institutes of Health (NIH) in 2006. Designed to create an academic home for innovative clinical and translational research, the CTSAs set their sights on several goals, including speeding the process from discovery to use. Consistent with their awards, each CTSA site developed a program for improved conduct of clinical research. With concepts that have proven useful in multiple industries, several CTSAs have used such techniques as process maps, value-stream mapping, and lean thinking to identify redundancy, tandem steps, endless loops, and wasted steps [see (*20*) for a good list]. Other CTSA sites have used similar tools on problems with respect to the protocol development processes and contract negotiation improvement activities, instituting continuous process improvements across a broad range of clinical research management issues and thus focusing on shortening protocol approval and contract execution times. Others sites have enhanced the features of their clinical trials units and addressed communication systems, electronic management, and expanded recruitment programs.

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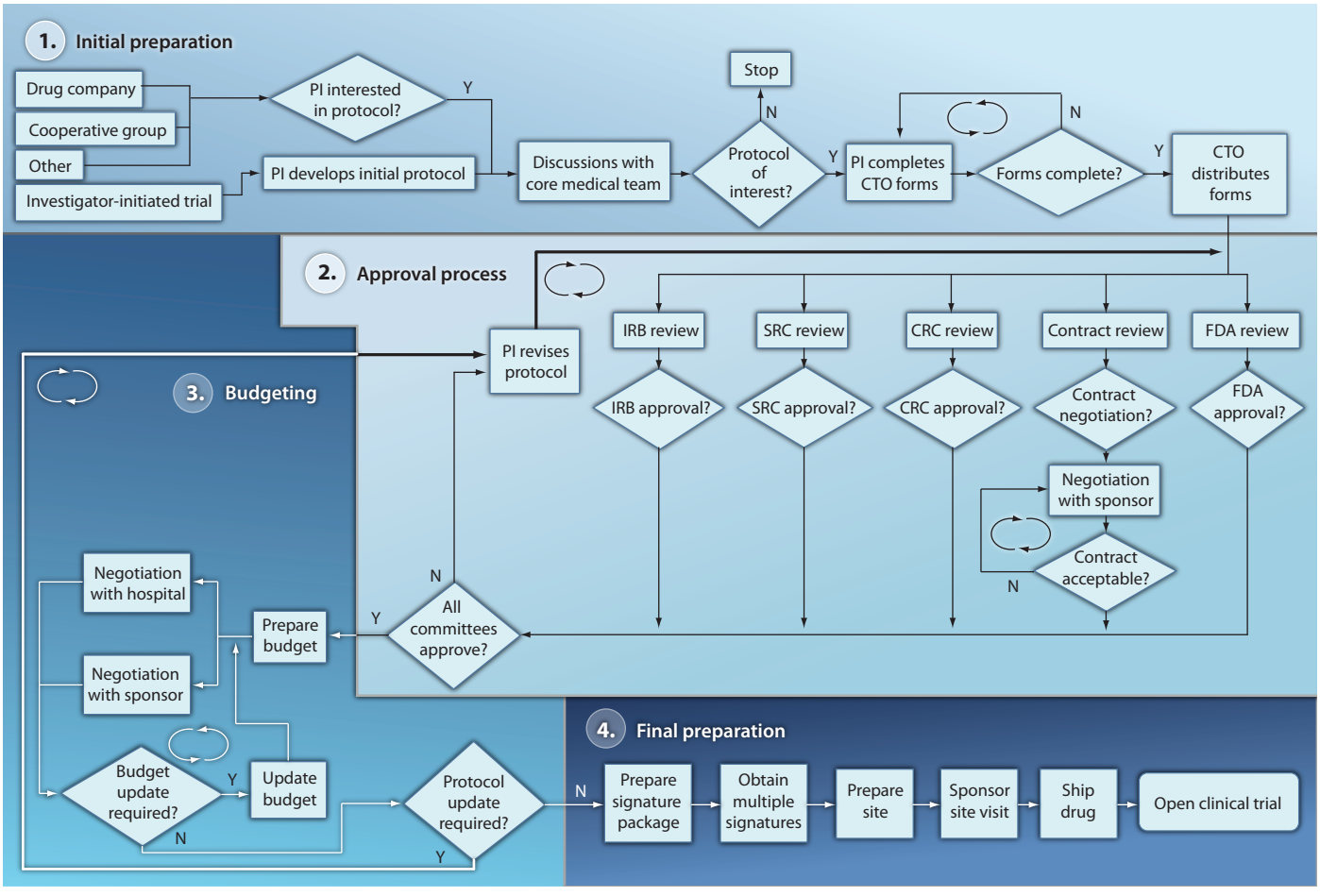

Fig. 1. High level process flow map for opening a cancer clinical trial. There are four components in the process: initial preparation of the trial documents, approval processes for the trial, estimation of the costs of the trial, and final preparation of the approved and budgeted clinical trial protocol. For a more comprehensive view of the process flow map, see www.cmrhc.org/ClinicalTrialsProcess/ProcessMap.pdf. Symbols are as follows: box, process; diamond, decision; arrow, flow; circular arrows, loop or repeat steps. CRC, clinical research center; CTO, clinical trials office; FDA, Food and Drug Administration; N, no; PI, principal investigator; SRC, scientific review committee; Y, yes.

Although each of these individual efforts is admirable, there was no agreed-upon methodology for establishing national benchmarks to measure the benefits of tracking project-completion times, instituting changes based on performance metrics, and analyzing processing data. In brief, it has been a challenge for sites that have implemented improvements to benchmark their performance on the basis of only the data they accumulated at their own sites. What was needed was objectively adjudicated parallel comparisons of multiple sites' management processing against peer performance and national standards.

Nevertheless, implementation of local improvements will do little to change national performance of biomedical translation, which requires synchronous multisite completion of clinical trials in order to move products through the pipeline. Understanding this, the National Center for Research Resources (NCRR) and the Yale Center for Clinical Investigation instituted a series of national information-sharing workshops and meetings focusing on clinical research management. The fourth annual meeting, completed in June 2011, provided a forum for the current CTSA sites to note their progress in confronting the challenges the CTSA consortia had previously identified as high priority. As noted in Table 1, 91% of the active sites participated in a voluntary process analysis study for protocol approval and contract execution times, and 93% appointed Champions of Change (individuals in leadership positions at individual CTSAs) to direct and implement process improvements. This will continue to be a key program as NCRR transitions into the National Center for Advancing Translational Sciences (NCATS).

Additionally, participants described three separate regional reliance IRB agreements; one involves many of Harvard's associated institutions; a second involves five institutions in Wisconsin; a third includes 15 institutions in Texas. Each regional agreement permits an IRB at a participating institution to rely on the review of a protocol for a multisite study by an IRB at another institution that participates in the agreement. The regional agreements have eliminated hundreds of duplicative IRB reviews of multisite protocols. Some CTSA sites have developed data-driven, continuously correcting model recruitment programs that include clinical research–centered public communication and outreach programs, feasibility studies, prospective recruitment

Table 1. A sampling of CTSA site participation in consortium process improvement strategies. This table lists challenges in clinical research management and the methods used by the CTSA consortium ($n = 60$ sites) to address them.

Identified challenges in clinical research management	Strategic intervention team	Intervention	CTSA participation [No. of sites/total sites at time of intervention (%)]
Lack of institutional commitment to efficiency	Appoint champions of change	Implement process improvement as guided by Consortium-wide studies, data, analysis, and recommendations	51/55 (93%)
Lengthy protocol processing	Protocol Review Committee	Two Consortium-wide studies of protocol processing times	50/55 (91%)
Lengthy contract negotiation	Contract Review Committee	Two Consortium-wide studies of contract negotiation times	42/46 (91%)
Multisite IRB review of identical multisite clinical protocols	Reliance IRB Agreements Groups	Regional agreements member CTSA site (number of institutions) that signed agreement: Harvard (*10*), University of Wisconsin, Medical College of Wisconsin (Milwaukee) (*5*), The University of Texas (*15*), The University of California (*4*), Case Western (*4*), University of Rochester (*16*), University of Colorado (*5*), other sites (*2*, *3*)	>20/60 (>33%)
Delayed study start-up, inadequate enrollment of study participants	Recruitment Group	Recruitment model demonstrations: Rockefeller University, Washington University, Ohio State University, University of California, San Francisco, Virginia Commonwealth University	N/A
	Web-based recruitment	ResearchMatch	54/55 (98%)
Delayed completion of studies	Feasibility Group	Pending	
	Research participant survey	A quality and research experience assessment	13/38 (34%)

planning, population targeting, and dedicated staff. For example, in 2009, after its first year of operation, the Recruitment Enhancement Pilot at Washington University reached 125% of its target enrollment in 25 trials (www.ctsacentral.org/committees/available-documents/307: 6/22/2010 Clinical Research Management Workshop: Successful Recruitment Strategies 2: Comprehensive Recruitment Service: Infrastructure, Expertise, Service: Rathmann.ppt). By mid-2011, a Web-based, nationwide recruitment program, ResearchMatch (www.researchmatch.org), which was developed through the CTSAs with NCRR funding, has facilitated the registration of participants in over 250 studies. Efficient data collection for multisite clinical trials at CTSA sites is facilitated by a Web-based data management program called REDCap (Research Electronic Data Capture; http://project-redcap.org), which supports rapid development of case report forms, central control of data and participating sites, and seamless data downloads in a secure environment.

Although these are worthwhile initiatives, it is time to pool these efforts to create a community of practice so that individual institutional efforts can be evaluated by using national performance data and the execution of multi-institutional efforts can be based on an informed, data-driven analysis of the entire CTSA Consortium. "Task forces," comprising individuals at CTSAs who have been charged with monitoring clinical protocol processing and contracts negotiation, are positioned to acquire and report follow-up process data using standard templates and protocols for process-mapping and milestone achievement. An advisory group of CTSA members with expertise in process analysis and clinical trials management identified barriers to process completion on the basis of its analysis of process streams.

With achievable goals and motivated by the visibility of the data, the CTSA sites have organized a Process Excellence Group to test methodologies and teach each other how to significantly streamline approaches to the often "invisible" barriers to clinical research (*11*). Thus, much like the basic sciences, the CTSAs are combining their efforts to create a virtual national laboratory for clinical translational research. This structure will allow for the sharing of successful process interventions, positive changes, and lessons learned along the way.

ADVANCING BEYOND THE FOUNDATION

With all of these foundations to drive change in place, what more could be needed? The organizational components that must do the work have been formed. Participants at the ground level accept the central concepts of process-mapping, project-tracking, analysis, implementation of change, and systematic reevaluation. It remains, then, for national leadership, government, academia, and the private sector to support the fledgling virtual national laboratory of CTSAs as it begins the task of building on these initial efforts in process improvement. What the consortium has learned is that there are no easy fixes, no simple solutions, no universal remedies for the inefficiencies in U.S. health care research, which now includes over 9700 active, interventional studies and trials in phases I through III supported by the NIH and by industry (http://clinicaltrials.gov/).

The key process-engineering methodologies have been piloted and refined, but, as with all change, not every process refine-

ment will succeed. Indeed, even if process changes do succeed, downstream effects may, at times, impede overall completion times. For example, shortening and simplifying the IRB review and approval process may have no measurable effect on study completion if the investigators are not prepared for study start-up and participant accrual. With leadership and support, adequate allocation of resources, and CTSA consortia committed to facilitating the clinical and translational scientific process, the virtual national laboratory is positioned to provide an environment where each proposed improvement can be systematically tested, so that the successful ones may be retained and the failures rejected quickly. The expectation is that this incremental evolution will move progressively toward making clinical research more efficient and timely. The initial results suggest that significant improvements in clinical management are already being translated into reality. Many CTSA sites have produced process maps that show shortening of processing time by up to 45 days and improvement of protocols presented to IRBs such that many more are approved with requests for revisions. Examples of process maps that have been made public may be found among Workshop posters (www.ctsacentral.org/committees/available-documents/307); one developed by Yale University was used to reduce processing time by 35 days (www.ctsacentral.org/documents/bahdocs/Yale.pdf).

Now is the crucial moment for leveraging the CTSA Consortium to broaden the scope of its efforts to test and implement additional improvements that seek to eliminate wasteful complexity and increase timely clinical trial completion. There is an ever-increasing need for more complex clinical trials that include "–omics" information. Costs of trials continue to increase while the private and federal funds available to complete such studies are limited (*15*). Finally, international competition is on the rise. Improving time and quality are of the essence in clinical research if the U.S. is to remain world class and not fall into the difficulties that have faced many other U.S. industries, such as the automotive, consumer electronics, and textile industries—all of which have experienced major declines from foreign competition (*21*, *22*). The current virtual national laboratory for reengineering clinical translational science is following a path similar to that of SEMATECH (Semiconductor Manufacturing Technology), which revitalized the U.S. semiconductor industry. Following this path will require a sustained, prolonged, and consistent effort that is more analogous to a marathon than to a sprint—an effort that is well underway in the CTSA virtual national laboratory.

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