Using Research Metrics to Improve Timelines: Proceedings from the 2nd Annual CTSA Clinical Research Management Workshop

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Abstract

The Clinical and Translational Science Award (CTSA) Consortium Workshop was conceived as a venue to foster communication among Academic Medical Centers (AMCs) in the development of methods to improve clinical research management. The consortium, comprised of 46 awardee sites as of 2009, many with multiple AMCs, is expected to expand to 60 sites when fully implemented. At the 2nd Annual CTSA Clinical Research Management Workshop held on June 22nd and 23rd, 2009, on the National Institutes of Health (NIH) campus, consortium members and potential CTSA sites gathered with stakeholders from private industry, the NIH, the Food and Drug Administration, and private research organizations, to formulate a plan to address challenges in clinical research management. Specific aims included improving protocol processing and sharing process improvement initiatives in the expectation that best practices will be implemented and improvements will be measured and reported. The findings presented at this workshop indicated significant variance in Institutional Review Board approval of protocols and contract execution by AMC and CTSA sites. Most represented marked delays compared to non-AMC sites and that, as a likely consequence, AMCs were later to enroll patients and/or meet enrollment targets compared to dedicated or professional sites. Clin Trans Sci 2010; Volume 3: 305–308

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Introduction

With objectives of enhanced efficiency, cost control, and improved quality of clinical research, the newly formed Clinical and Translational Science Award (CTSA) Consortium sought to identify and remedy obstacles within the clinical research management process as a top priority at its first meeting in 2006. A commitment to clinical research is a core value for nearly all of the CTSA applicants and, therefore, maintenance of optimal performance standards for clinical research is of central concern. Clinical research is also a major priority for the public and private sectors, as evidenced by its strong support by the National Institutes of Health (NIH), industry, and a broad spectrum of health care advocacy groups.

According to workshop presenter Robert Califf, M.D. (Duke University), a lynchpin of healthcare reform is considered to be the development and objective assessment of new diagnostics, drugs, devices, and behavioral interventions, because these will provide a rational basis for choice when evaluating health care options. However, the development and assessment of products and interventions depends entirely on a firm platform for the performance of clinical research, much of which is conducted at Academic Medical Centers (AMCs), and critical to the achievement of these goals is the development of objectively verifiable methods to measure the improvement of research management and conduct.

In February 2010, www.ClinicalTrials.gov listed 13,000 open, interventional clinical trials in the United States. However, there is widespread concern that the trials are being conducted with less than maximal efficiency, thus implying a need for improvement in clinical research management at AMCs. Many AMCs have developed robust clinical research programs, which operate largely in isolation from each other with little opportunity for sharing lessons learned and best practices for conducting clinical research.

Among its many other functions, the CTSA Consortium provides a setting where clinical research management counterparts at CTSA-associated AMCs can exchange ideas and strategies to improve the processes that support clinical research. The 2nd Annual CTSA Clinical Research Management Workshop provided a face-to-face venue whereby representatives from industry, research, NIH and Food and Drug Administration (FDA) could gather to exchange initiatives and methodologies (http://www.ctsaweb.org/index.cfm?fuseaction=meeting.viewMeeting&year=2009&com_ID=221#mtg_ID_1160).

Delays in initiation of clinical research

The conduct of clinical research is challenged by the complexity of the regulatory environment, limited funding opportunities, institutional inefficiencies, and inadequate patient recruitment, enrollment, and retention. Attendees at the workshop learned of instruments used in the private sector to assess the efficiency of clinical trials activation, enrollment, and completion. Tracy Blumenfeld (RapidTrials; Tufts) reported that between 2002 and 2007, for selected industry sponsored trials, the time from protocol approval, by the regulatory sponsor, to the date of the first visit of the first subject had increased by 74%. Moreover, under-enrollment was severe. Up to 25% of clinical trials Rapid Trials reported failed to enroll a single patient even after spending many hours and dollars activating them. Almost half of research sites report that studies are delayed by intermediaries; since 2006, administrative procedures and protocol amendments have increased by 12% and 50%, respectively (RapidTrials). According to data gathered by the Tufts Center for the Study of Drug Development, over 90% of all clinical trials fail to meet expected completion dates because of overly optimistic timelines and inadequate patient enrollment (Califf). Patient advocacy

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groups consistently identify delay times as adverse to the interests of patients (Califf). Even after activation, an estimated 20% of clinical trials fail to enroll a single patient and an additional 30% under-enroll (Califf; Tufts). Clinical research is increasingly being conducted abroad: one-third of phase III trials conducted by the 20 largest U.S. pharmaceutical companies are being conducted solely outside the United States (NEJM; 2009 Feb 19;360(8):816–823). Since 2002, the number of FDA investigators outside the United States has grown by 15% annually, whereas the number in the United States has declined by 5.5%.

Using metrics to drive clinical site performance improvement

The use of metrics to evaluate the management of clinical research process is a logical approach to understanding why and where delays occur and as a tool for measuring baseline and improvement. Pharmaceutical companies have shifted toward this approach as a basis for site selection, with a trend toward eliminating poor or non-performing sites (RapidTrials). The shift toward performance characteristics was further accentuated during the recent economic downturn which sharpened concerns about maximizing the value of investments in clinical research. At the 2009 CTSA Clinical Research Management Workshop, private industry and members of the CTSA Consortium presented clinical research process data to develop methods for improving research timelines on both an institutional and collective level. Leaders of the CTSA Consortium have proposed the application of a standardized set of metrics for clinical research management across multiple academic sites, allowing for comparisons and the identification of best practices. Standardized metrics have the potential of establishing benchmark performance and reducing variability between AMCs at CTSA sites. If successful, standardized metrics could be expanded to clinical research centers outside of the CTSA sites as well.

In the private sector, Briggs Morrison from Pfizer surveyed the company's clinical trials conducted between 2006 and 2009; he compared CTSA-associated AMCs with other AMCs and non-AMCs and showed that each of these institutions had similar patient enrollment rates but that about 30% of activated sites did not enroll any patients and about half enrolled no more than three patients. The duration between protocol approval and initiation of patient screening was less at non-AMC sites (median 210 days) than at CTSA or other AMC sites (median 265.5 and 257 days, respectively). The duration between protocol approval by Pfizer and the receipt of a signed contract was longer at CTSA and AMC sites than at non-AMC sites: for non-AMCs the median was 42 days, while the median for CTSA and AMC sites was 165 and 141 days. Once patient enrollment was initiated, the time from first screened patient to last screened patient was comparable across the three types of institutions (Pfizer). Thus, the Morrison analysis indicated that contracting times were prolonged at AMCs (including CTSA sites) when compared to non-AMC sites, which was also identified by the CTSA Consortium as a concern. Indeed, the CTSA Consortium had launched pilot studies to identify potentially correctable causes of prolongation of contracting times at CTSA-related AMCs.

In one of the largest cross-company, independently collected data sets analyzed to date, RapidTrials examined research metrics at AMCs, dedicated research centers, and professional sites with which it contracted on behalf of pharmaceutical companies for clinical research. The survey, which included data collected from 1997 to 2008 from 5 of the top 10 pharmaceutical companies, examined studies involving 7,049 principal investigators, 14,857 sites and 91,783 subjects in trials on 121 compounds in 10 therapeutic areas. The data showed that study initiation at academic centers takes 49 days longer than at professional and community sites, placing academic centers at an enrollment disadvantage. Once studies are initiated, AMCs are approximately 10% slower to enroll than dedicated and professional sites, and although AMCs are better at screening for appropriate study participants, more participants remain on study until completion at non-AMC sites than at CTSA and other AMC sites.

CTSA Pilot Studies to Identify Study Initiation Bottlenecks

IRB metrics

At the 1st Annual CTSA Clinical Research Management Workshop (2008), the consortium reached a consensus to use research metrics to evaluate time to study initiation and began by conducting a pilot study on Institutional Review Board (IRB) metrics as a first step. A pilot protocol for the study of protocol processing by IRBs at individual CTSA-associated AMCs was designed to gather the data necessary to provide a better understanding of trends and review processes and to establish baseline data to promote the understanding of review characteristics common at all participating CTSA sites (http://www.ctsaweb.org/uploadedfiles/Final_CTSA_IRB1.pdf). The purpose of the study was to identify common practices that exist at all AMCs, regardless of process, to be used in future research so as to further identify, implement, monitor, and standardize protocol process improvements across the CTSA Consortium. The objectives were to collect data pertaining to the complete review of up to 25 comprehensive clinical protocols by fully convened IRB(s) at each CTSA site; to determine the median times for completion of approvals (75%, 90%, and 100%) for protocols approved in the month of February 2009. The intent was to develop an understanding of the process based on data analysis which, in turn, could be used to define relevant metrics that could serve as tools to improve and monitor the management of clinical trial protocol approvals. A total of 200 protocols were targeted, but that number was exceeded when 31 of the 38 CTSA sites reported on 378 protocols.

A preliminary review of the data showed no variance by year of award or by volume of protocols in 2008. However, the results showed that there is wide variability among institutions on definitions and steps in the IRB review and approval process. Many CTSA sites review some studies through external IRBs and other studies through internal IRBs; some sites include comprehensive scientific review in the IRB process and others do not. Ancillary data showed that 18 sites (out of 28 submitting data on this topic) have a system for electronic submission of at least half of all protocols, with 11 sites utilizing full electronic submission for all protocols. The mean number of IRB support staff per site was 15.4 (29 sites reporting), the majority of sites (25 out of 28) had five or fewer biomedical IRBs, and 21 sites reported using an external IRB.

This study, with more than 75% of CTSA sites participating, in a collaborative process, identified the variances in the IRB process across sites and the challenges associated with developing an IRB metrics repository of comparative data to facilitate IRB process improvements (CTSA Regulatory and Ethics IRB Taskforce). During the past year, many CTSA sites have examined, evaluated and modified their approval processes and have taken steps to reduce study initiation timelines. Workshop participants had

the opportunity to view this progress at a poster session, during which they exchanged information with colleagues.

Contract execution metrics

In addition to the study on IRB metrics, a pilot study was initiated to determine whether the CTSA could study the contract execution processes to develop objective metrics to be used for process improvement (http://www.ctsaweb.org/uploadedfiles/Contracts_CTSAContractsTaskfor14.pdf). The objectives included the collection of defined time data points at all CTSA sites, the determination of median completion times for execution of contracts, and the collection of information on factors that may influence contract negotiation times. This study is especially relevant in light of the data presented by Pfizer in which delays in executing contracts were a major factor in study initiation delays. The study, which focuses on industry-initiated, industry-sponsored clinical trials, began on April 1, 2009 and was scheduled to end when all participating sites had recorded the execution date of 90% of the contracts that site was tracking in the study. At the time of the presentation, 30 CTSA sites had submitted data on 498 contracts. When complete, the information obtained from the study will be used to develop future studies to provide evidence to support efforts to improve timelines for contracts negotiation, to examine processes with a view towards improvement, to develop methods of data collection, to identify obstacles to collecting data, and to inform the design of future studies.

Conclusion

The operations associated with the management and conduct of clinical research resemble other enterprises that combine human effort and technology to produce a product and should have similar goals of standardization, systems development and measurement to produce a better product (Califf). The CTSA is well positioned to oversee the collection, analysis and application of research metrics that will help its AMCs move toward this goal and has taken steps to set the process in motion. In addition to presentations and discussions of pilot data from CTSA sites, several themes emerged from the workshop that will set the stage for improvements in the quality and efficiency of clinical research.

The consortium's clinical research management improvement plan includes continued pursuit of data-driven, transparent approaches to process improvement. This includes mapping and analysis of prestudy processing and assessment of performance times as a function of study characteristics such as number of sites, type of population, previous experience of investigator, investigational agent (under the Investigational New Drug program), or sponsor. Transparent reporting, such as might be accomplished by posting metrics on a website, would demonstrate responsibility and accountability; these factors would improve the research process for investigators, sponsors, research teams, and patients. Although participants at the workshop contemplated more aggressive goals, such as a maximum number of days from final protocol approval, by the sponsor, to first patient first visit, they reached a consensus: individual institutions might best begin by evaluating their internal processes and eliminating steps that do not add value. Sites might also benefit from standardization of contracting terms or the development of a standard menu that could be adapted to eliminate or reduce contract negotiation delays. Beyond examining ways in which clinical trials could be conducted more efficiently, the consortium intends to tackle additional measures of performance such as issues related to quality, trial completion (e.g., recruitment and retention), and costs. To this end, the CTSA Regulatory and Knowledge Support Key Function Committee convened a Recruitment/Retention Taskforce, which has begun to examine practices across the consortium.

The sharing of best practices, the development of consortium standards and the review of data on an annual basis will all play an important role in future Clinical Research Management Workshops. The 2009 workshop revealed a collaborative and cooperative environment between CTSA Consortium members, boding well for future gatherings. In the meantime, effective teamwork across and among institutions, motivated leadership, a supportive culture, and above all, a willingness to examine and change systems and processes that are in place will all contribute to substantial improvement in clinical research management.

Glossary of Terms

AMC: Academic Medical Center.

Clinical research: Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects; excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: mechanisms of human disease, therapeutic interventions, clinical trials, development of new technologies, epidemiological and behavioral studies, or outcomes and health services research.

CRO: Contract Research Organization, also called a Clinical Research Organization, (CRO), a service organization that provides support to the pharmaceutical and biotechnology industries. CROs offer clients a wide range of "outsourced" pharmaceutical research services.

CTSA Consortium: A national consortium of medical research institutions, funded through CTSA, working together to improve the way biomedical research is conducted nationwide. Consortium members share a common vision to reduce the time it takes for laboratory discoveries to become treatments for patients, to engage communities in clinical research efforts and to train clinical and translational researchers.

CTSA Regulatory and Ethics IRB Taskforce: A consortium subgroup formed to create a document that embodies suggestions for improvements to the process of IRB oversight of multicenter studies.

FDA: Food and Drug Administration.

IND: Investigational New Drug program is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. Interventional Clinical Trial: Studies in human beings in which individuals are assigned by an investigator based on a protocol to receive specific interventions. Subjects may receive diagnostic, therapeutic, or other types of interventions. The assignment of the intervention may or may not be random. The individuals are then followed and biomedical and/or health outcomes are assessed.

IRB: Institutional Review Board; an organizational committee that reviews and approves biomedical research that uses humans as subjects.

Key Function Communities/Committees (KFCs): Consortium-wide forums for communication and sharing best practices across areas of clinical and translational research.
KFC Task Force: Implementation groups developed from volunteer members drawn from the KFCs to initiate and carry out specified consortium projects such as developing resource networks, completing white papers, and others; groups will sunset on project completion
NIH: National Institutes of Health
Phase III Trial: Clinical trial to evaluate a drug or treatment that has proven effective in the phase I and II trials and is tested on a large population (1,000–3,000) to confirm its effectiveness, reveal any rarer side effects, and gather information that will allow the drug or treatment to be safely marketed.
PI: Principal investigator; the individual responsible for the conduct of the study at each participating institution.
RapidTrials: A Contract Research Organization (CRO) formed to help sites optimize performance on clinical trials.
Translational Research: Transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce morbidity and mortality and improve population health.

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