

2nd Annual Clinical Research Management Workshop Website Report

Leaders of the CTSA Consortium announced a plan to improve clinical research management (CRM) at the 2nd Annual Clinical Research Management Workshop sponsored by the Consortium, hosted by the Yale Center for Clinical Investigation, and held at the Natcher Conference Center on the NIH Campus June 22-23, 2009. Data documenting wastefulness and inefficiency were of major concern in a variety of presentations. The plan for improvement is based on data collection on protocol and contracts processing at all CTSA sites, public display of comparative metrics, shared lessons learned and best practices, and empowerment of Champions of Change at each site with tools to institute improvement.

Michael Joyner (Mayo CTSA) led off with a discussion about process improvement based on systems re-engineering prompted by investigator complaints, compliance gaps, a change in research leadership, and process changes related to competing for the Clinical and Translational Science Award. To make effective change, the process must be system wide, based on performance data, and continually subjected to analysis and improvement. Briggs Morrison (Senior VP, Pfizer) stressed that industry bases its selection of sites for clinical trials on the quality of trial conduct, the speed of performance, and the cost. He compared multi-center, Pfizer-sponsored US-only studies performed at CTSA sites, non-CTSA academic sites, and non-academic sites between 2006 and 2009. In general, CTSA sites were the same or a little worse than the other sites. 30% of sites never enrolled a single subject on a trial, 50% never enrolled more than 3 subjects. As a quality of performance measure, Pfizer tracked protocol deviations. CTSA sites had a discouraging average of 4 deviations/study. It took 200 – 400 days to initiate a study from the time a final approved protocol was received by the site and 4-7 months to negotiate and sign a contract. Trials cost from \$6,000 to \$14,000/patient at CTSA sites, the average is \$9,100. Joseph Camardo (Senior VP, Wyeth) commented on the advances in clinical research with the attendant

complexity of trials, contracts, processing, and specific concerns about indemnification, subject injury, insurance, and intellectual property. The arena has expanded from one confined to US academic medical centers to a global territory. The complexity has resulted in communication challenges, frequent revisions of policies and contract templates, changes in master agreements, and misunderstandings. He addressed these issues in detail, reflecting industry's view of them, suggesting an avenue for resolution. He challenged CTSA sites to consider redefining its focus to research (Phase II or less) instead of development (Phase III or IV), to improve protocol development and contracts, to shorten timelines, reduce costs, and develop national master agreements.

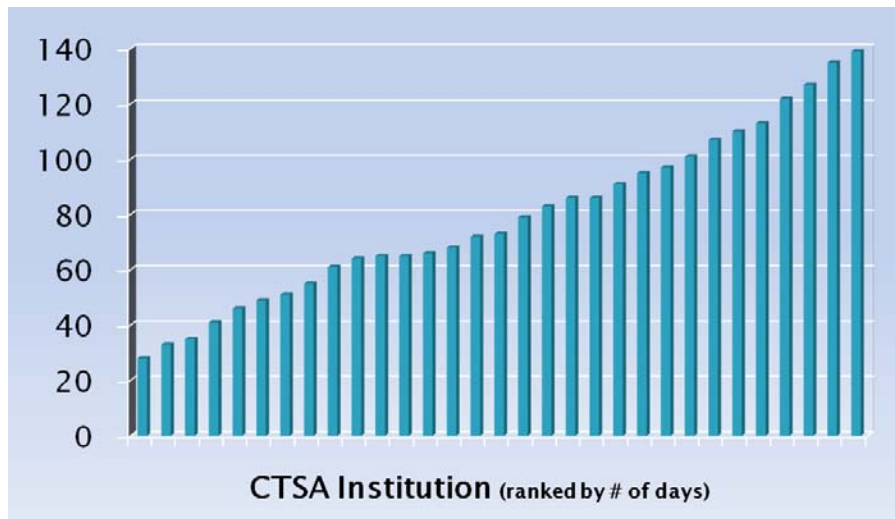
Sheila Prindiville (Director, Coordinating Center for Clinical Trials, NCI) described a plan that integrates the individually strong components of the current NCI system into a cross-disciplinary, scientifically-driven, cooperative research effort. The effort includes elimination of duplication, standardization of terms, definitions for key clauses and phrases in order to develop acceptable agreement language, and simplify protocol processing. The NCI contracted with David Dilts to help identify systems and employ systems analysis to reduce processing time. Using this approach, the Comprehensive Cancer Centers were able to reduce process steps from >300 to >136, to reduce working steps from >239 to >74 compared to CTEP. However, accrual per site remains at a dismally low level, with 25% never registering any subjects and another 30% accruing 1 – 4 subjects. To improve the data, the NCI is working cooperatively with all its centers to achieve named goals to document measurable process improvement. Jonathan Kagan (Assistant Director for Special Projects, NIAID, presentation not archived on the CTSA website until after publication, later in 2009) described an approach to simplifying complexity, avoiding lost opportunities, and improving the efficiency of approval and start up in AIDS trials currently being performed by NIAID sponsored investigators on a global basis. Using process metrics, he was able to identify outliers, address registration issues, and improve management.

Rebecca J Williams (Assistant Director, ClinicalTrials.gov) provided historical and background information on the website, updated the data on registration of trials (11, 529 observational and 62,210 interventional trials as of 6/17/09, total 74,623 (some missing study type data) since opening 12/31/04). She also detailed reporting requirements, time-frames, and general characteristics of the basic results database. The development of a high quality database has taken many iterations with National Library of Medicine staff. The system still depends on an adequate understanding by the data providers who perform better if the investigator and a statistician are involved.

Barbara Bierer (Senior VP Research, Harvard Catalyst CTSA) presented a brief overview of the development of an IRB reliance agreement at 9 centers within the 18-institution Harvard Catalyst CTSA site. Signatories to the agreement include Beth Israel Deaconess MC, Brigham and Women's Hospital/Faulkner, Children's Hospital Boston, Dana-Farber Cancer Institute, Joslin Diabetes Center, Massachusetts General Hospital, Harvard University, Harvard Medical School, and Harvard School of Public Health. Their challenge was to create a centralized process in a decentralized environment, while respecting that each Harvard signatory is a separate legal entity with separate (and mostly accredited) human research protections programs. Issues requiring resolution included definitions of terms, scope of agreement, and jurisdiction of principal investigator, management of requests, and duties and responsibilities of investigators. Early steps required agreement not to "check the box" on federalwide assurances to ensure consistent OHRP reporting requirements, align HRP to 3-year renewals, accept zero dollar COI disclosures, and harmonize regulatory processes including HIPAA compliance. Juan Cordero (Regulatory Knowledge Facilitator, Weill Cornell MC CTSA) discussed facilitated review and process management for shared protocols at four institutions within one CTSA. The process began with

a mutual agreement to accept facilitated review and to use an IRB of record with facilitated communication between the institutions.

Ray Hutchinson (Associate Dean of Regulatory Affairs, Michigan CTSA) and Kathleen Uscinski (Deputy Director Human Investigation Committee, Yale University CTSA) presented preliminary data from a pilot project consisting of data on the IRB protocol approval process that had been gathered from 31 institutions as of June 18, 2009. They described the process by which a taskforce had agreed upon the terms of the protocol, the conduct of the study with data coordinators at each site and a central data coordinator, Susan Bankowski, (Director, Research Ethics Program, OHSU CTSA), and the use of a central data registry (REDCap, Vanderbilt CTSA). In essence, the sites agreed to report studies approved in February 2009 and retrospectively gather and report the dates on which they had passed certain milestones beginning with submission to the IRB office. The presenters emphasized that the study does not examine processes in a way that captures the variability in pathways between institution, does not account for variance in complexity of the protocols, and did not take workload or other factors into account. The intention is to submit the data to careful analysis associated with process modeling. However, the participants did consider it appropriate to report to the Workshop participants that the sites are gathering and reporting processing data on themselves and do plan to be held accountable for process improvement based on objective criteria. As of the data of collection, the 31 institutions reported data on 378 protocols, with a mean processing time of 78.8 days, a minimum of 28.2 and a maximum of 139.4 days. Preliminary review showed no variance by year of award or by volume of protocols in 2008. The data by site were displayed anonymously in a bar graph, showing the number of days for each institution, in ascending order from the shortest mean review time to the longest.



Adam Rifkind (Associate Director, Corporate Contracts, U of Pennsylvania CTSA) and Libby Salberg (Director, Office of Grants & Contracts Management, Vanderbilt CTSA) presented comparable data for contracts execution. Their study was also derived from the efforts of a taskforce that worked over many months to reach agreement about data points and handling of exceptions. Their goal was to determine median and completion times for execution of contracts from the data of receipt by the contracts office. Data was collected from each participating site from April 1, 2009 until May 31, 2009 or until the site reached 25 contracts, whichever occurred first. The termination of the study will occur when the site has executed or terminated negotiations on 90% of the contracts entered into the study. Preliminary data for this study was included in the discussion, but it is important to note that the execution times for the relatively few studies that were completed did not reflect a majority of the 498 contracts that were reported by the 30 institutions that submitted data. However, the data did include some interesting information about achievement of intermediate process milestones.

Dan Ford (Vice Dean Clinical Investigation and Principal Investigator, Hopkins CTSA) talked about the future. He emphasized the unique opportunity for the CTSA Consortium to work cooperatively to implement process improvement based on standardized metrics to be used across the consortium. He stated that public posting of metrics would show sponsors and the public the consortium's commitment responsibility and accountability. The mechanisms are in place. The sites have agreed to collect and report data. Each site has appointed a Champions of Change to take the lead in implementing and monitoring process improvement. The Consortium will have to go farther, identify protocol, contracts, and sponsor characteristics and other variables that influence data points. It will have to look at resources, quality of performance, and costs. But the die has been cast. It is time to act.

Tracy Harmon Blumenfeld (President, Rapid Trials) discussed ten years of data on CTSA sites' performance of industry sponsored trials. The processes and the trials themselves have become more complex with time. The academic sites have not improved processing or moved with efficiency or effectiveness in addressing issues of concern to industry. Of particular concern is the lack of sufficient enrollment on trials. Her data confirmed that, across the spectrum of studies, specialties, and institutions, 25 – 30% of studies never enroll any subjects and 50% under-enroll. Coupled with the high costs of performance at academic centers, there is little incentive for industry to perform trials at CTSA sites, particularly in Phase III when information is needed urgently.

Robert Califf (Vice Chancellor for Clinical Research, Principal Investigator, Duke CTSA) stressed the need for consortium-wide adoption of standardized metrics and processing performance assessment.

American pharmaceutical companies have looked to off-shore sites to perform studies in increasing numbers. The US performance is wasteful of time, our industry is lagging in production of new products. Worse, our healthcare system fails to deliver optimal outcomes, our life expectancy lags behind other nations, and our healthcare costs are excessive. He cited data documenting reasons for delay in trial

initiation, lack of enrollment, and the reluctance of 38% of investigators to conduct a second trial because of their discouragement about the burdens experienced with their first one. It is discouraging also that 50% of sponsored Phase III trials did not achieve 25% of minimum projected accruals at closure and 64% do not achieve minimum projected accruals at closure. He described the goal of the Clinical Trials Transformation Initiative (CTTI) which is a collaborative effort seeking solutions to the problems he described.

Anthony Hayward (Division Director, Clinical Research Resources, NCRR) reported on the adaptive organizational structure of the Consortium's governance, the use of the Consortium Steering Committee to identify priorities, a Strategic Goal Committee to work on a group of priorities with a common theme, and Key Function Committees and Taskforces to implement the projects designed to achieve the goals. He described the Clinical Research Innovation KFC, a new committee that combines Clinical Research Management KFC, Regulatory Knowledge KFC, and the PCIR KFC to streamline activities related to clinical research management. He also mentioned the continuing goal of the NCRR to fund 60 CTSA sites by 2011, to support promising efforts by the sites and groups of sites with administrative supplements, as funds become available, and the expectation that the NCRR will award approximately \$60 Million to such projects in 2009.

Barbara Bigby (Director Regulatory Services, Scripps CTSA) described the Scripps experience in implementing process improvement and the early phases of electronic protocol processing. Kathleen Uscinski (Deputy Director Human Investigation Committee, Yale University CTSA) discussed the educational and outreach process to community physicians and institutions who wish to engage in clinical research. Deborah Roth (Chief Operations Officer, Duke CTSA) described the Clinical Trials Network, a national site, initially developed with NIH Roadmap funds, dedicated to sharing information about the development of public-private partnership, facilitating collaborations between investigators at

different sites, and supporting a range of activities required for effective clinical research program development.

In Summary: The Consortium acknowledged a need for substantial improvement in clinical research management and decided to emphasize improvement in protocol processing and contracts execution as a first step. At this meeting it reported preliminary pilot data on centrally collected and analyzed studies that each CTSA site conducted on its own process times for protocol approval and contract execution. The Consortium's improvement plan includes the following: 1) Data-driven, transparent approaches to process improvement, 2) Champions of Change at each AMC, leaders with the authority to make changes, 3) Publicly presented metrics, data on relevant processes, 4) Sharing of best practices, 5) Consortium standards, and 6) Annual review of data. All 39 CTSA sites have engaged in the initiative for improvement in CRM. For details on Workshop presentations, visit

http://www.ctsaweb.org/index.cfm?fuseaction=meeting.viewMeeting&year=2009&com_ID=221#mtg_1

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