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Integrating utilization-focused evaluation with business process modeling for clinical research improvement

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New discoveries in basic science are creating extraordinary opportunities to design novel biomedical preventions and therapeutics for human disease. But the clinical evaluation of these new interventions is, in many instances, being hindered by a variety of legal, regulatory, policy and operational factors, few of which enhance research quality, the safety of study participants or research ethics. With the goal of helping increase the efficiency and effectiveness of clinical research, we have examined how the integration of utilization-focused evaluation with elements of business process modeling can reveal opportunities for systematic improvements in clinical research. Using data from the NIH global HIV/AIDS clinical trials networks, we analyzed the absolute and relative times required to traverse defined phases associated with specific activities within the clinical protocol lifecycle. Using simple median duration and Kaplan-Meyer survival analysis, we show how such time-based analyses can provide a rationale for the prioritization of research process analysis and re-engineering, as well as a means for statistically assessing the impact of policy modifications, resource utilization, re-engineered processes and best practices. Successfully applied, this approach can help researchers be more efficient in capitalizing on new science to speed the development of improved interventions for human disease.

BASIC SCIENCE IS advancing at unparalleled rates, generating new findings and insights into the causes of human disease, creating extraordinary opportunities to design novel treatments and preventions. But before they can be approved for use in people, all new therapeutics, vaccines, and interventions for human use must be proven safe and effective through testing in controlled clinical trials. At the same time, the ability to carry out clinical trials is becoming ever more complex, costly and time-consuming. A host of legal, regulatory, policy and operational factors, few of which necessarily enhance research quality, the safety of study participants or research ethics, are increasingly impeding the progress of clinical research in the United States and around the world. In a number of instances, important clinical trials have been seriously delayed, rendered infeasible or blocked.

The pressing issue addressed in this article is the need to identify ways to improve the efficiency and effectiveness of clinical research. Using the National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS extramural clinical trials networks as an exemplar of large-scale, global clinical trials programs, this report examines how the integration of utilization-focused evaluation with elements of business process modeling can reveal opportunities for systematic improvements in clinical research. Successfully applied, this approach can help researchers be more efficient in capitalizing on new science to speed the development of improved interventions for human disease.

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Context and background

The NIAID HIV/AIDS clinical trials networks are comprised of six extramural cooperative groups whose goals are to design and carry out hypothesis-driven clinical research to identify new and improved interventions for the prevention and treatment of HIV/AIDS around the world. The six groups include:

1. *The AIDS Clinical Trials Group* to optimize clinical management of HIV/AIDS, including co-infections and other HIV-related conditions, and conduct translational research for new drug development.
2. *The HIV Prevention Trials Network* to evaluate non-vaccine HIV prevention strategies.
3. *The HIV Vaccine Trials Network* to evaluate preventive HIV vaccines;
4. *The International Maternal Pediatric Adolescent AIDS Clinical Trials Group* to evaluate ways of preventing mother-to-child transmission of HIV, optimizing clinical management of HIV, including co-morbidities and other HIV-related conditions in children, adolescents and pregnant women.
5. *The International Network for Strategic Initiatives in Global HIV Trials* to optimize clinical management of HIV/AIDS, including co-infections and other HIV-related conditions.
6. *The Microbicide Trials Network* to evaluate microbicides for HIV prevention.

Organizationally, each group/network has a central leadership component to set priorities and manage the effort, and varying numbers of clinical trials units, each led by a principal investigator and featuring an administrative component, community advisory board and one or more clinical research sites (e.g. medical schools, academic health centers, hospitals or outpatient centers) where the clinical trials are performed. Since their inception in 1987, the guiding philosophy behind the networks has been to bring together multidisciplinary expertise to create (and sustain) both a leading-edge HIV/AIDS research agenda, and a reusable clinical research infrastructure. The success of this approach has been demonstrated by the groups' exceptional scientific productivity (e.g. 562 protocols in the past four years, 161 current active trials, ~69,000 participants presently enrolled, ~200 publications/year), and the significant impact of their findings in both clinical practice and basic research.

However, despite enormous global efforts, the HIV/AIDS epidemic continues to expand virtually unabated, with nearly 2.5 million new infections per year worldwide (UNAIDS, 2007). And after nearly 20 years of unprecedented growth, due largely to fiscal constraints and competing priorities, funding for the HIV/AIDS networks has begun tapering. Simultaneously, a proliferation of legal, regulatory and policy requirements have, in many instances, added to the burden and complexity of the research. Given the vital role of the networks in developing and optimizing HIV treatments, vaccines and preventions, it was essential that these programs not lose ground. Accordingly, NIAID resolved to evaluate how, in the face of financial constraints and mounting barriers to clinical research, the networks could continue (and even grow) their vital role in responding to the epidemic.

Development of conceptual framework for evaluation

The NIAID HIV/AIDS clinical trials networks are an example of a broader trend in the organization and management of science towards large-scale research initiatives (Edgerton, 1999; Nass and Stillman, 2003). Several challenges in developing appropriate evaluation approaches for large research initiatives have been identified, including:

- Ensuring the highest-quality evidence;
- Minimizing burden and the intrusiveness of the evaluation system; and
- Yielding data that can satisfy a myriad of scientific, managerial, financial, and regulatory requirements (Quinlan *et al*, 2008).

One of the first and most complex aspects of this endeavor involved identifying the goals of the networks as seen across a wide array of stakeholders, each with its own set of expectations as to what constitutes success. There were few precedents to guide evaluation planning for such efforts. With the expectation that the enterprise be collaborative and coordinated at multiple levels, several sources of input were needed to define the goals of these complex and diverse stakeholders, develop strategies to work across disciplines in innovative ways, and evaluate the outcomes of collaborative work. Due to the broad range of activities, potential outputs, and outcomes of network activities, it was essential that a comprehensive framework be developed to serve as guide for evaluation (Trochim *et al*, 2008).

The centerpiece of our evaluation framework development process was collaboratively authored using a group conceptualization approach known as concept mapping — a rigorous, mixed methods approach that blends familiar qualitative processes with several multivariate analyses that yield shared conceptualizations of complex issues (Kane and Trochim, 2007; Trochim, 1989). The concept mapping methodology has been used successfully in similar large-scale research initiatives as the method for the development of conceptual models (Stokels *et al*, 2003; Andersen *et al*, 2006).

Specifically, for this project NIAID worked with HIV/AIDS network leadership to identify a broad range of stakeholders, including scientific

researchers, community members, government and non-government staff and industry representatives (Kagan *et al*, 2009). Participants in the evaluation framework development process represented six different areas of HIV clinical science, ten different roles in the AIDS community, and six continents. Individuals were selected based on their unique insights and knowledge of the HIV/AIDS clinical trials networks specifically, and/or HIV/AIDS clinical research generally. A cross-section of perspectives and ideas were secured by inviting a broad sample of individuals to participate. In the end, more than 300 individuals contributed to the generation of over 1,500 ideas; 90 stakeholders participated in a conceptual sorting process and 323 completed ratings of importance. A final set of 91 statements that described the success factors for the HIV/AIDS clinical research networks were captured and organized, by the stakeholders, into eight specific clusters and four overarching 'regions':

- Scientific agenda and objectives;
- Community and participants;
- Operations, policy and resources; and
- Communication, collaboration and harmonization (Figure 1).

A cross-network task force was then convened to assist in interpreting the framework, share relevant existing evaluation resources, tools, measures and experiences, and contribute to the development of the evaluation plan components. Task force members representing the four regions of the concept map identified evaluation questions that corresponded with the major groupings of success factors, potential measures that aligned with those questions, approaches for measurement and next steps for moving forward with an evaluation agenda for their assigned conceptual area. From this highly engaged and collaborative work, a matrix of priority questions, measures and data sources to guide the conduct of pilot studies was designed and the initial evaluation pilot studies carried out.

Stakeholders wanted to determine how the process of clinical trial protocol development could be improved to increase efficiency and shorten the timeline to complete clinical trials

Integration of utilization-focused evaluation and business process modeling

This report focuses on studies addressing the top priority question articulated by task force members in one of the four success factor 'regions', specifically: operations, policy and resources. Above all else, stakeholders wanted to determine how the process of clinical trial protocol development (and implementation) could be improved to increase efficiency and shorten the timeline to complete clinical trials. Specific 'sub-questions' included:

- How long does each phase of the protocol development/implementation take?
- Which elements are the most rate-limiting?
- What can be done to shorten the timeline without compromising scientific quality?
- How can the process be improved?
- What might be reasonable targets for each phase?

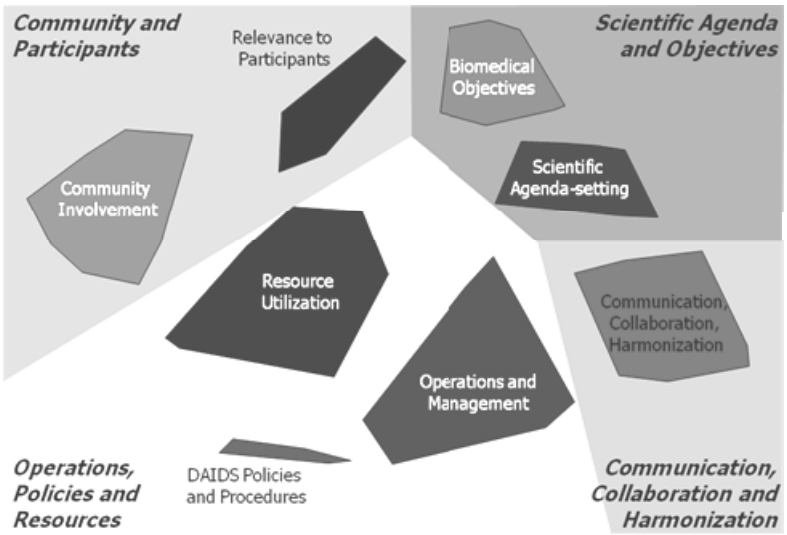

Figure 1. Collaboratively authored concept map of HIV/AIDS clinical trials network success factors
Source: Kagan *et al* (2009)

At this juncture the integration of utilization-focused evaluation (Patton, 2008) with business process modeling was initiated. Business process modeling involves the representation of the flow and logic of activities or actions in a business or organization so that the processes can be studied, simulated, monitored and potentially improved (Havey, 2005; Schedlbauer, 2010). The flow of activities and actions can be sequential and linear or it can be dynamic and nonlinear and involve feedback processes (Edquist and Hommen, 1999). The key in integrating evaluation with process modeling is to identify points or 'markers' along the process flow where measurement can be operationalized. Note that such markers will be useful whether the true process is linear or nonlinear, although one's interpretation of the results may differ in each case.

Clearly, the stakeholders had articulated a need for practical evaluative information about their most important business process — the development of clinical trials protocols — asking where the obstacles were, their relative contribution to the overall timeline, and how the time for protocol development could be shortened. The integration with business process modeling was formed by linking these evaluative questions to specific 'time-to-event' data which provided the ability to analyze the actual duration of each element of the clinical protocol development process specifically, and by inference (albeit with limitations) a view of the resource consumption associated with each phase.

Briefly, time-to-event data was obtained from the protocol management component of the Division of AIDS Enterprise System (DAIDS-ES) (Kagan *et al*, 2010), a management information system which had been modeled around a cross-network harmonized protocol lifecycle paradigm, featuring standardized protocol status, milestone and event definitions. Providing an accessible, quality-assured source of specific date-based protocol tracking information from across the networks, the DAIDS-ES enabled precisely the type of time interval analyses that were needed to answer the key questions posed. The results presented herein were based on 97 protocols over a two-year period from April 2006 to April 2008.

Results

Primary analyses determined the interval for each of six discrete statuses (or elements) of the protocol lifecycle, beginning with the initial submission of a protocol, through the enrollment of the first participant:

1. *Scientific review* (beginning with receipt of protocol/concept)
2. *Regulatory review* (NIH and FDA regulatory consideration)
3. *Pending* (including several 'in progress activities')
   - 3a. Regulatory and other specific protocol requirements
   - 3b. Database, case report forms, data screens, randomization
   - 3c. Clinical trials agreement and contract development
   - 3d. Study product acquisition, distribution, importation
4. *Open to accrual* (*pending* activities complete; protocol open for participant enrollment)
5. *Enrolling* (enrollment of the first participant on a protocol)
6. *Protocol registration* (an element in protocol implementation; site and investigator credentialing, institutional review board approval).

Figure 2 shows a composite view of the median duration for each of the six protocol statuses/ elements across the protocol set analyzed. (Protocols for which missing time points precluded a specific interval determination were excluded from that calculation, but were included in other median interval analyses where they had data.) The graph shows both the absolute and relative duration of each protocol status. The median time from initial concept submission until a protocol reached enrolling status was slightly more than one year. On average, iterative scientific review of new trial concepts took longer than four months, with approximately the same median time required for the collective activities of the pending phase. In contrast, the median time for protocol registration, during which clinical research sites complete requirements to be able to initiate protocol enrollment, was 160 days for US sites, whereas meeting the same requirements, on average, took over 500 days for non-US sites. In some instances, the long time involved in meeting requirements for non-US sites resulted in sites being excluded from protocols.

Without consideration of the underlying processes/ activities captured in each protocol status, the value of these time-based results would be of limited use. However, to those with responsibilities for managing clinical research, these kinds of data can guide and inform more detailed studies as to how operations, policy and resource utilization impact the efficiency with which clinical trials are developed and implemented. For example, protocol registration, in essence a repetitive 'requirements' process (versus a creative one) takes longer than all other pre-enrolling statuses. This suggests that there ought to be ways to streamline this process in order for trials sites to begin getting participants into trials sooner. Also, that there is such a substantial difference between the median protocol registration times for US vs. non-US sites warrants examination, given the importance of conducting HIV/AIDS clinical trials in the areas of the world hardest hit by the epidemic.

Focusing on the time for protocol registration for US and non-US sites shows that the US sites, with

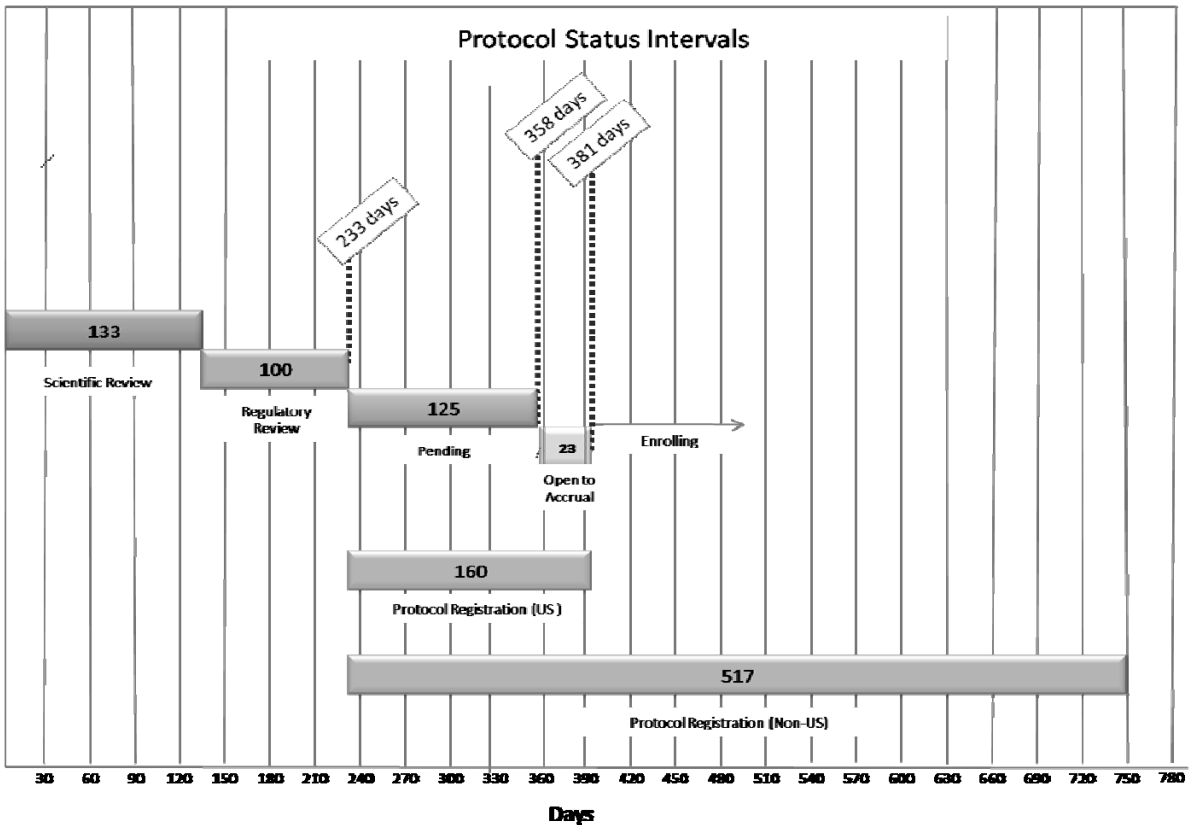

Figure 2. Status intervals for HIV/AIDS clinical trials network protocols

few exceptions, are clustered tightly around the 160-day median and that relatively few sites are either much quicker or slower than the others, in getting through the process (Figure 3). This consistency suggests that there probably are similarities in how these sites carry out their protocol registration activities. By contrast, approximately 16% of the non-US sites complete protocol registration in one third less time compared to the group median (343 days vs. 517 days) (Figure 4).

Even though these sites still take roughly twice the time needed for protocol registration at US sites, there may be some key differences in the ways they carry out this function compared to the others that take much longer. Looking at the enrolling status interval, the results indicate that it's not simply that every process takes longer at non-US sites. Once a trial is opened to accrual, and a site is registered on the protocol, the median time to enroll the first participant was 65 days for US and 70 days for non-US sites.

For a more detailed comparison of these time-to-event processes, Kaplan-Meier (K-M) analyses were conducted for the same two intervals (i.e. protocol

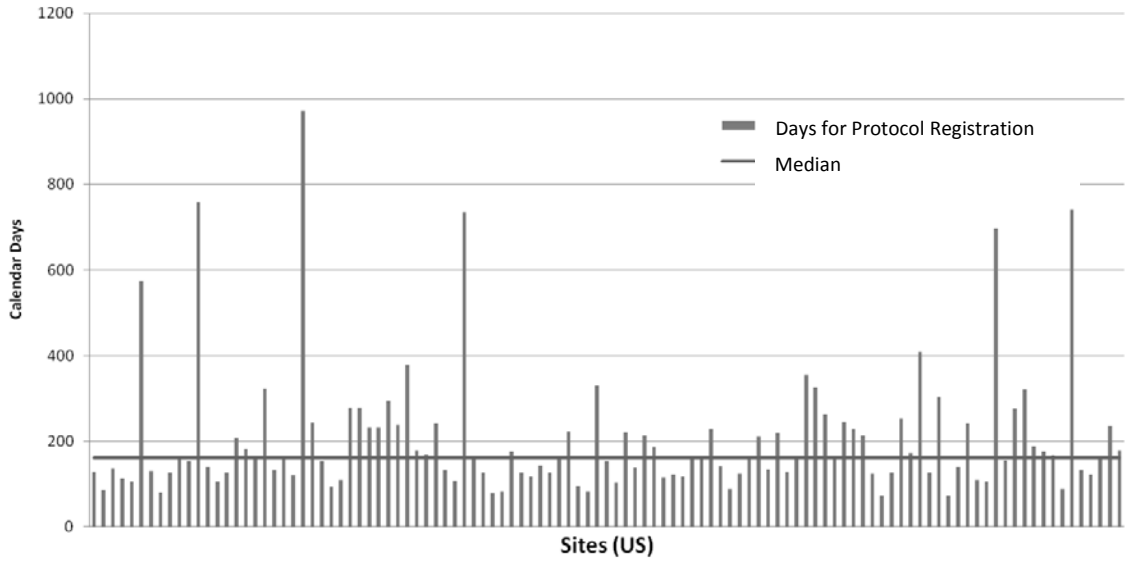

Figure 3. Days for protocol registration, US clinical research sites

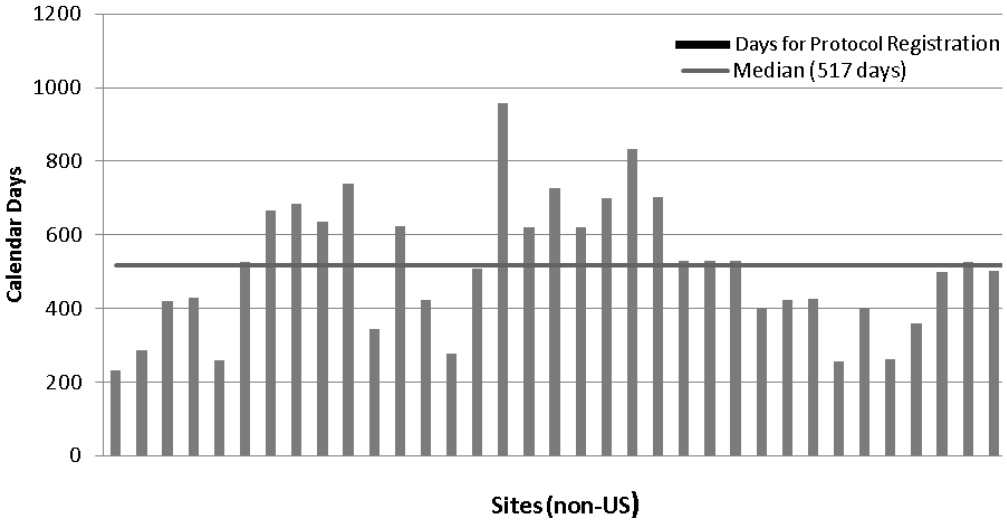

Figure 4. Days for protocol registration, non-US clinical research sites

registration and enrolling) for US and non-US sites. Modeling the time required to reach a well-defined endpoint through survival analysis offers a more precise picture of the timing patterns across the research process lifecycle (vs. comparisons of the number of days). For each interval, survival probability was calculated as the number of cases surviving divided by the number of cases that reached the terminal event. The probability of surviving to any point was estimated from the cumulative probability of surviving each of the preceding time intervals, calculated as the product of preceding probabilities. Since all protocols used in the K-M analysis had reached the respective endpoints of the two intervals under investigation, all cases were uncensored.

As shown in Figure 5, for protocol registration, the survival curves for US and non-US sites were significantly different (χ^2 = 39.34, p < 0.001; log-rank Mantel-Cox test). At the 50% survival mark, at which point half of the sites had completed registration, the remaining international sites were expected to take 508 additional days to reach the endpoint milestone (registration), whereas for the US sites, 160 more days (three times fewer) were required. These findings more clearly reveal the distribution of results across sites and confirm the median estimates for a much longer time for international sites to register for protocols. However, this same contrast was not observed once protocols reached the open to accrual status. As suggested in the earlier comparisons, the K-M analyses (Figure 6) confirmed no significant difference between US and non-US sites, for the time it takes to enroll the first participant on a protocol (χ^2 = 1.57; p = 0.282; log-rank Mantel-Cox test). Thus, while the cumulative time for US sites to move all protocols through the two consecutive time periods is significantly less than for international sites, the difference can be attributed to the protocol

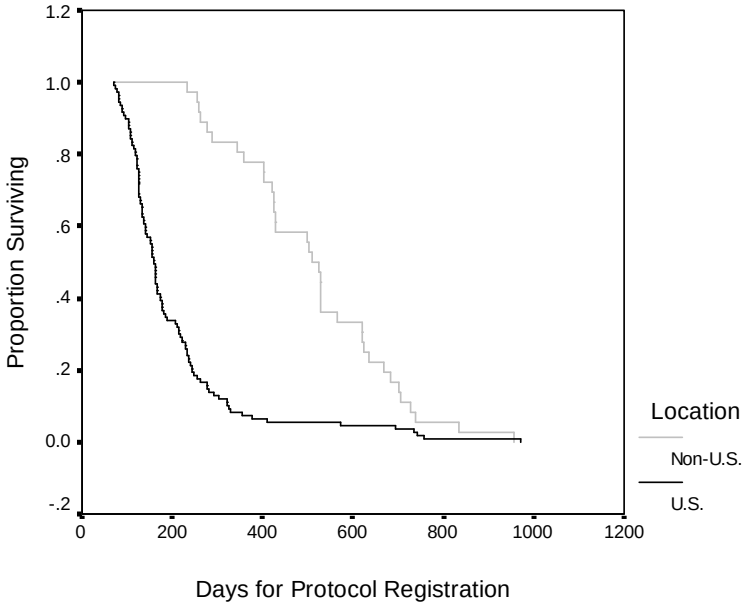

Figure 5. Kaplan-Meier plots for protocols in US and non-US sites: days for protocol registration

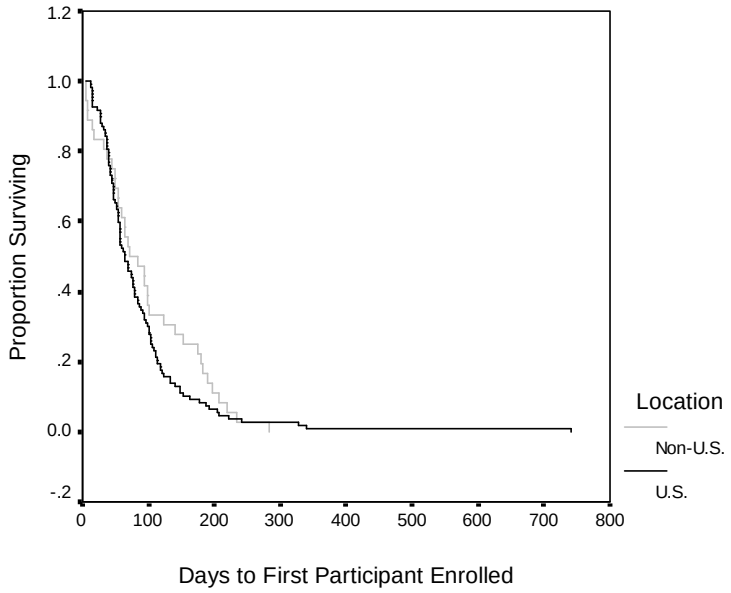

Figure 6. Kaplan-Meier plots for protocols in US and non-US sites: days to first participant enrolled

registration-related processes and not the first participant accrual period.

Taken together, the results of both the simple median analyses and the K-M curves show how time-based analyses can provide a rationale for the prioritization of research process analysis and re-engineering, as well as a means for monitoring the impact of policy modifications, resource utilization, re-engineered processes and best practices. K-M analyses such as those employed here can be used to statistically test the effect of process interventions on the timing patterns of protocols across different intervals of the research lifecycle. K-M analyses also allow for the inclusion of protocols that are within the interval under investigation but have not yet completed the interval (i.e. censored cases), thereby affording greater precision in estimating the rate at which protocols reach different milestones. Future K-M analyses will include additional variables (e.g. protocol phase, treatment vs. prevention, complexity, size, numbers of participating sites) in order to model covariate effects to gain an even better understanding of the factors contributing to these time-to-event results.

Kaplan-Meier analyses such as those employed here can be used to statistically test the effect of process interventions on the timing patterns of protocols across different intervals of the research lifecycle

Even in instances where process re-engineering, policy improvement and/or more efficient resource utilization appear infeasible, studies of this sort can provide 'as is' evidence-based time projections for protocol development which can support more accurate planning and budgeting for clinical trials. But the greatest potential of K-M models is in statistically assessing the effects of subsequent process interventions on clinical trials efficiency.

Discussion

The trend toward large-scale scientific research initiatives calls for the development of systems for managing and evaluating multi-institutional, collaborative scientific research. The need for evaluation systems is particularly great given increasing pressure for accountability within public programs. Yet, large-scale science has its own unique goals, context, requirements, and outcomes that must be taken into account when designing ways to evaluate success. Evaluation of such research programs needs to focus on gathering systematic evidence on program performance and relying on multiple lines of evidence to draw conclusions about efficiency and effectiveness as reported to program managers, participants and other stakeholders, and the public at large (Cozzens, 1997). An ideal scientific research enterprise is viewed as one that:

- Invests in work that impacts significant social and scientific challenges and responds to new discoveries;
- Fosters a wide network of relationships that generates relevant questions, recognizes emerging issues, and sustains significant, cutting-edge programs of work;
- Develops and nurtures the human and organizational capacity to conduct research; and

- Recognizes and communicates its impact on the world (Pardo *et al*, 2002).

The evaluation of large-scale research initiatives is a relatively new discipline. Consequently, there are few models and examples to guide work in this area. Some have suggested that what is needed is a theory of innovation that describes from a multiple-level systems perspective (macro, meso, micro) the complex networked structure of the research enterprise (Jordan *et al*, 2008). Others have argued for a model that encompasses efforts to estimate the 'societal quality of research' rather than only the scientific quality (Van der Meulen and Rip, 2000; Larédo, 2001).

In contrast to these more theoretically focused efforts, our work is motivated by a more pragmatic and empirical emphasis on utilization. We undertook an integrative approach to evaluating the NIAID HIV/AIDS clinical trials networks with the relatively modest goal of increasing the efficiency with which clinical researchers capitalize on new science to speed the development of improved interventions for this, and potentially other diseases. While we support the efforts of our more theoretically driven colleagues to address the complex organizational and systems issues involved in research evaluation, our approach, while perhaps less ambitious and theoretically encompassing than theirs, emphasizes the practical empirical utility of obtaining estimates of the duration of key segments of the research process, and the value of such estimates for process improvement generally.

Beginning with an evaluation planning stage, a stakeholder-constructed framework of critical success factors was developed that enabled a prospective view of four major evaluative domains. For each domain, broad evaluation questions were articulated by stakeholders, and addressed through pilot studies designed to generate information in a continuous fashion across the research lifecycle. Iterative cycles of focused evaluation 'experiments' were (and are being) designed to test the feasibility and utility of the data, sources, and methods, to address specific evaluation questions in each domain. This approach is viewed as a scientific process designed to generate results that can be utilized in the near-term to improve network functions, and incrementally improve the quality of the overall evaluation system as the state of knowledge evolves, in effect a 'science of science management.' As new information is gathered and changes are made based on that feedback, specific questions are expected to change over time.

The majority of our studies to date have been descriptive in nature, documenting practices across the network enterprise and enabling a clearer view of research processes, including identification of similarities, differences, gaps and opportunities. Accurate measurement tools or instruments, reasonable standards or targets and identification of feasible points of intervention in existing processes depend upon the documentation of current practice. But once this descriptive work is complete, it is expected to lead naturally to the development of hypotheses regarding potential process improvements. The measures and methods piloted here will be useful in testing these hypotheses in a rigorous manner.

By their very nature, the HIV/AIDS clinical trials networks (a potential exemplar for large, global clinical research programs) must evolve dynamically to stay in step with the rapid scientific, ethical and demographic changes that characterize the epidemic. Accordingly, the evaluation activities and processes need to be continuously adjusted to provide information that aligns with the research initiative. In this report, we have described our early experience using an approach that integrates stakeholder-driven, utilization-focused evaluation, with elements of business process modeling with the objective of identifying ways of improving the efficiency of clinical trial development.

Our initial results using time-to-event data indicate that this approach can (at least within certain domains) reveal the ways in which discrete elements of a complex process (e.g. clinical trial protocol development) contribute to overall timelines, and can guide more fine-tuned analyses of operations, policy and resource utilization with the potential to improve clinical research efficiency.

Our efforts build upon and complement the research of Dilts *et al* (Dilts and Sandler, 2006; Dilts *et al*, 2006, 2008, 2009), whose work has incorporated extensive research process mapping with analyses of the time to design and activate oncology clinical trials in a variety of research settings, including community-based clinical trials, the National Cancer Institute (NCI) Comprehensive Cancer Centers (CCC), and NCI's Clinical Trials Cooperative Groups. But we go considerably beyond that pioneering work through our use of rigorous methods for conceptualizing a broader framework of evaluation questions and through incorporation of a statistical modeling approach that is valuable for both descriptive and hypothesis-testing purposes.

Even at this early stage of our investigations, and despite differences in science, demographics, terminology, structure and processes, we can still see hints of both similarities and differences between our findings in HIV/AIDS and the cancer clinical trials. For example, the median time for NIAID scientific review of HIV/AIDS trial concepts (all phases) was 133 days, compared with 126 days for the NCI Cancer Therapy Evaluation Program (CTEP) review of phase III concepts from the Cancer and Leukemia Group B (CALGB) (Dilts *et al*, 2006), and 70 days for the NCI community-based and CCC trials (Dilts and Sandler, 2006).

Median times from initial concept submission to trial activation (open to accrual) varied more widely, ranging from 171 to 191 days for NCI community-based and CCC trials, to 381 days for HIV/AIDS network trials, and 602, 784 and 808

days respectively for phase III trials in NCI CTEP, CALGB, and the Eastern Cooperative Oncology Group (Dilts and Sandler, 2006; Dilts *et al*, 2006, 2008, 2009). Interestingly, in the cancer trials, no differences were found in the time to open a trial based on phase (Dilts and Sandler, 2006); our own studies are currently investigating whether the same is true or not for HIV/AIDS network trials.

Lastly, a particularly interesting observation emerging from these kinds of studies is that despite a common perception among clinical researchers that IRB review and approval is a major rate-limiting factor for clinical trials (Burman *et al*, 2001, Emanuel *et al*, 2004, Gunsalus *et al*, 2006), time-to-event analyses (Dilts and Sandler, 2006; Trochim, 2010) suggest otherwise. Thus, while streamlining efforts should not be discouraged, data from time interval studies indicate that shortening the time for IRB review would not be expected to significantly affect protocol development times without also reducing the time required for other much more lengthy processes (e.g. contracting, in certain settings) (Dilts and Sandler, 2006).

Interest in business process analysis and time-to-event studies, in the context of clinical research, has been growing. NCI, having taken the lead in this area, is now actively utilizing and applying its findings to try to reduce steps and procedures that do not add value to the science, safety or ethics of trials, as well as experimenting with more specified time limits for various protocol activities. NIAID, in late 2007, launched its Barriers to Clinical Research initiative with the goal of identifying the key policies, practices, regulations and legislation governing clinical research that limit effectiveness and efficiency, but do not advance human subject safety, research ethics or study quality. Activities under this initiative include process analysis and re-engineering, as well as monitoring and evaluation with priorities to:

1. Facilitate clinical research in the setting of conflicting US and international regulations;
2. Improve the efficiency of ethical review through optimal use of alternative IRB models;
3. Provide greater assistance to NIAID intramural investigators in meeting clinical research requirements;
4. Streamlining serious adverse event reporting; and
5. Optimizing the return on investment in clinical site monitoring.

Similarly, the National Center for Research Resources, which funds and oversees the nationwide consortium of Clinical and Translational Science Awards (CTSA), has mounted a significant effort to improve clinical research management and increase efficiency within and across these centers. Its Evaluation Key Function Committee and Clinical Research Management working groups are actively addressing issues of protocol processing, including:

- Designing, drafting, and editing of protocols;
- Review and revision by supervisory and regulatory bodies;
- Contracting and other intellectual property issues;
- Compliance with regulations and policies budgeting and funding considerations;
- Administrative, facilities, and technical support issues.

This group has, during the past year, undertaken studies to identify obstacles, improve processes, and develop objective metrics which can be used for process improvement for both IRB review and contracting (Trochim, 2010). These efforts not only hold promise for greater efficiency in investigator-initiated clinical research across the country but, since many of the CTSA institutions participate in NCI, NIAID, and other NIH Institute and Center-sponsored trials, also offer the potential for broad systematic improvements in clinical research across many disciplines. Finally, the FDA has utilized survival analyses to look at the impact of prescription-drug user fees on approval times (Berndt *et al*, 2005), providing another example of how these kinds of time-based studies are being utilized in the context of clinical research.

Returning the focus to NIAID HIV/AIDS trials networks and the time-to-event analyses performed in this context, a number of specific follow-on actions have taken place that build upon what's been learned. Recognition of the lengthy times for protocol registration (discussed above) was instrumental in fueling the development and implementation of a new component within the DAIDS-ES clinical trials management system, to support online protocol registration. Using the system, clinical research sites can now electronically tender protocol registration submissions, track and monitor progress of submissions, provide updated/corrected information, and respond to requests for additional materials. At the other end of the process, regulatory specialists are supported in managing protocol registration review and decision-making, and can utilize system data to monitor business process performance for continual improvement. For this and other processes (e.g. serious adverse event reporting, clinical site monitoring) where business processes with discrete steps have been well-characterized, information technology solutions are not only saving time, but also providing databases for business process and value

Interest in business process analysis and time-to-event studies, in the context of clinical research, has been growing

monitoring. The K-M methodology described here will be essential in assessing whether these changes have a significant effect on clinical trials efficiency.

Time-based business process analyses are not without their critics, who frequently point to the fact that processing time has no obvious relation to the quality of the outcome. There is no debate that, where possible, quality should be evaluated. Significant advances have been made in recent years, especially in the use of publication data such as co-authorship patterns and citation rates to assess the quality of research. Time-based measures, in contrast, provide information that people intuitively understand and, with relevant background knowledge, can react to in terms of a sense of 'reasonableness'.

Time measures can also be easily integrated with other information, such as costs, to gain accuracy in financial projections and reduce trial cost overruns due, for example, to overly optimistic accrual projections. For example, a recent CenterWatch survey of clinical trials sites found that 90% of industry trials fail to complete enrollment within the planned time period, resulting in an average delays to completion of at least six weeks (Bain, 2005). A 2009 report from Cheng *et al* (2009) showed that 40% of the NCI CTEP trials studied did not reach their minimum accrual goals; interestingly, increasing trial development time correlated with decreased likelihood of successful trial enrollment.

Another way of looking at time-based process intervals is that of opportunity cost. Al-Shahi Salman and colleagues (2007), based on actual randomization rates from participating trials sites, have shown how delays to clinical research in the UK, caused by research governance approval processes, translate to numbers of participants that could have been enrolled into studies during that time.

And finally, looking to the future, it is increasingly recognized that the lengthy time requirements for clinical research are figuring as a significant disincentive for young physicians considering careers in medical research. Taken together, time-based process measurements can contribute important information for assessing and managing clinical research operations, policy and resource utilization and in some instances may help to predict the likelihood of trials meeting their accrual goals.

Going forward our intent is to build on our increasing experience and sophistication gained from the initial studies, to optimize evaluation measures, and ensure the accuracy, relevance, and utility of evaluation information to serve the overall goal of improving the efficiency and effectiveness of these vital global health research programs. We plan to emphasize the use of both quantitative and qualitative data, systematically integrated for analysis and reporting, in order to develop summary performance indicators and specifications for evaluation measures.

More specifically, we plan to continue working with the diverse stakeholders of the HIV/AIDS networks (and perhaps other clinical research programs), identifying utilization-focused evaluation questions and coupling these with business process-based analyses and investigations. The work reported herein focused on only one of four regions (operations, policy and resources) of the HIV/AIDS network success factor framework (Figure 1). We are presently extending our studies in this area to include two intervals not yet captured:

1. The time from origination of a trial proposal to concept submission; and
2. The time to enroll a trial.

In addition we are beginning to analyze two 'composite' intervals: protocol development (from concept to first enrollment), and protocol implementation (from first enrollment to last participant off-study).

We are also undertaking and planning further studies in the other three regions. In the scientific objectives and agenda region, we are currently assessing the scientific impact of network research using bibliometrics as a tool to evaluate the selection of research objectives and priority setting in the networks. We are also interested in determining the time it takes to translate HIV/AIDS clinical research findings into medical practice. For this we are planning studies with medical educators and organizations that develop clinical guidelines, in order to determine how to gauge the level of penetration of network findings among HIV care providers, and assess the translation of network research outputs into standards of care and clinical guidelines (Balas and Boren, 2000).

In the community and participants region, we are examining the roles and functions of community members in the HIV/AIDS research networks and the relationship, if any, to perceptions of network research relevance within affected communities.

Finally, within the coordination, communication and harmonization region, we are determining the impact and effectiveness of cross-network coordinating groups, web-based information portals, and efforts to harmonize network policies and procedures, especially as relates to the accomplishment of network priorities. In addition, it is anticipated that the results of ongoing and future studies will not only be useful in improving the current networks, but may also provide information on network structure, design, and processes which can inform planning for the next generation of NIAID (and other) clinical research networks.

By comparison with previous network evaluation approaches that have utilized segmented, 'snapshot' approaches to rate and/or compare networks or clinical research sites to one another, the utilization-oriented focus, with its continuity across the research lifecycle and practical application, is broadly seen as adding greater value and, at the same time, is perceived as less threatening by the research

community. Experience shows that when investigators view evaluation as something 'external', imposed by the sponsor, and to which they have had little input with respect to review criteria or measures (e.g. peer review, 'expert' panels), inclinations towards suspicion (or mistrust) can dispose them to respond in ways intended primarily to limit potential harm, rather than risk any negative critique.

Arguably, approaches such as that described here, emphasizing practical knowledge that can be utilized to strengthen the research effort, may favor the development of a sustainable culture of evaluation that will tend towards empowering investigators to take greater ownership in assessing their programs. This type of evaluation equity would seem more balanced, durable and, hopefully, a step forward in terms of how evaluation science can help to advance clinical science in the interest of improved public health.

Conclusion

Clinical trials are an essential component of research to develop treatments and preventions for human disease. Increasingly, such studies are being conducted globally under many different (sometimes conflicting) regulatory authorities, across a large number of institutions, involving multidisciplinary investigators and with the input of numerous diverse communities. In these ways, global clinical trials share many of the challenges associated with other large complex research initiatives, one of which is the need for evaluation models that can comprehensively assess such programs, providing meaningful feedback to investigators, funders and constituents that can be utilized to gauge progress and identify opportunities for improvement.

This report examines how the integration of utilization-focused evaluation with elements of business process modeling can reveal opportunities for systematic improvements in global clinical research. We highlight the importance of:

1. Collaboratively authored evaluation frameworks;
2. Integrating evaluation efforts across multiple success factor domains;
3. Both qualitative and quantitative approaches; and
4. Researcher ownership in the evaluation process.

Successfully applied, elements of this approach can enhance the ability to capitalize on new science and speed the development of improved interventions for human disease.

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