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Assessing the Challenges of Multi-Scope Clinical Research Sites: An Example from NIH HIV/AIDS Clinical Trials Networks

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Abstract

Rationale, aims, and objectives—Large-scale, multi-network clinical trials are seen as a means for efficient and effective utilization of resources with greater responsiveness to new discoveries. Formal structures instituted within the National Institutes of Health (NIH) HIV/AIDS Clinical Trials facilitate collaboration and coordination across networks and emphasize an integrated approach to HIV/AIDS vaccine, prevention, and therapeutics clinical trials. This study examines the joint usage of clinical research sites as means of gaining efficiency, extending capacity, and adding scientific value to the networks.

Methods—A semi-structured questionnaire covering 8 clinical management domains was administered to 74 (62% of sites) clinical site coordinators at single- and multi-network sites to identify challenges and efficiencies related to clinical trials management activities and coordination with multi-network units.

Results—Overall, respondents at multi-network sites did not report more challenges than single-network sites, but did report unique challenges to overcome including in the areas of study prioritization, community engagement, staff education and training, and policies and procedures. The majority of multi-network sites reported that such affiliations do allow for the consolidation and cost-sharing of research functions. Suggestions for increasing the efficiency or performance of multi-network sites included streamlining standards and requirements, consolidating protocol activation methods, using a single cross-network coordinating center, and creating common budget and payment mechanisms.

Conclusions—The results of this assessment provide important information to consider in the design and management of multi-network configurations for the NIH HIV/AIDS Clinical Trials Networks, as well as others contemplating and promoting the concept of multi-network settings.

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Keywords

HIV/AIDS; multi-network clinical trials; cross-network collaboration; resource sharing; clinical trial efficiency

Introduction

Large networks and consortia have figured prominently in the National Institutes of Health's (NIH) efforts to reengineer the clinical research enterprise [1,2]. The NIH HIV/AIDS Clinical Trials Networks, within the National Institute of Allergy and Infectious Diseases (NIAID) and the Division of AIDS (DAIDS), are an example of a large-scale scientific endeavor engaged in clinical research to support the development of therapies, vaccines, and other prevention strategies for HIV/AIDS. The six NIH HIV/AIDS Clinical Trials Networks¹, each with independent structures and operational cores, are deeply rooted in pathogenesis research and practically oriented, with missions devoted to improving clinical practice and health outcomes. Built on the premise that such systems are positioned to conduct research on a variety of health topics simultaneously at multiple locations [3], the networks were re-designed in 2006 to facilitate collaboration and coordination of the networks through resource sharing and consolidation, thereby expediting successful discovery and benefit. Collaboration across the NIH HIV/AIDS Clinical Trials Networks through the joint usage of common clinical research sites (CRSs) is widely seen as a means of gaining efficiency, extending capacity, and adding scientific value to the research enterprise. The centralization of these clinical trials allows them to take advantage of accumulated scientific knowledge while utilizing standardized methods of protocol development, scientific and safety review, and safety reporting [4]. Several have described successful multi-center collaborative research networks where resources were shared in order to meet the common objectives of a research enterprise [5,6]. Despite this, the shared use of site resources and capacities are not without challenges.

The movement toward large-scale, multi-network clinical trials raises considerations for how such configurations can be successful through innovative solutions to technical challenges. Some evidence suggests that productivity can be modified in research consortia, where optimization of collaborative processes contributes to achievement of common scientific goals [7,8]. However, there may be drawbacks to working across networks, including increasing complexity, loss of autonomy, and information asymmetry, all of which can hamper innovation and learning [9]. Size, structure, and complexity impact the ability of multiple organizations to adapt in a collaborative environment and may modify efforts to maximize the shared use of resources [10]. Challenges related to purpose, sustainability, information complexity, and cooperative spirit can compromise the success of research alliances [11]. Moreover, several technical and human barriers associated with the interoperability of information systems have been identified [12] and others have found multi-center cooperative group studies require substantially more preparation and support than grants for single-center clinical or laboratory research [13].

Given these issues, the purpose of this study is to examine the differences across several clinical trials management domains of the joint usage of common clinical research sites (i.e. multi-network configurations). Through the administration of a semi-structured

¹The six NIH HIV/AIDS Clinical Trials Networks include the AIDS Clinical Trials Group (ACTG), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network (HVTN), the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT), the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), and the Microbicide Trials Network (MTN).

questionnaire to both single- and multi-network CRS coordinators, we determined which clinical trials management activities were highly challenging. Moreover, we gathered input from multi-network CRS coordinators on the ways that efficiencies may be realized and improved in such large-scale configurations, thus providing insight about how the approach may affect the processes and outcomes of clinical trials research.

Methods

Sample

Multi-network configurations are operationalized at both the clinical trials unit (CTU) level and the clinical research site (CRS) level. Multi-network CTUs are clinical trials units affiliated with two or more networks, independent of the number of networks that are affiliated with sites. Multi-network CTUs oversee both single- and multi-network affiliated CRSs.

A clinical trials unit (CTU) is a specialized biomedical research unit, typically an organization or institution, which centrally coordinates clinical trials. CTUs are composed of multiple components, including an administrative office, often with one or more community advisory boards (CABs), one or more laboratories, and one or more pharmacies. CTUs conduct various clinical research activities at the unit-level, including but not limited to: data management, quality management, regulatory assurance, and training. CTUs provide the scientific and administrative expertise to their affiliated CRSs, creating an infrastructure to support the NIH HIV/AIDS Clinical Trials Networks.

A clinical research site (CRS) is a component of a CTU, and it is defined as a discrete location (e.g. hospital, outpatient clinic, community health center, private practice, local health department clinic) with appropriate access to identified trial participants (e.g. demographics, incidence, and prevalence of HIV/AIDS). CRSs conduct site-specific clinical research activities. Responsibilities of CRSs are to: (a) recruit, screen, and enroll participants; (b) collect and process specimens; (c) perform required protocol assessments and procedures; (d) collect, manage, and submit clinical research data; (e) monitor for, assess, and report adverse events; and (f) create, maintain, and store research records, including source documents, regulatory files, and case report forms (CRFs). The distribution of NIH HIV/AIDS CRSs are spread over 20 countries, and it has been predominantly reflective of the communities most heavily impacted by the HIV/AIDS epidemic. CRSs may be geographically clustered near the CTU or they may be spread apart. Additionally, CTUs may be located within the US and their affiliated CRSs outside of the US, or vice versa. The CTU-CRS structural relationship (see Figure 1) has been viewed by NIAID as an important means for developing and extending the clinical research capacity at resource-limited sites, including non-US based sites.

Survey Development

We convened a small evaluation team made up of representatives of the Cross-Network Site Coordinator Working Group facilitated by the Office of HIV/AIDS Network Coordination (HANC) to provide specific input on the: (a) design, development, and administration of a survey; (b) interpretation of the data collected; and (c) implications of the results. These perspectives and experiences were instrumental in aiding the identification of key areas for assessment, analysis, and for the utilization of findings for improvement. In order to ensure adequate coverage of the clinical trials management responsibilities of the sites, we began with a review of the key clinical trials management activities. Over a period of several weeks, the evaluation team helped to identify eight key clinical trials management domains, reviewed the definitions of the eight domains, and clarified, edited, and contributed

additional activities for each domain. Table 1 lists and defines the eight domains covered in the inquiry.

Through several iterative reviews, the evaluation team identified a subset of items that best represented each of the eight domains. Next they crafted a set of questions based on the items selected for each domain and then drafted an online version of the survey for further input. The Office of Clinical Site Oversight (OCSO), responsible for oversight, evaluation, and monitoring of clinical sites associated with the NIH HIV/AIDS Clinical Trials Networks, as well as others within DAIDS reviewed the items and provided input throughout the survey development process. Additional feedback was gathered through beta testing with a small set of CRS coordinators who volunteered to review the survey for relevancy and applicability to their clinical management settings.

The final survey consisted of several multipart questions asking CRS coordinators affiliated with multi-network CTUs about the specifics of their affiliations and their perceived level of challenge in completing specific activities at their sites across the eight domains. The survey also included several open-ended questions asking CRS coordinators about their perspectives working with their affiliated CTUs, their perceived areas of greatest challenge, and any suggestions about opportunities for efficiencies to be gained in the multi-network context. The survey protocol and procedures were reviewed and approved as exempted research by the Fred Hutchinson Cancer Research Center's Institutional Review Board.

Data Collection and Analysis

To obtain a full listing of the CTUs and their respective CRSs, we queried the Division of AIDS Enterprise System (DAIDS-ES) for information on the number of multi-network CTUs. The DAIDS-ES is a management information system that warehouses data elements reported by the network-specific data management centers, and it includes information on CRS locations and affiliations [14]. At the time of data extraction, there were 42 multi-network CTUs listed in DAIDS-ES with 120 affiliated CRSs, including 65 single-network CRSs and 55 multi-network CRSs. Figure 1 shows the relationship of the CTUs and CRSs from the data extraction.

A list of the CRS coordinators from the 120 CRSs affiliated with the 42 multi-network CTUs was extracted from DAIDS-ES, and an invitation to participate in the survey was sent via email to CRS coordinators at all 120 sites. Both single- and multi-network CRSs (all affiliated with multi-network CTUs) were asked to participate to better understand the complexities and challenges from both perspectives. CRS coordinators were instructed to complete and submit one survey per site; however, they were invited to consult with other research site staff, as needed. Online and paper surveys (for those sites that determined a paper submission was more useful) were collected from May 7 through June 12, 2012.

We conducted both descriptive and inferential analyses across the eight domains. These analyses included comparisons between single- and multi-network sites in order to detect differences in group responses. The quantitative data was analyzed using SPSS V16.0. We also analyzed the responses to the three open-ended questions through traditional qualitative data reduction and coding techniques to identify themes for each of the questions. Two researchers (SR & MC) experienced in qualitative analysis worked in tandem to iteratively review the data reduction process and confirm the emergent coding scheme. Employing a keyword in context (KWIC) approach [15], keywords were identified and highlighted in the text responses to each of the three open-ended questions, separately. The keywords were then grouped together to form categories of meaning, of which were subsequently coded within each open-ended question. The coded categories were reviewed by the two researchers, and the redundant or overlapping codes were confirmed and collapsed. The

final set of categories of meaning constituted unique constructs and were retained as themes for each open-ended question.

Results

We received survey submissions from 74 out of 120 (62%) CRSs, which were affiliated with 37 out of 42 (88%) multi-network CTUs. These included surveys from 31 out of 65 (48%) single-network CRSs and 43 out of 55 (78%) multi-network CRSs (see Figure 1). Descriptively, about the same proportion of single- and multi-network CRSs were located in the US. Similarly, about the same proportion of single- and multi-network CRSs were affiliated with US based CTUs. In terms of multiple pharmacies and community advisory boards (CABs), the same proportion of single- and multi-network CRSs were observed. In contrast, a significantly greater proportion of multiple statistical and data management centers (SDMCs) and multiple operations centers were found for the multi-network CRSs than the single-network CRSs (64% vs. 10%; 61% vs. 27%, respectively). Table 2 lists the results of the descriptive analysis.

For each of the eight domains, we conducted a series of Mann-Whitney tests of significance to determine if multi-network sites reported significantly more moderate and significant challenges than single-network sites. To facilitate these comparisons, we dichotomized the ratings from CRS coordinators on their perceived level of challenge into two levels: “low challenge” (i.e., minimal, some) and “high challenge” (i.e., moderate, significant). We then assessed the frequency of which each activity was endorsed as either a low challenge or high challenge. The results of these analyses are reported in Table 3.

In the domain of *Study Prioritization*, multi-network CRSs endorsed three activities as high challenges more frequently than single-network sites. Specifically, “determining criteria for which studies should be prioritized,” “establishing an equitable process for study priority setting,” and “ensuring consistency with network-specific study priorities” were significantly reported by multi-network CRSs as more challenging than single-network CRSs ($p = .03$; $p = .02$; $p = .02$, respectively). Under the domain of *Management and Operations*, none of the activities were endorsed by multi-network CRSs as a high challenge more frequently than single-network sites. However, “managing IRB submissions” was one of the most frequently high challenge activities endorsed by both single- and multi-network sites. In the *Community Engagement* domain, only one activity, “providing support to site CABs (e.g. administrative, logistical)” was rated as a high challenge for multi-network CRSs significantly more than single-network CRSs ($p = .04$). For both types of CRSs, “disseminating results to the broader community” was endorsed as a high challenge in more than 20% of all sites. Under *Staff Education and Training*, “meeting network-specific requirements for staff training” was rated as high challenge for multi-network CRSs significantly more than single network CRS ($p = .02$), with none of the single-network sites indicating this as a high challenge.

None of the activities were endorsed by multi-network CRSs as a high challenge more than single-network CRSs in the *Protocol Implementation* domain. Nevertheless, several high challenge activities reported by both types were found in this domain. These included “recruiting study participants,” “recruiting underrepresented populations as study participants,” and “retaining study participants,” which were found to be a high challenge for more than 20% of single- and multi-network CRSs. In the *Policies and Procedures* domain, “developing SOPs with support contracts” was rated as a high challenge for multi-network CRSs significantly more frequently than single-network CRSs ($p = .02$). Two activities in the domain of *Fiscal and Resources* were rated as a high challenge for multi-network CRSs significantly more frequent than single-network CRSs. Specifically,

“allocating resources equitably” and “conducting research in resource-limited areas” were rated as a high challenge for multi-network CRSs significantly more frequent than single-network CRSs ($p = .03$, $p = .05$, respectively). Lastly, in the *Communications* domain, none of the activities were endorsed by multi-network CRSs as a high challenge more than single-network CRSs. However, “providing information on clinical trials to the community” and “utilizing new media and technology to share information” were endorsed as a high challenge for both single- and multi-network CRSs.

CRS coordinators also indicated on the survey the extent to which coordinating with their affiliated CTU was a challenge (none, minimally, some, moderate, significant). From these responses, we eliminated sites that indicated “none” in response to the level of challenge ($n = 24$; 34%), and dichotomized the variable to reflect two levels; “low challenge” (minimally, some) and “high challenge” (moderately, significant) for coordination with their CTU. Thirty-seven (52%) were characterized as low challenge sites in relation to the coordination with their CTU and 10 (14%) were characterized as high challenge sites in relation to the coordination with their CTU.

Next, we tallied the number of moderate and significant challenges endorsed by the sites related to specific activities within each domain. A Kruskal-Wallis test was conducted for each domain to evaluate differences between groups of sites reported level of challenge coordinating with their respective CTU (low vs. high) on the median number of items endorsed as either a moderate or significant challenge. The test, which was corrected for tied ranks, was significant for all eight domains ($p < .05$). Thus, those characterized as high challenge sites in coordinating with their CTU also endorsed significantly more moderate-significant challenges at their site within each domain ($p < .05$). The largest differences between the groups were found in the *Staff Education and Training, Protocol Implementation*, and *Fiscal and Resources* domains. The proportion of variability in the ranked dependent variable accounted for by level of challenge variable was between $\eta^2 = .10$ and $\eta^2 = .24$, indicating a moderate to strong relationship between level of challenge coordinating with the CTU and the number of items endorsed as moderate or significant across the eight domains. The results of these analyses are listed in Table 4 below.

Open-Ended Responses

We asked a series of open-ended questions to elicit more detail regarding the nature of operating in multi-network environments. First, we asked survey respondents (i.e. CRS coordinators) to articulate the specific areas that they found most challenging coordinating with their CTU. The most prominent themes identified from the responses following the qualitative analysis described above included challenges related to: (a) the allocation and consolidation of resources; (b) communications between networks; (c) limited staff and funding to work on multiple trials; (d) network-specific differences in regulations and SOP requirements; (e) maintaining the quality of community engagement efforts; and (f) substantive differences in protocol approval, activation, and implementation procedures².

Second, we asked CRS coordinators to describe areas where multi-network affiliations allow for the consolidation and cost-sharing of research functions based on their experiences at their site. The majority (80%) of respondents at multi-network CRSs reported that multi-

²Collectively, the system of networks develop and implement both therapeutic and prevention clinical trials. In terms of approval processes, therapeutic protocols are submitted to the clinical science review committee (CSRC) and are usually reviewed earlier in their development. Prevention protocols are submitted to the prevention science review committee (PSRC) and are typically further along in their development. In addition, there are differences between therapeutic and prevention protocols regarding study product registration and acquisition, accrual targets and rates, and projected study length. These differences are often magnified at CRSs where both types are implemented.

network affiliations do allow for the consolidation and cost-sharing of research functions. Thematically, respondents indicated consolidation and cost-sharing could be found in: (a) flexible staffing and movement of staff across networks for protocol implementation; (b) common laboratory functions and processes; (c) staff education and training; (d) outreach and recruitment of study participants; (e) sharing of resources such as vehicles, facilities, clinic materials, and equipment and security; and (f) pharmacy operations.

Finally, we queried CRS coordinators about their suggestions for increasing the efficiency or performance of multi-network CRSs. Respondents indicated that streamlining standards and requirements, including data management and reporting processes, and utilizing common case report forms (CRFs) across networks could aid in increasing efficiency and performance. From the CRS coordinators perspective, this could be facilitated through the use of informatics technologies to improve performance and efficiency, including moving towards paperless data collection. Furthermore, ensuring consistency of policies and procedures across networks, as well as consolidating regulatory processes and harmonizing oversight mechanisms across networks, were viewed as potential sources for improvement.

The consolidation of protocol activation methods was also identified by CRS coordinators as a means to increase efficiency and improve performance, and it was consistently emphasized in combination with suggestions for working under a single cross-network coordinating center. Reducing the duplication of effort across networks, such as synchronizing lab procedures and requirements across networks and by consolidating some services at the sites, was commonly articulated as a means for increasing efficiency. The creation of common budget and payment mechanisms across networks were thought to assist in ensuring similar budgeting requirements and approaches to budget allocation across networks. The provision of additional staff training and shared staff training across networks was acknowledged, including more training and education on DAIDS and its requirements. Given the limited-resource settings of many sites, facilitating resource sharing across networks to fill gaps in resources, especially those sites in close proximity, was viewed as potential means for maximizing efficiencies. To do this, some sites recommended greater authority and control of resources at the site-level.

Discussion

In this study we sought to understand, from the perspective of the CRS coordinators across the NIH HIV/AIDS Clinical Trials Networks, the challenges and opportunities encountered at sites in the context of a multi-network clinical trials enterprise. Networks, as a means for organizing and conducting clinical trials, have been recognized for their potential to expedite the sequential development of new therapies, and they represent logical extensions of previous work conducted by those with demonstrated leadership in the field. Indeed, the structure and support provided by a network can be used to facilitate clear communication of results and provide consistency in new emerging fields for which there is both great promise and apprehension [3]. From this perspective, the NIH HIV/AIDS Clinical Trials Networks have been very successful and have produced highly reputable scientific output in key HIV/AIDS scientific areas, which are recognized worldwide [16]. While these networks have functioned at a high-level in terms of research productivity, there are clearly operational challenges that exist as a product of the shared use of sites by multiple networks.

We found clinical trials sites affiliated with more than one network were distinguished from their single-network counterparts in several important areas. The prioritization of studies presented a significant challenge for multi-network sites, as reported by the CRS coordinators. Having established criteria, ensuring an equitable process, and ensuring consistency in the prioritization of study protocols were frequently noted. Multi-network

CRS coordinators also reported substantive differences in protocol approval, activation, and implementation procedures in multi-network configurations, making the coordination with their respective CTUs a challenge. Although multi-network sites did not report to have more CABs than single-network sites, providing logistical and administrative support to CABs was of greater challenge for multi-network CRSs. This may have to do more with resource allocation than the support of a substantially broader community engagement infrastructure. Indeed, multi-network CRS coordinators reported significantly more challenges in allocating resources equitably and conducting research in resource-limited settings than single-network CRS coordinators. Moreover, challenges in allocation and consolidation of resources was one of the more consistent themes acknowledged by multi-network CRS coordinators in their working relationship with their CTUs.

Procedurally, “developing standard operating procedures (SOPs) with support contracts” was a greater challenge for multi-network than single-network sites. This was not surprising given the greater number of statistical and data management centers (SDMCs) and operations centers affiliated with multi-network CRSs as compared to single-network CRSs. Although SDMCs and operations centers are designed to coordinate and harmonize the common clinical trials elements of sites within networks, combinations of multiple networks may present a set of unique challenges counter to the purpose of efficient coordination. Thus, multi-network CRS coordinators seeking to maintain consistency across such an expanded set of centers may need to facilitate substantial coordination of activities, and in some cases, these might be out of the control or influence of the sites. Several recommendations from CRS coordinators emphasized standardization and coordination of data, procedures, and technologies across networks, with a specific suggestion for the need to consider a single cross-network coordination mechanism. Moreover, multi-network CRS coordinators reported “meeting network-specific requirements for staff training” as a greater challenge than single-network CRS coordinators, and several recommended shared cross-network trainings.

Several clinical trials management activities surfaced as greater challenge, irrespective of whether CRS coordinators were from single- or multi-network sites. “Managing IRB submissions,” “disseminating results to the broader community,” “recruiting study participants,” “recruiting underrepresented populations as study participants,” “retaining study participants,” and “preparing clinical trial budgets” were found as difficulties encountered by all sites. It was interesting to note that although the difference did not reach statistical significance, more single-network CRSs reported challenges with IRB submissions than multi-network sites. This difference appeared to be driven by the number of non-US based sites reporting it as a challenge, and suggests further attention of how to address and improve the oversight system for human subjects’ review, particularly in international settings. It is not surprising that these clinical trials management activities would be seen as challenges across all sites. Such activities have been found to present barriers in other clinical trials management examinations [17], with implications for successful trial implementation and completion. Dealing with multiple IRB reviews [18,19], meeting accrual sufficiency [20,21], recruitment and retention, generally and of minority populations specifically [22], budgeting and cost allocation [23], and results dissemination [24] have all been identified as potential barriers in the clinical trials literature and have been shown to impact successful clinical trials outcomes.

The CRS coordinator plays a crucial role in organizing a site’s participation in multi-network biomedical and pharmacological clinical trials. Successful management requires an interdependent relationship with the site principal investigator (PI), careful protocol assessment, team building and staff feedback, and regulatory accountability [25]. In our study, CRS coordinators in multi-network settings were faced with balancing competing and

often contradictory demands from affiliated networks. We believe this assessment represents the first of its kind to articulate the challenges of multi-network sites from the point of view of CRS coordinators. Their perspective and input in this examination has been instrumental in identifying activities that present a challenge in their work and in suggesting ways in which efficiencies might be found.

Overall, CRS coordinators identified several concrete ways that efficiency in multi-network settings could be improved. Their recommendations not only included more local control and flexibility in staffing, budgeting, and resources allocation, and the sharing of vital clinical trials resources and supports across networks, but also more systemic changes such as standardization and harmonization of policies, compliance mechanisms, data terminology, and study activation procedures between and within networks. Many of the suggestions from CRS coordinators are similar to and align with human and technical factors previously identified as common challenges to increasing the expansion and interoperability of clinical research networks [10].

One of the strongest findings in our analysis was the significant differences across all eight domains between sites reporting a high challenge coordinating with their CTU and those reporting a low challenge coordinating with their CTU. In other words, those reporting a high challenge coordinating with their CTU also reported high degree of challenges on activities in all eight domains. A review of the sites endorsing high challenges across the domains revealed no detectable patterns that would suggest reasons for the presence of such challenges. Indeed, the high challenge responses across the domains indicated a fairly widespread variation among sites (e.g., single- vs. multi-network, US based vs. non-US based CRS, US based vs. non-US based CTU, etc.). Thus, high challenge activities were not limited to a handful of multi-network sites, for example, but rather activities within certain domains were endorsed by a variety of sites. It is not clear, however, if the challenges experienced across the domains at sites made coordination with their CTU more difficult or difficulties coordinating with their CTUs impacted activities in every area. However, it is likely that the challenges between levels are transactional in nature, but additional study is needed to more fully understand this dynamic.

Several limitations to this study are worth noting. The constraints associated with survey methodology, including the subjective nature of self-reporting and underreporting of difficulties, may have influenced our ability to accurately assess the presence of challenges at the sites. Similarly, the small sample size affected the statistical power in our analysis, diminishing the ability to detect significant differences. Despite these issues, the results of this assessment provide important information to consider in the design and management of multi-network configurations for the NIH HIV/AIDS Clinical Trials Networks, as well as others contemplating and promoting the concept of multi-network settings. Although the clinical focus of the networks is on HIV/AIDS, these findings are not strictly dependent on the clinical area of study, as the networks could be focused on cancer, diabetes, hypertension or any number of conditions for which large-scale, multi-site clinical trials are a typical research mechanism. Thus, the methods, approach, and findings may be applicable to other long-term chronic disease conditions where the use of major trials conducted over multiple sites is prominent. Efficient sharing of resources in multi-network environments requires more than the provision and accumulation of instrumental supports. The success or failure of a system of shared resources depends on appropriate institutional policies, and it requires effective institutional governance regarding decisions on staffing, existence and composition of advisory committees, policies and defined mechanisms of reporting, and budgeting and financial support of each resource [26]. Given that many of the issues identified in this study were organizational in nature, organizational theory concepts such as distributed networking and chaordic organizations, with their emphases on decentralization and purpose over

structure, may be particularly relevant to understanding and developing effective coordination mechanisms for clinical research networks [10,27].

We believe these results can provide useful input and guidance in the planning, development, and evaluation of a multi-network infrastructure for sharing resources across the NIH HIV/AIDS Clinical Trials Networks, and potentially for other systems of clinical trials research worldwide, irrespective of the clinical research focus. Specifically, the results provide insight in the future development of a clinical trials system that incorporates new expertise for expanded infectious diseases clinical research portfolio of HIV/AIDS co-morbidities (e.g. tuberculosis, hepatitis) and enhanced capability to address non-HIV/AIDS infectious diseases. As the NIH HIV/AIDS Clinical Trials Networks become increasingly multi-scope in focus in order to capitalize on its current infrastructure, considerations such as those found in this study are applicable to the implementation of robust, flexible clinical research site capacity to respond quickly to research priorities. While it may be that multi-network CRSs do not necessarily have more challenges than single-network CRSs, they have unique challenges to overcome. More generally, these results contribute to a growing body of research on the management issues associated with large-scale clinical trials systems. Such information is pertinent in situations where new systems are developed or existing systems are re-designed to maximize clinical research capacity while maintaining efficient and effective utilization of resources with an emphasis on cost containment.

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Figure 1. Clinical trial unit (CTU)-clinical research site (CRS) network configurations for sample (in bold) and responses (in italics).

Table 1

Key domains and definitions of clinical site management responsibilities for NIH HIV/AIDS clinical research sites (CRSs).

Domain	Definition
Study Prioritization	Prioritization of clinical studies based on the resources available, study performance expectations, and the urgency, importance, and quality of study designs to promote scientific advances in the prevention and treatment of HIV/AIDS.
Management and Operations	Clinical research management and operations day-to-day efforts, including: data collection and management, specimen collection and storage, laboratory processing, investigational drug dispensing and storage, clinical monitoring and auditing, data analysis and reporting, and safety reporting.
Community Engagement	Community input and involvement in the research process, including in every phase (concept, design, implementation) and in multiple levels (community advisory boards (CABs), participants) to increase the likelihood that affected communities are invested in, and supportive of, the research being conducted.
Staff Education and Training	Education and training of the research staff about the community, regulatory compliance, and best practices, including orientation and continuing education, to ensure ethical and high quality research.
Protocol Implementation	The development and conduct of clinical trials, including study design and protocol development, protocol implementation, statistical design and analysis, protocol and regulatory compliance, and ethical conduct.
Policies and Procedures	Policies and standard procedures for clinical research, including Standard Operating Procedures (SOPs) to ensure consistency, efficiency, accountability, and compliance with Good Clinical Practice (GCP), Human Subject Protection (HSP), International Conference on Harmonization (ICH), and other applicable regulations and guidelines.
Fiscal and Resources	Financial, physical, and human resources needed to conduct clinical trials (facilities, staffing), and the fiscal management of clinical trials, including budgeting, reporting, and other administrative and financial responsibilities.
Communication	Communication with the community, the public, and across networks through a variety of media, including HIV/AIDS awareness, clinical trial recruitment, study materials, and results dissemination, and following best practices such as cultural appropriateness.

Table 2

Characteristics of single- and multi-network clinical research sites (CRSs) responding to the survey.

Characteristic	Single-Network CRS	Multi-Network CRS	χ^2
	n (%)	n (%)	
Located in US	12 (39)	21 (49)	.75
Located outside US	19 (61)	22 (51)	
Affiliated with US based CTU	13 (42)	24 (56)	1.39
Affiliated with non-US based CTU	18 (58)	19 (44)	
2 or more Statistical and Data Management Centers (SDMCs)	3 (10)	27 (64)	21.08**
2 or more Operations Centers	8 (27)	25 (61)	7.62*
2 or more Pharmacies	6 (20)	7 (17)	.12
2 or more Community Advisory Boards (CABs)	4 (13)	9 (23)	.80

*
 $p < .01$

**
 $p < .001$

Table 3

Number and percent of moderate or significant challenges reported by coordinators by clinical research site (CRS) type.

Domain and Activity	Single-network CRS n (%)	Multiple-Network CRS n (%)	Z	P
Study Prioritization				
Assessing the capacity and resources of the site	3 (10.0)	6 (15.0)	-0.61	0.27
Assessing the needs of the community	3 (10.0)	5 (12.5)	-0.32	0.38
<i>Determining criteria for which studies should be prioritized</i>	0 (00.0)	5 (13.2)	-1.98	0.03
<i>Establishing an equitable process for study priority setting</i>	0 (00.0)	6 (15.8)	-2.19	0.02
<i>Ensuring consistency with network-specific study priorities</i>	0 (00.0)	6 (15.4)	-2.20	0.02
Management and Operations				
Managing IRB submissions	11 (36.7)	8 (20.5)	-1.48	0.07
Collecting study data	2 (06.5)	4 (10.0)	-0.49	0.32
Submitting study data	4 (12.9)	3 (07.5)	-0.75	0.23
Storing study data, including source documentation	2 (06.5)	4 (10.0)	-0.53	0.30
Ensuring the quality and integrity of the data	2 (06.5)	6 (15.0)	-1.12	0.13
Meeting network-specific regulatory compliance requirements	2 (06.7)	7 (17.5)	-1.33	0.09
Collecting, processing, and storing specimens	1 (03.2)	2 (05.0)	-0.37	0.36
Ensuring specimen quality	1 (03.2)	2 (05.0)	-0.37	0.36
Storing and dispensing study drugs	2 (06.5)	2 (05.0)	-0.26	0.40
Managing support contracts	4 (14.3)	5 (13.5)	-0.09	0.47
Community Engagement				
Recruiting site CAB members	3 (10.3)	8 (21.1)	-1.16	0.13
Retaining site CAB members	3 (10.3)	6 (15.8)	-0.64	0.26
Educating and training site CAB members	3 (10.3)	3 (07.9)	-0.35	0.37
Facilitating community input into the research process	4 (13.3)	6 (15.0)	-0.20	0.43
Ensuring relevance of site research to community needs/concerns	4 (13.3)	4 (10.0)	-0.43	0.34
Assessing community awareness of site research	4 (13.8)	7 (17.5)	-0.41	0.34
Disseminating results to site CABs	0 (00.0)	3 (07.7)	-1.54	0.06
Disseminating results to the broader community	7 (24.1)	8 (20.5)	-0.35	0.36
<i>Providing support to site CABs (e.g. administrative, logistical)</i>	0 (00.0)	4 (10.5)	-1.82	0.04
Staff Education and Training				
<i>Meeting network-specific requirements for staff training</i>	0 (00.0)	6 (15.0)	-2.20	0.02
Meeting DAIDS-specific requirements for staff training	1 (03.3)	3 (07.5)	-0.74	0.23
Identifying training needs and establishing training plans	3 (10.0)	2 (05.0)	-0.80	0.22
Orienting new staff	3 (10.3)	3 (07.7)	-0.40	0.36
Providing continuing education for staff	2 (06.7)	3 (07.7)	-0.16	0.44
Building staff expertise, knowledge, and skills	2 (06.7)	5 (12.5)	-0.80	0.21
Documenting staff training	0 (00.0)	3 (07.5)	-1.52	0.07
Training staff for specific protocols	2 (06.7)	4 (10.0)	-0.49	0.32
Training staff about SOPs relevant to study roles/responsibilities	1 (03.3)	3 (07.5)	-0.74	0.23

Domain and Activity	Single-network CRS n (%)	Multiple-Network CRS n (%)	Z	P
Training staff about network-specific compliance requirements	2 (06.7)	5 (12.8)	-0.83	0.21
Training staff about community needs	2 (06.5)	6 (15.4)	-1.02	0.16
Protocol Implementation				
Implementing network-specific protocols	4 (13.3)	6 (15.0)	-0.20	0.43
Adhering to protocols and handling protocol deviations	2 (06.7)	2 (05.0)	-0.30	0.39
Coordinating protocol revisions	3 (10.0)	3 (07.5)	-0.37	0.36
Recruiting study participants	8 (26.7)	9 (22.5)	-0.40	0.35
Recruiting underrepresented populations as study participants	8 (33.3)	9 (26.5)	-0.56	0.29
Retaining study participants	7 (23.3)	6 (15.4)	-0.83	0.21
Securing informed consent	0 (00.0)	2 (05.0)	-1.23	0.11
Ensuring ethical conduct	0 (00.0)	2 (05.1)	-1.25	0.11
Reviewing and reporting Adverse Events/Serious Adverse Events	1 (03.3)	5 (12.5)	-1.35	0.09
Coordinating with monitoring groups (e.g. IRB, DSMB)	2 (06.7)	3 (07.5)	-0.13	0.45
Preparing and submitting case report forms	1 (03.4)	5 (12.5)	-1.31	0.10
Policies and Procedures				
Developing site-specific SOPs	0 (00.0)	5 (18.5)	-0.80	0.21
<i>Developing SOPs with support contracts</i>	0 (00.0)	5 (18.5)	-2.11	0.02
Ensuring uniformity of site-specific SOPs with network SOPs	3 (10.0)	8 (20.5)	-1.17	0.12
Monitoring compliance with various regulations and guidelines	2 (06.7)	3 (07.5)	-0.13	0.45
Ensuring compliance with DAIDS policies and procedures	2 (06.9)	3 (07.5)	-1.00	0.47
Coordinating clinical site monitoring visits (e.g. OCSO)	0 (00.0)	2 (05.0)	-1.23	0.11
Correcting issues identified during clinical site monitoring visits	0 (00.0)	3 (07.5)	-1.52	0.07
Adhering to network-specific evaluation standards and processes	0 (00.0)	2 (05.1)	-1.25	0.11
Fiscal and Resources				
Retaining research site staff	3 (10.0)	5 (12.8)	-0.36	0.36
Providing administrative support to research site staff	2 (06.9)	1 (02.6)	-0.83	0.21
Preparing clinical trial budgets	5 (20.0)	6 (16.2)	-0.38	0.35
Calculating indirect costs	1 (04.3)	2 (05.6)	-0.20	0.42
Modifying clinical trial budgets	4 (17.4)	5 (13.9)	-0.36	0.36
Negotiating expense coverage with sponsors	4 (18.2)	4 (12.1)	-0.62	0.27
Billing and reporting, including tracking payments	4 (17.4)	5 (13.5)	-0.41	0.35
Ensuring high quality research facilities	2 (07.4)	5 (12.8)	-0.70	0.25
<i>Allocating resources equitably</i>	0 (00.0)	6 (15.8)	-1.91	0.03
<i>Conducting research in resource-limited areas</i>	1 (04.8)	6 (21.4)	-1.63	0.05
Communications				
Adhering to network communication guidelines and procedures	0 (00.0)	3 (07.5)	-1.52	0.07
Promoting information sharing and collaboration across networks	1 (05.3)	5 (14.3)	-1.00	0.16
Providing information on clinical trials to the community	5 (17.2)	4 (10.0)	-0.88	0.19
Utilizing new media and technology to share information	5 (17.9)	3 (08.3)	-1.13	0.13
Ensuring timeliness of communications between site & network(s)	1 (03.4)	3 (07.5)	-0.71	0.24

Domain and Activity	Single-network CRS n (%)	Multiple- Network CRS n (%)	Z	P
Ensuring timeliness of communications between site & community	2 (06.7)	4 (10.3)	-0.52	0.30

Note: Statistically significant items are italicized.

Table 4

Low vs. high challenge coordinating with clinical trial unit (CTU) across eight clinical trials domains.

Domain	Low Challenge Coordinating with CTU		High Challenge Coordinating with CTU		Kruskal-Wallis	
	M	Mn	M	Mn	χ^2	p
Study Prioritization	.27	0.00	1.90	1.50	8.74	.003
Management and Operations	.81	1.00	3.10	2.50	4.95	.026
Community Engagement	1.00	0.00	3.40	2.50	4.58	.032
Staff Education and Training	.51	0.00	3.50	2.50	10.64	.001
Protocol Implementation	1.03	0.00	4.10	3.00	10.88	.001
Policies and Procedures	.43	0.00	2.30	0.50	5.24	.022
Fiscal and Resources	.68	0.00	3.30	3.00	11.18	.001
Communications	.41	0.00	1.70	1.00	4.37	.037