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Quality assurance of research protocols conducted in the community: The National Institute on Drug Abuse Clinical Trials Network Experience

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Abstract

Background: Quality assurance (QA) of clinical trials is essential to protect the welfare of trial participants and the integrity of the data collected. However, there is little detailed information available on specific procedures and outcomes of QA monitoring for clinical trials.

Purpose: This article describes the experience of the National Institute on Drug Abuse's (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) in devising and implementing a three-tiered QA model for rigorous multi-site randomized clinical trials implemented in community-based substance abuse treatment programs. The CTN QA model combined local and national resources and was developed to address the unique needs of clinical trial sites with limited research experience.

Methods: The authors reviewed internal records maintained by the sponsor, a coordinating site (Lead Nodes), and a local site detailing procedural development, training sessions, protocol violation monitoring, and site visit reporting.

Results: Between January 2001 and September 2005, the CTN implemented 21 protocols, of which 18 were randomized clinical trials, one was a quality improvement study and two were surveys. Approximately 160 community-based treatment programs participated in the 19 studies that were monitored, with a total of 6560 participants randomized across the sites. During this time 1937 QA site visits were reported across the three tiers of monitoring and the cost depended on the location of the sites and the salaries of the staff involved. One study reported 109 protocol violations ($M = 15.6$). Examples are presented to highlight training, protocol violation monitoring, site visit frequency and intensity and cost considerations.

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Limitations: QA data from the entire network were not easily available for review as much of the data were not electronically accessible. The authors reviewed and discussed a representative sample of internal data from the studies and participating sites.

Conclusions: The lessons learned from the CTN's experience include the need for balancing thoroughness with efficiency, monitoring early, assessing research staff abilities in order to judge the need for proactive, focused attention, providing targeted training sessions, and developing flexible tools. The CTN model can work for sponsors overseeing studies at sites with limited research experience that require more frequent, in-depth monitoring. We recommend that sponsors not develop a rigid monitoring approach, but work with the study principal investigators to determine the intensity of monitoring needed depending on trial complexity, the risks of the intervention(s), and the experience of the staff with clinical research. After careful evaluation, sponsors should then determine the best approach to site monitoring and what resources will be needed.

The consensus among experts in the addiction field is that for most individuals, treatment and recovery work best in a community-based, coordinated system of comprehensive services [1]. In 1999, the National Institute on Drug Abuse (NIDA), within the National Institutes of Health, established the National Drug Abuse Treatment Clinical Trials Network (CTN). The goal of the CTN is to foster the translation of research into practice by conducting rigorous, multi-site clinical trials of behavioral, pharmacological, and integrated behavioral and pharmacological interventions directly within community-based treatment programs. This goal is achieved by partnering an academic center with several treatment programs within its region, a partnership designated as a CTN Node [2,3]. As of September 2008, there were 16 Nodes and approximately 240 affiliated community treatment programs within the CTN. NIDA serves as the government sponsor for all research conducted within the CTN. The first CTN protocol was launched in January 2001, and as of September 2008, the CTN had developed and implemented 27 multi-site protocols.

There is a trend towards adopting evidence-based practices into community substance abuse treatment programs [4]. This requires rigorous randomized clinical trials to demonstrate which interventions are effective in these settings. Data derived from the CTN trials are being used for this purpose, and it was decided from the beginning to establish a system of monitoring, support, and oversight to ensure the reliability of data sets generated from CTN trials and the protection and safety of the individuals participating in the clinical trials.

The CTN's characteristics – translational research, federally funded cooperative agreements, and rigorous multi-site trials conducted at community-based treatment programs involving vulnerable populations – have created important research opportunities, as well as challenges. This paper describes the development and implementation of a multi-level model for quality assurance (QA) that addressed these challenges over the CTN's first 5 years of data collection, January 2001 to December 2005, a period when there was minimal available guidance for such an endeavor. At the time this model was developed, the CTN did not have a coordinating center. NIDA began funding a Clinical Coordinating Center in the summer of 2005, altering the model described in this report somewhat by replacing the direct involvement of NIDA's staff. However, the fundamental model and the principles of strong oversight involving the Node and participating sites continue.

The three-tier model

The CTN QA program began as a three-tiered model to specifically address the needs of research-naive study sites by providing in-depth monitoring and support at multiple levels. Because many of the CTN community treatment programs had never participated in research, a robust QA program was needed. From the beginning, the International Conference on

Harmonisation (ICH) E6 Good Clinical Practice: Consolidated Guidance [5] has served as the standard by which CTN studies have been conducted.

Tier one

The grantee at the academic center of each Node participating in a CTN protocol had direct oversight of research in that Node's community treatment program(s), and each Node identified its own QA staff to conduct site-monitoring visits. The academic center served as a regional resource for the sites, providing daily communications, regulatory compliance oversight and training related to Good Clinical Practice standards, and frequent on-site monitoring. Participating Nodes could also opt to intensify monitoring for sites with performance problems. The participating local Node QA monitors were responsible for filing visit reports, problem-solving site issues, implementing adequate corrective actions, and directly communicating study site progress to the participating local Node's principal investigator, the study leadership and NIDA staff.

Tier two

Leadership for each study centered on one CTN Node, termed the Lead Node. The Lead Node developed the protocol, an informed consent template, study procedures and all other study materials. The Lead Node also provided protocol-specific training sessions to ensure consistency across sites. During the trial, the Lead Node reviewed all site visit reports and communicated regularly with the participating sites (during weekly conference calls), providing leadership support and identifying corrective actions as necessary. The Lead Node also had the prerogative to request an increase in the monitoring frequency of all sites or send out its own QA staff to conduct site visits if necessary.

Tier three

NIDA's staff (partnering with independent contracted monitors) conducted site visits to meet the sponsor's regulatory obligations. NIDA's monitoring covered similar content to local QA monitoring, but with less frequent visits to each individual site and a broader scope across multiple sites. NIDA assigned Project Officers to (1) work closely with the contracted monitors and provide Good Clinical Practice guidance and leadership to the QA program, (2) work directly with each protocol team, (3) coordinate independent peer review of the protocol, and (4) report regularly to a Data and Safety Monitoring Board (DSMB). Table 1 presents a summary of how responsibilities were shared across the three levels of oversight.

CTN QA development

The CTN chartered a QA Subcommittee to develop standard operating procedures and guidelines for the QA process, to review and recommend approval of protocol-specific QA plans, and to coordinate training sessions regarding QA monitoring and Good Clinical Practice topics. The CTN QA Subcommittee reviewed relevant literature that was available at the time and sought guidance from other institutions. It adopted the principles and recommendations for QA published by Knatterud, *et al.* [6], the Veterans Affairs Cooperative Studies Program site monitoring program [7], the Veterans Affairs Cooperative Studies Program: Guidelines [8], and the FDA Guidance for Industry: Guideline for the Monitoring of Clinical Investigations 1988 [9].

The data presented throughout the remainder of this paper cover the period of January 2001 to December 2005. During this time the CTN implemented 21 protocols, of which 18 were randomized clinical trials, one was a quality improvement study, and two were surveys. Approximately 160 community-based treatment programs across all Nodes participated in the 19 studies that were monitored, with a total of 6560 participants randomized across the sites.

QA plan template

The QA Subcommittee created a QA Plan Template to guide Lead Nodes in developing protocol-specific QA plans. The resulting product was a fill-in-the-blank template that defined the minimum monitoring expectations with flexibility to fit the needs of a specific protocol (visit <http://ctndisseminationlibrary.org/QAmaterials.htm> to view this document).

Training

CTN training sessions were divided into two categories: protocol-specific and non-protocol-specific. As noted earlier, the protocol-specific training sessions were coordinated and delivered by the Lead Node. The non-protocol-specific training sessions were sponsored by NIDA or individual local Nodes and included Good Clinical Practice (including Human Subject Protections) training for all staff involved in the study. To decrease travel burden and reduce costs, the CTN used a train-the-trainer model, whereby key individuals at each Node were identified to receive specific training to serve as their Node's own trainers when necessary.

The following data provide some perspective on the number of training sessions conducted at the sponsor and Node levels. An internal 2005 training report indicated that during a five-month period between July 31, 2005 and December 31, 2005, some Nodes conducted between one and three training sessions for their research staff, while another Node conducted approximately 40 sessions. Between October 1, 2005 and September 30, 2006, an estimated 184 clinical providers received training for behavioral interventions associated with three clinical trials. These three trials involved 21 sites that recruited 1330 participants.

NIDA sponsored QA monitor training at both a basic and an advanced level for all CTN QA staff. These monitoring training sessions included discussions and tools regarding following up with issues and corrective actions. A well-received training tool was a brochure developed by the QA Subcommittee and NIDA to educate protocol team members and staff at the community-based treatment programs about QA expectations and responsibilities [10].

Currently, the Lead Node of each study continues to provide the protocol-specific training sessions, and most of the non-protocol-specific training sessions (such as Good Clinical Practice) are now supported via web-based technology or web-assisted conference calls and are conducted by the Clinical Coordinating Center staff. Some training sessions are still offered face to face, using the train-the-trainer model.

Data and safety monitoring plan

Monitoring the safety of the study was a major focus at all levels. For each trial, the Lead Node (along with NIDA staff) developed a Data and Safety Monitoring Plan and standard operating procedures that detailed the instructions for assessing adverse events reporting and monitoring and overall safety at each site. NIDA staff prepared guidelines to assist the Lead Node with this task (for more information, visit <http://ctndisseminationlibrary.org/QAmaterials.htm>). A NIDA appointed DSMB reviewed the plan and recommended changes to NIDA. Once the study was underway, the DSMB met regularly to review study performance and safety.

The QA monitors followed the established adverse event monitoring procedures when assessing the reporting and follow-up of these events. Adverse events were assessed at each site by qualified clinicians. To complement and support the work of the clinicians at each site, and to meet regulations and guidance, the Lead Node team included a study clinician, who was responsible for verification and consultation on an as needed basis. NIDA's Center for the CTN also appointed an internal medical safety officer for each study, who assisted the sites and the Lead Node with the assessment and reporting of adverse events. Ultimately, all study related

adverse events were reported in tabulated form to the DSMB. As an example, Killeen et al [11] published results from a CTN study with 353 randomized participants indicating that 110 participants reported a total of 190 adverse events. Eighty-three of these adverse events were considered study related, meaning that participation in the study could not be ruled out as a possible contributor (e.g., increases in substance use or psychiatric symptoms).

Protocol deviations/violations

The CTN developed a Protocol Violation Policy and a reporting template (visit <http://ctndisseminationlibrary.org/QAmaterials.htm> to view the protocol violations categories). Protocol violations were defined as *any* non-adherence to the written protocol, and the categories also included procedures that were required by local IRBs, in addition to other established regulations/guidelines. Local Node QA monitors reviewed protocol violations, implemented appropriate corrective action plans and provided specific re-training to minimize future violations. The Lead Node reviewed the sites' protocol violations logs, followed up with the corrective action plans at each site and discussed common violations across sites. This transparent process also facilitated study-wide protocol amendments, when necessary.

To quantify protocol violation collection, one example is a behavioral intervention study with seven participating sites that identified a total of 109 protocol violations (mean = 15.6/site). The majority of violations were related to the consent process (35%), general procedural issues (31%), and timing problems (i.e., assessments conducted outside the designated window) (31%). The remainder (3%) was a combination of other categories. The types and number of protocol violations varied across sites. At one individual site, for example, a total of 26 protocol violations were reported (15% consent-related, 15% adverse event reporting procedures, 43% study procedures, and 27% timing). As a point of comparison, another behavioral study conducted within the CTN with less complicated procedures (e.g., shorter intervention, randomization by cohort, no assessments administered during treatment), reported 142 protocol violations across 12 sites (11.8/site). In both studies, most protocol violations were minor in nature; for example, the majority of the informed consent violations were due to using expired forms (some IRBs did not stamp the forms), failing to initial all the pages of the consent form once presented to the participant (required by some IRBs), or dating the consent incorrectly. The majority of the adverse event protocol violations involved failing to report to the sponsor or IRB within the necessary timeframes rather than not reporting them at all. Another common violation reported (often at the beginning of the study) was the practice of pre-dating the case report forms or study notes. Although larger protocol violations were certainly captured through this process (e.g., not administering an entire measure), the value of this process was in minimizing drift from important procedural and ethical practices, including informed consent and maintaining the integrity of data collection.

The findings of the Warning Letters issued by the Food and Drug Administration can have some value for comparison, although most of the trials in the CTN were non-pharmaceutical studies. In reviewing the online Food and Drug Administration (FDA) Warning Letter Index from February 2002 through February 2004, involving 58 clinical drug and device research protocols, Bramstedt notes that the most common regulatory violations were deviation from the research plan, a flawed or nonexistent consent process, and failure to report or late reporting of adverse events [12]. These types of protocol violations reflect those described above in several CTN trials. Eight percent of the Warning Letters mentioned study misconduct, including data fabrication. The CTN has had only two documented episodes of study misconduct since its inception. The comparison reflects well on the performance of the CTN sites.

General QA guidelines

Frequency of monitoring

The QA Subcommittee established parameters for the minimum frequency, quantity, and scope of local Node monitoring. One key factor in determining the monitoring needs of a CTN study was the nature of the study intervention – a medication versus a behavioral therapy, or a combination of both. Behavioral trials required local monitoring visits a minimum of once every 8 weeks from randomization of the first participant. The frequency of visits could then be reduced to once every 12 weeks based on site performance and recruitment. Medication trials required monitoring visits a minimum of once every 6 weeks from randomization of the first participant. The frequency of visits could then be reduced to once every 8 weeks based on site performance and recruitment. NIDA's contracted monitors conducted site visits approximately every 6–8 months for behavioral studies and every 3–4 months for medication studies.

Currently, the local Nodes are still conducting site visits at the participating sites, but the visits are referred to as site management instead of QA/monitoring visits. Each Node is required to establish its own parameters for site management, taking into consideration the same factors (study needs and staff experience with research) as well as the Lead Node requirements.

Types of visits

Site visits were required for site initiation, interim monitoring (active enrollment and follow-up phase of the study) and closeout. These visits were conducted by the local Node QA monitors, the NIDA contract monitors and the Lead Node as needed.

Initiation phase

Each community-based treatment program had to satisfy specific site initiation requirements and obtain approval from the participating local Node principal investigator, the Lead Node, and NIDA prior to enrolling participants. Local Node monitors conducted a pre-initiation site visit to identify outstanding issues to be resolved and reported findings to the Lead Node and NIDA staff. To facilitate this visit, the QA Subcommittee developed site and Node Pre-Initiation worksheets (visit <http://ctndisseminationlibrary.org/QAmaterials.htm> to view these documents).

After receiving the local Node pre-initiation visit report, the final initiation visit was conducted by the NIDA contract monitors. Particular emphasis was placed on items pending after the Local Node QA initiation visit (see Table 2 for a list of initiation visit tasks). Following this visit and resolution of all unresolved issues, a final report was submitted to the Lead Node and NIDA's Center for the CTN and the site was officially endorsed to begin recruiting and enrolling study participants. Currently, the local Node staff uses the pre-initiation checklists and the Lead Node conducts site visits as necessary, both for site selection and to assess readiness. The Clinical Coordinating Center conducts site selection and site initiation visits and reports to NIDA staff for site endorsement.

Active enrollment and follow-up phase

During the active enrollment, recruitment, treatment, and assessment phases of the study, site monitoring continued to occur at all oversight levels. At each interim visit the monitors assessed protocol compliance, reviewed recruitment and retention strategies, checked study source documents and other records, and provided training sessions and overall guidance. The Lead Node staff was available for consultation when questions about study procedures violations arose during the site visits, as well as to discuss potential corrective actions. See Table 3 for a list of interim monitoring visit tasks.

At the end of each visit, identified issues were discussed with the research staff, and the resolution of any issues raised during previous visits was confirmed. Findings were documented using the standardized Local Node QA Interim Monitoring Report Template (<http://ctndisseminationslibrary.org/QAmaterials.htm>) and reported to the local Node staff, the Lead Node and NIDA. The Lead Node and NIDA staff reviewed the monitoring reports, assessed the protocol violations, and discussed the issues reported with the study staff during their regular conference calls. The Lead Node would also conduct QA site visits to the participating sites as needed.

The NIDA contract monitors reviewed all Node QA site visit reports and any Lead Node site visit reports prior to their visit to focus on unresolved or recurrent issues. Monitoring visits often spotted protocol violations, with the most frequent corrective action being enhanced training sessions. In rare instances staff terminations were recommended.

Currently, the local Nodes still conduct site visits (termed site management visits) where the staff assess protocol compliance, check study records, follow up with data queries and provide training as necessary. The visits follow the Lead Node and local requirements and are not formally reported to NIDA.

To fulfill the sponsor's regulatory obligations, monitors from the Clinical Coordinating Center conduct interim site visits quarterly. These visits are reported to the site staff, the Lead Node and NIDA and provide a more manageable system given that only one set of reports (instead of two or three) is recorded per site to officially document overall site performance. Staff from the Clinical Coordinating Center also conducts 'for cause' visits when performance questions are raised, either by NIDA or the Lead Node staff.

Closeout phase

Closeout visits were initiated by the local Node QA staff and then by NIDA contract monitors prior to site data lock. (See Table 4 for a list of closeout visit tasks.) After the final follow-up assessments were completed and sites began closeout procedures, the Lead Node monitored final study data lock. The Lead Node conducted a final review of data, and certified the full study database. Nodes were responsible for the appropriate storage of data, unless other arrangements had been made. Once the data were locked, the Lead Node developed and executed data analysis and publication planning, in collaboration with participating academic centers and community-based treatment programs.

Currently, the Clinical Coordinating Center staff conducts the final closeout visit, working closely with the local site, the Lead Node, and the data center. The local Nodes are still responsible for storing the records, and the Lead Node manages data analysis and publications.

Cost considerations

As noted earlier, in the 19 studies that were monitored there were a total of 6560 participants randomized across the sites, and a total of 1937 QA site visits were reported from the sponsor, the Lead Node, and the local Nodes (Table 5).

The cost for the monitoring activities varies based on geographic location of the Nodes and the actual salaries of the staff involved. Please note that the dollar costs included here are not weighted figures (including fringe, overhead, etc.), or inflation adjusted. The estimated cost is as follows:

- (1) NIDA (sponsor): Each site visit averaged approximately \$1500. In addition to these costs, NIDA staff time dedicated to QA activities is estimated to have been ~50% of a master's level employee (estimated between \$35,000 and \$50,000 annually). Other staff

time averaged ~5–10% of a doctoral level employee (estimated about \$5,000 to \$10,000 annually).

(2) Lead Node: Using one CTN study as an example, each Lead Node site visit averaged \$675 (depending on travel distance). Monthly conference calls were about \$250. In addition to these costs, Lead Node staff time devoted to QA tasks amounted to ~30% of a master's level project director (estimated \$15,000 to \$30,000 annually).

(3) Local Node: The cost of local Node monitoring depended greatly on the proximity of each site, the number of protocols conducted by the Node, and the number of sites participating in a CTN trial. For one of the Nodes, the average yearly cost of QA monitoring ranged from \$13,000 to \$16,000 per study and included the following expenses: (1) salary and benefits for 30% project manager time dedicated to QA activities (approximately \$13,000); (2) travel costs for 8 visits a year ranged from \$0 for one site located adjacent to the home academic center to \$3000 annually for visits to the site furthest away, and (3) nominal QA supply costs.

Currently, the cost of the Coordinating Center site visits ranges from \$1500 to \$2000. At the local and Lead Node levels, personnel costs are unchanged (when adjusted for inflation). The Lead Nodes continue to conduct site visits as necessary and hold weekly conference calls. Local Nodes have shifted their QA monitoring staff to site management activities, but the costs for personnel and the site visits remain similar. One cost saving area for the local Nodes' staff has been the conversion of the data collection system from paper-based case report forms to electronic data capture systems. The incorporation of logic checks and QA into the electronic systems, plus fewer paper-based source forms, have reduced the site visit time by ~50% (for example, one day instead of two at the site).

Lessons learned/recommendations

The following are recommendations based on lessons learned during the CTN's formative phase:

Balance thoroughness with efficiency

Utilizing local monitors, who were typically in close proximity to the sites, allowed for issues to be resolved early and quickly during study implementation. Early resolution of issues also provided NIDA contracted monitors an opportunity to focus on more complex issues, as well as addressing noted trends across sites. However, there were too many site visits, sometimes three visits in a given month, requiring significant amounts of community-based treatment program staff time and coordination of efforts. It was also discovered that the local Node QA monitoring and staff experience was excellent at many sites, necessitating less NIDA contract monitoring than at other sites. To follow the same procedures for each site meant some did not get as much help as needed, while others felt burdened by the oversight. There was also redundancy in some oversight procedures, including documentation review. The number of crosschecks for the inclusion and exclusion criteria and the number of outcome measures stipulated by the Lead Node at times limited the local Node QA monitor's ability to address other site problem areas. In retrospect, many of these checks could have been more efficiently reviewed by data management with validation and edit checks.

In the case of monitoring of regulatory documents, monitoring quantity and frequency requirements evolved over time. Monitors initially were expected to review sites' regulatory files at each visit. This evolved into a more limited review schedule for the regulatory files at initiation, closeout, and annually, with only new significant regulatory changes, trigger events, and expiration dates to be monitored at each visit. Certain regulatory documents continued to be reviewed at each visit, including informed consents, HIPAA authorization forms, expedited

reportable adverse events and serious adverse events, and protocol violations. This change increased efficiency so that monitors could work on the site's more challenging issues.

Monitor early and manage protocol violations effectively

Local Node QA monitors visited sites more frequently during early stages of trial implementation, and violation trends were quickly identified to limit future errors, and to avoid the creation of patterns which would be difficult to change, or would result in lost data. Within these research naïve sites, a learning curve appeared to occur in consenting study subjects and properly performing study procedures. As the studies progressed, there was a trend toward violations such as completing assessments outside of study windows in order to capture data, and more complex issues related to the study procedures that required additional clarifications from the Lead Node. Identification and open discussion of protocol violations via regular study team teleconferences early in the protocol life cycle, especially in multi-site trials, are key to anticipating potential problems in protocol procedures and reducing the likelihood that multiple sites will make similar mistakes. This information exchange can also enhance future studies' procedures to avoid common protocol violations. For example, new studies have adjusted the windows for data collection based on the lessons learned in earlier trials, and training sessions include information gleaned from this experience.

Collect information, report and assess safety effectively

Establishing multiple levels of oversight provided an effective way of identifying and accurately reporting adverse events. Having more than one QA monitor increased the probability of catching unreported adverse events (e.g., through the review of research notes) and following up on adverse event resolution (e.g., obtaining hospital records).

Provide targeted training sessions

Although the CTN offered annual clinical trial management and QA monitoring training sessions to staff across all Nodes, staff turnover at the community-based treatment programs and at individual Nodes necessitated additional training through the life of the trial. Through train-the-trainer programs, the local Node QA monitor was invaluable in the re-training process. The CTN's more recent use of technology is also useful in targeting training sessions and allows for more frequent training offerings to address staff turnover.

Encourage objectivity

The level of involvement the local Node QA monitor experienced with the local sites facilitated rapport and communication with site staff. However, a disadvantage of such a close working relationship was the potential for a loss of objectivity on the part of the local Node QA monitor. Although the three-tier system was successful in addressing this, the current system whereby local Node staff conducts site management and NIDA conducts monitoring also maintains adequate objectivity.

Enhance resources

The NIDA contracted monitoring activity could be viewed as a duplicate effort; however, this monitoring was necessary in order to meet sponsor responsibilities and was completely independent from the Node, further increasing objectivity. When a NIDA contract monitor conducted a site visit, he/she also assessed the local monitoring procedures and reported concerns to NIDA. To ensure ongoing communication and adequate protocol knowledge, the NIDA contract monitors were involved with the Node monitoring process by participating in QA Subcommittee activities and assisting with QA related standards and procedures. NIDA contract monitors were assigned on a study-by-study basis, and to the extent possible, the same

individual monitored all sites involved with a specific protocol through closeout to promote consistency and efficiency.

Create flexible tools

The QA Plan and site-reporting templates were detailed, comprehensive and rigid, which served to meet the needs of inexperienced staff, but the inflexibility sometimes hampered the monitors' ability to address problems that were identified during the visits or to adjust visit schedules for workloads and site needs. Many times the need to review certain documents conflicted with the need to investigate issues, provide training or conduct an in-depth review of a specific problem area. This was overcome by the development of collaborative relationships with data managers who could provide information and lists of missing documents, reported adverse events/serious adverse events, and common data errors.

Think outside the box

With advancing technology and diminishing resources, oversight of clinical trial performance has room for creative alternatives. Using secured internet sites, web-assisted conferencing with electronic data capture and faxing of documentation could potentially reduce the number of in-person site visits. The CTN is engaged in ongoing discussions to consider innovative approaches to trial monitoring and oversight.

Conclusion

The current trend of community substance abuse treatment programs adopting evidence based practices calls for scientifically rigorous randomized clinical trials to demonstrate which interventions are effective. Data from the CTN are being used for this purpose, and the network's system of monitoring and oversight effectively ensures the reliability of data sets generated from a wide range of CTN trials and ensures greater protection and safety of the individuals participating in the clinical trials.

The process of adopting, implementing, and adapting a QA monitoring system has been a fluid process in determining the exact role and function of QA within community-based research. In our experience, with a total of 19 studies monitored closely, we learned that when participating sites are not experienced in implementing research studies, it is essential for local staff to conduct monitoring or site management visits as early as possible, and to continue the visits until the study leadership is comfortable with the site performance. These visits keep open communication lines to discuss all necessary study, consent and safety procedures, and identify areas where the staff needs additional training. In our model we had two additional layers of oversight, the Lead Node and the sponsor, that could have been combined to provide a more effective process.

In this particular organizational context, the three-tier monitoring model was transitioned to a more streamlined process, both to reduce redundancy and because of institutional restructuring. The CTN has now limited required monitoring activities to the sponsor. This aspect is consistent with many industry-sponsored trials. At the participating Node level, QA staff has shifted their efforts to site management duties; their intimate knowledge of the protocols and the sites within their Nodes makes them ideal for this task. They continue to participate in quality assurance, protocol-specific and substance abuse training. Lead Investigators still have the option to require stricter local monitoring if necessary.

There are currently no regulatory requirements for study monitoring. We believe that all clinical trials should be monitored to the sponsor's standards and hope that there will be further regulatory guidance regarding these standards. In the CTN, local staff was trained to perform

QA procedures, thereby maximizing sponsor resources, reducing the number of sponsor site visits, enhancing the quality of the research processes, and enhancing overall site performance. This model can work for sponsors overseeing studies at sites with limited research experience that require more frequent, in-depth monitoring. We recommend that sponsors work with the study principal investigators to assess the level of necessary monitoring and site visits depending on trial complexity, risks, and the experience of the staff with clinical research. After careful evaluation, sponsors should determine the best approach to QA and site monitoring and what resources will be needed.

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Table 1

Roles and responsibilities of the three levels of monitoring

	Protocol development	Regulatory	Training	Study coordination	Quality assurance	Data
NIDA-Center for the Clinical Trials Network (sponsor)	<ul style="list-style-type: none"> Approves protocol Reviews study team member qualifications 	<ul style="list-style-type: none"> Reports to FDA, NIH, etc. Constitutes DSMB Collects essential documents 	<ul style="list-style-type: none"> Identifies and facilitates core training needs 	<ul style="list-style-type: none"> Protocol administration, oversight, and final decisional authority 	<ul style="list-style-type: none"> Authorizes site initiation Provides independent monitoring Tracks QA issues 	<ul style="list-style-type: none"> Contracts data repositories
Lead Node	<ul style="list-style-type: none"> Develops protocol Selects sites Prepares study standard operating procedures 	<ul style="list-style-type: none"> Verifies regulatory readiness Provides protocol revisions Tracks site compliance 	<ul style="list-style-type: none"> Develops training plan Conducts protocol training sessions Certifies staff in intervention 	<ul style="list-style-type: none"> Overall guidance and oversight for all participating sites Facilitates national conference calls Reports to Steering Committee 	<ul style="list-style-type: none"> Develops QA plan Reviews all QA visit reports Visits sites as needed 	<ul style="list-style-type: none"> Develops data plan, case report forms, database Conducts study data QA & data analysis
Participating Node	<ul style="list-style-type: none"> Participates in protocol development Identifies potential sites Hires staff Prepares local standard operating procedures 	<ul style="list-style-type: none"> Obtains and maintains local IRB and other regulatory approvals Ensures participant safety 	<ul style="list-style-type: none"> Provides local Good Clinical Practice and assessment training Certifies and tracks those training sessions 	<ul style="list-style-type: none"> Local site coordination and management, safety, and recruitment and retention plans 	<ul style="list-style-type: none"> Conducts local QA monitoring Implements corrective action plans Prepares & disseminates QA reports 	<ul style="list-style-type: none"> Performs data entry Completes case report forms Resolves queries Conducts local data QA audits

Table 2

Initiation visit

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- Discuss Good Clinical Practice guidelines and regulations
 - Check that all relevant regulatory documents are present in the study file
 - Assess that site personnel understand all study procedures, including drug accountability procedures, and ensure that study staff are aware of their roles and responsibilities with regard to the protocol; conduct training as needed
 - Assess that site personnel understand the processes for recognizing, recording, and reporting adverse events and serious adverse events; conduct training as needed
 - Assess that site personnel understand methods for case report forms completion and data submission; conduct training as needed
 - Assess the site's overall readiness to conduct the protocol; e.g., study supplies are in place and facilities are adequate
-

Table 3

Interim visit

-
- Review 100% of subjects' charts and laboratory reports for adverse events and serious adverse events
 - Review at least 10% of subjects' case report forms against source documents at each visit ¹
 - Review the randomization process for each subject
 - Assess that each subject enrolled met inclusion/exclusion criteria
 - Assess that a properly executed consent form exists for each subject
 - Assess that the study and regulatory binders are complete and properly maintained
 - Assess that all adverse events are documented properly and all serious adverse events are reported in a timely manner to the study sponsor and Institutional Review Board (IRB)(s)
 - Assess that all protocol procedures are being followed and any nonadherence to the protocol has been reported to the responsible IRB as required
 - Assess that the study drug is stored properly and drug accountability records are maintained properly
 - Assess that the data are being submitted to data management at appropriate intervals and data queries are adequately resolved within the established timeframe
-

¹In practice, virtually all source documents were reviewed to verify adverse event reporting

Table 4

Closeout visit

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- Assess that the study binder is complete and that all regulatory documentation is in order
 - Instruct site personnel in the proper procedures for returning remaining study drug supplies
 - Instruct site personnel to notify the responsible IRB of completion or premature discontinuation of study, as applicable
 - Assess that appropriate procedures are in place for remaining data submission and resolution of data queries
 - Assess that proper record retention procedures are in place
-

Table 5

Site visits reported to NIDA (From January 1, 2001 to September 1, 2005)

	Initiation	Active enrollment (Interim)	Closeout
NIDA contract monitors	134	250	41
Local Node monitors	176	1251	58
Lead Node monitors	4	23	0
Total	314	1524	99