# Clinical Trial Management: Monitoring Progress, Sites and Safety; New Paradigms for Efficiency

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## Abstract

There has been a recent focus on providing adequate clinical oversight in a shrinking economic support environment. Concepts of remote monitoring to decrease travel costs and time, on-site monitoring that is structured to review specific information and developed with a frequency based on the risk level of the intervention, and streamlined safety reporting all combine to allow comprehensive clinical trial oversight. The use of robust web-based data systems allows for daily updates of clinical trial progress, automated notification of specific events, data quality checks at the time of data entry, built-in logic checks, remote monitoring capabilities and real-time review of safety events. The NIDA CTN experience serves as a model to transition to real-time reporting of trial progress, to risk based clinical site monitoring and strategic risk based safety reporting. A comprehensive clinical trial progress assessment has been created with site and safety monitoring plans that can improve the efficiency of monitoring programs. These examples and tools will offer alternatives to standard clinical trial oversight and to 100% data auditing while maintaining data and ultimately study integrity.

## Trial Progress Reports

The NIDA CTN has developed a comprehensive set of web-based Trial Progress Reports (TPR) to use as a management tool to monitor the progress of on-going clinical trials in real-time. These reports track the progress of each protocol within the CTN from the date of first randomization to final closeout and publication of main results. The content includes recruitment, retention, availability of primary outcome, treatment exposure, quality assurance, and regulatory. The reports are updated daily and are available on a secure website to provide real-time access to critical protocol information. Metrics have been developed for key protocol components to provide feedback at a glance on the progress of the protocols. These metrics have been assigned color-codes, where green denotes good performance, yellow where problem areas are identified, and red where poor performance is noted and remedial actions required.

The TPR provides both a big-picture view and a very detailed view of the protocols to meet the needs of the varied audience, which include:

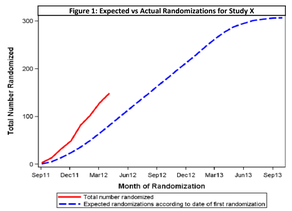
- The sponsor and study leadership to assess the overall progress of multiple on-going protocols. For example, reviewing statistics over all protocols with color coded boxes can be useful for the sponsor to assess study performance (Table 1).
- The protocol lead teams to monitor their respective protocols in order to identify areas of concern overall (e.g., Figure 1 in monitoring expected versus actual number of randomizations over time) or on an individual site level.
- The investigators and staff at each participating site within a protocol to monitor their individual site's performance against other sites. For example, retention as measured by attendance at follow-up visits is an important measure to be compared across sites (Table 2).

**Table 1: Color-Coded Metrics to Assess Performance Across All Protocols For Key Components**

| Study | Recruitment | Missing Forms | Data Audits | Regulatory | Availability of Primary Outcome | Treatment Exposure | Attendance at Follow-up Visits |
|---|---|---|---|---|---|---|---|
| Study 1 | 89% | 0.1% | 0.05% | None | 90% | 69% | 65% |
| Study 2 | 102% | 0.0% | 0.52% | None | 65% | 62% | 90% |
| Study 3 | 113% | 0.5% | 0.21% | None | 78% | 89% | 83% |
| Study 4 | 74% | 0.2% | 0.08% | None | 96% | 93% | 85% |
| Study 5 | 82% | 0.1% | 0.32% | None | 92% | 92% | 98% |

**Table 2: Attendance at Follow-Up Visits by Site For Study Y**

| Site | Participants Randomized | Attendance at Month 3 Visit | Attendance at Month 6 Visit | Percentage of Follow-up Visits Attended |
|---|---|---|---|---|
| Site 1 | 50 | 41/50 (82%) | 38/43 (88%) | 85% |
| Site 2 | 53 | 51/53 (96%) | 44/48 (92%) | 94% |
| Site 3 | 60 | 56/60 (93%) | 55/57 (96%) | 95% |
| Site 4 | 38 | 29/38 (76%) | 31/36 (86%) | 81% |
| Site 5 | 48 | 40/48 (83%) | 31/38 (82%) | 83% |
| Overall | 249 | 217/249 (87%) | 199/222 (90%) | 88% |

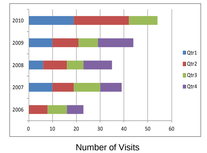



## Site Monitoring

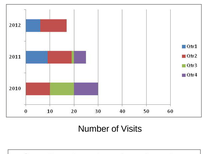
In response to growing concerns about the effectiveness and efficiency of monitoring clinical trials, the NIDA CTN has initiated a new strategy to reassess monitoring practices within their network. During the last two years, conventional monitoring plans implemented in previous trials have been gradually replaced with tailored plans that take into consideration the relative risk of a given trial and that are also flexible enough to allow for additional tailoring based on specific site performance variables.

To create these tailored monitoring plans, algorithms were developed to assist the CTN to determine the 'monitoring risk' of a trial and that take into account aspects of: 1) Trial design complexity including: study population, safety profile of the investigational product and critical study procedures; 2) Monitoring complexity including: number of participants and their length of study involvement, expected rates of enrollment, number of endpoints, number and experience level of sites and the complexity of related regulatory requirements; and 3) Sophistication of the EDC system and corresponding data management including: volume and availability of source documentation versus direct data entry.

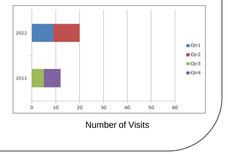
**Study X** – A conventional plan that did not take trial design or monitoring complexity into consideration. The EDC system used was inflexible and data management occurred sporadically. On-site visits conducted quarterly whether "required" or not resulted in some sites being over-monitored and others not being monitored enough. Monitors focused review on data not critical to assess participant safety and data quality. Data errors noted were not timely and failure to identify problem trends early on resulted in repetitive errors. Resulted in increased monitoring costs, a drain on a limited number of resources, decreased morale and monitor and site staff burnout.




**Study Y –** A modified approach**,** applied mid-trial, assessing site performance to determine quantity of visits. This approach maintained trial integrity, safety oversight and timely monitoring. The value for money invested and the morale of both monitors and clinical site staff improved.




**Study Z** – A tailored plan implemented from the beginning. Emphasis on early site visits to assess and correct processes, reviewing a random selection of data and leveraging sophistication of data system and real-time data management. Incorporating centralized and remote monitoring practices to allow for continuous communication of findings and to ensure proactive approach to maintaining data quality. Plan will further improve ability to focus on processes as well as reduce costs.

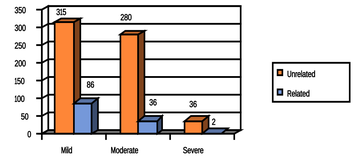



## Safety Monitoring

Since 2004 and the establishment of a single safety office as well as a central database, new studies have been assessed for possible participant risk based on the study intervention. Once risk has been determined, safety reporting parameters are tailored for each study accordingly. This assessment and tailoring process has been built upon the experiences of the review of safety data for previous NIDA CTN studies and reflects the interest of the CTN to consolidate and streamline implementation of their clinical trials while maintaining appropriate safety oversight.

1. Standardize safety definitions and specifications based on GCP definitions
2. Tailor type of events centrally reported based on severity or relationship to therapy (i.e., do not report grade 1 or 2 unrelated events)
3. Establish a standard safety reporting section for protocols
4. Provide Web-based EDC single database reporting and review of SAEs
5. Provide frequent training
6. Continue MedDRA coding

### New Strategy Applied Retrospectively




Above in orange, the number of events actually reported in a CTN trial. In blue, the number of events that would have been reported under the new strategy, a 70% reduction.

### New Strategy Applied Prospectively

**Study:** A six month trial with HIV testing and a psychosocial intervention enrolled 1281 participants using targeted safety reporting.

**Results:** 6 SAEs and a single related AE over a 6 month reporting period. No safety concerns raised by the DSMB.

**Study:** A three month IND trial is not reporting grade 1 unrelated AEs.

**Results:** This trial is ongoing and the AE reporting burden has been appropriately reduced.

The Sponsor, Institutional Review Boards, Data Safety Monitoring Boards and the FDA have accepted this strategy for safety reporting in CTN clinical trials. While safety for enrolled subjects, as assessed by the IRBs and DSMB, has been maintained, the safety reporting burden has been decreased.

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