Strategies to Collaboratively Manage Protocol Deviations in Multi-Site Clinical Trials: Perspectives from NIH

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SCT
SOCIETY FOR CLINICAL TRIALS

Celebrating 20 Years of
Research-Practice Partnerships

NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK

NIDA Clinical Trials Network (CTN)

- Established in 1999 the CTN is a collaborative effort partnering researchers, clinicians, patients and NIDA
  - Structures as group of “Nodes” (between 13 and 19) which consists of an academic center or major institution (Hub) partnering with performance sites
- Conduct rigorous, multi-site clinical trials to determine efficacy and effectiveness of substance use disorders treatment and dissemination strategies in diverse settings
  - Testing pharmacotherapies, behavioral, treatment integration, health services, etc.
- Involved in approximate 150 studies across the U.S. and abroad with over 20,000 participants recruited

NIDA Clinical Trials Network

Appalachian Node
University of Pittsburgh
West Virginia University

Big South/West Node
UT Southwestern Medical Center
UT Health Science Center at San Antonio
University of California, Los Angeles

Clinical Coordinating Center
The Emmes Corporation

Data & Statistics Center
The Emmes Corporation

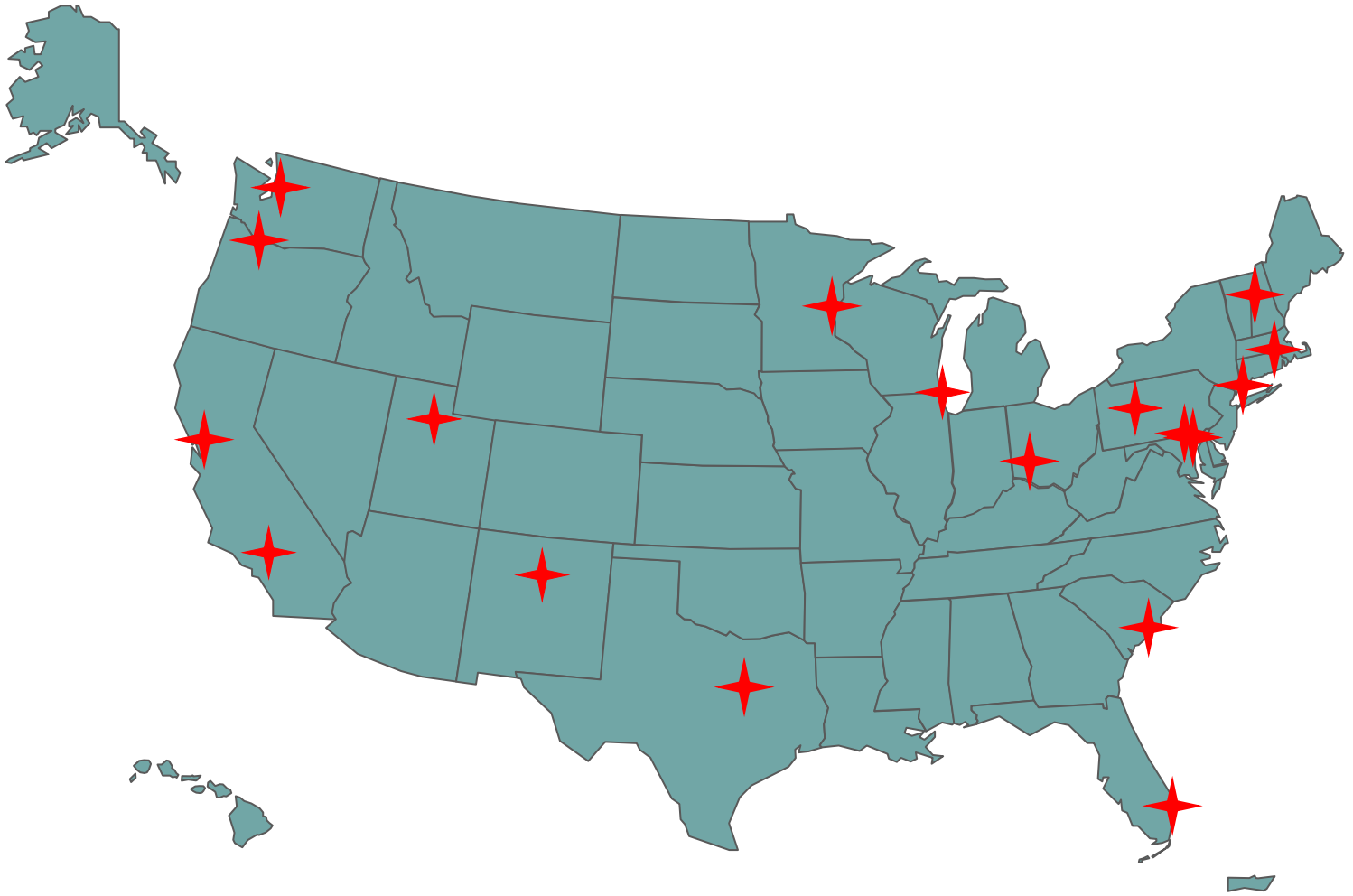
Florida Node Alliance
University of Miami
Columbia University

Great Lakes Node
Rush University

Greater Intermountain Node
University of Utah

Greater Southern California Node
University of California, Los Angeles

Health Systems Node
Kaiser Foundation Hospitals



New England Consortium
Yale University
McLean Hospital

New York Node
New York University
New York State Psychiatric Institute

Northeast Node
Dartmouth College

Northstar Node
Hennepin Healthcare Research Institute

Ohio Valley Node
University of Cincinnati

Pacific Northwest Node
University of Washington
Washington State University

Southwest Node
University of New Mexico

Southern Consortium Node
Medical University of South Carolina

Western States Node
Oregon Health & Science University
Stanford University

Protocol Deviations (PD): Definition

- Generally, a PD is an unplanned excursion from the protocol that is not implemented or intended as a systematic change (The Bioresearch Monitoring Program- BIMO, 2015).
- Is a broad term covering all instances when the protocol, as designed by the study team and approved by the IRB, is not followed.
- Two categories: minor or major
  - Minor deviation usually doesn't involve significant consequences to the study integrity. Examples: study assessments/procedures not followed in accordance with the study protocol; missing study visits
  - Major deviations are serious non-compliances that may render the participant ineligible from analysis would, such as: not obtaining consent prior to engaging a participant in the study; inclusion/exclusion criteria not met prior to enrollment; randomization and/or dosing errors

Protocol Deviations: Need for Study Integrity

- RCTs are the cornerstone for assessing the efficacy and effectiveness of interventions, but in order for study findings to be trusted, the study must be conducted following GCP and protocol procedures
- Sponsors need to establish procedures/guidelines for sites to follow to ensure appropriate trial conduct and safeguard participants safety
- Study sites need to follow the protocol and established procedures in order to obtain consistent, complete, accurate data and maintain the study rigor

Potential Implications

- Non-adherence to proper procedures may result on exclusion of data from participants or discontinuation of a site participation in the study
  - However, sometimes it means that protocol needs revision
- Ultimately, the whole study data could be questionable if sites performance is not monitored properly and corrective actions are not implemented timely
- …But **expect** protocol deviations, a “perfect” performance should be closely investigated (must likely errors were not reported for fear of punitive actions)

Protocol Deviations: Early Monitoring in CTN

- The CTN operated without a coordinating center for the first 5 years
- During that time, the CTN Steering Committee established quality assurance and regulatory standards, SOPs and guidelines for conducting research with each participating site. Most of the sites were research naïve and each Node was responsible for conducting site management and managing protocol violations (term used in the beginning for all deviations)
- Few of the Nodes had experienced staff to conduct monitoring
- Established committees and engaged experienced staff in training Nodes in conducting site management/ongoing monitoring of the studies at each site

Protocol Deviations: Categories

Created list of categories of protocol violations (PV) for site staff to use when conducting site visits. The PVs were entered into a paper log that was reviewed by monitors during site visits and summarized into their site visit report for reporting to NIDA and DSMB.

The PV Code List included the following categories:

01 – Informed Consent procedures
02 – Inclusion/Exclusion criteria
03 – Concomitant Medication/Therapy
04 – Laboratory Assessments/Procedures
05 – Study Procedures
06 – Serious Adverse Event
07 – Randomization Procedures
08 – Study Drug Dosing
09 – Behavioral Intervention Compliance
10 – Visit Schedule/Interval
99 – Other – Specify in description

Protocol Deviations: Lessons Learned

- Early studies used pharmacological interventions with complex procedures necessitating vigilance and increased monitoring at each site
- Sites were not familiar in conducting research or being closely monitored by others
- Provided extensive training to minimize negative perceptions when PVs were identified
- Used a PV data form (or log) for reporting
- Established coordinating center who used the existing categories and procedures for a few years, then collaborated with data center and established a more efficient process using data algorithms to detect deviations and report to staff for follow up at the sites

Protocol Deviations: Points to Consider

- To minimize deviations, streamline protocol procedures as much as possible. More complexity in the protocol will result in more deviations. Have a plan for minimizing errors, involve local staff with coordinating centers and establish good relationships.
- Conduct training to sites as early as possible about the value of following the procedures, but that as humans we all make mistakes, PD occurs in every study and reporting errors will not result in punitive actions.
- Identify PDs as early as possible, establish corrective actions. Site staff will learn and with time the PD will be minimal.
- For trials with many endpoints, give priority to items related to primary outcome(s).
- Work with coordinating center to establish algorithms to detect errors, even if the site staff is not reporting directly in the PD data forms.
- Again, expect PDs, there is no perfect site!