STANDARDIZING AND STREAMLINING SAFETY REPORTING IN SUBSTANCE ABUSE TRIALS

National Drug Abuse Treatment
Clinical Trials Network

Robert Lindblad, M.D.,[1] Maria Campanella, RN,[1] David Styers,[1] Prasad Kothari,[2] Steve Sparenborg, Ph.D.,[3] and Carmen Rosa, M.S.[3]
[1]The EMMES Corporation, Rockville, MD; [2]Synergy Enterprises, Inc., Silver Spring, MD; [3]National Institute on Drug Abuse, Bethesda, MD

National Drug Abuse Treatment
Clinical Trials Network

Introduction

Safety reporting in psychosocial trials is controversial. Reporting of all adverse events yields limited relevant safety information and is burdensome to clinical sites. Since 1999, the National Institute on Drug Abuse (NIDA), National Drug Abuse Treatment Clinical Trials Network (CTN) has conducted 24 randomized clinical trials in the field of drug abuse. Safety reporting was variable, reflecting the numerous investigators' experience, data centers, and study types. In 2004, the CTN created a centralized safety office. This office describes strategies to standardize safety data collection, reduce site reporting burden, and maintain appropriate safety monitoring.

Previous Reporting Strategies

	Investigational Pharmaceutical Intervention	Combination Investigational Pharmaceutical/ Psychosocial Intervention	Combination Marketed Pharmaceutical/ Psychosocial Intervention	Psychosocial Intervention Alone
Number of trials	3 (859 Subjects)	1 (154 Subjects)	1 (255 Subjects)	12 (5499 Subjects)
Adverse Event	All	All	All	1 No Reporting 2 AE Logs (6 studies) 3 Specified Criteria 4 Related Events
Serious Adverse Events	All	All	All	1 All 2 All plus added Criteria

Methods

Datasets from 17 individual protocols were obtained from the NIDA CTN Data Share web site (http://www.ctndatashare.org) and were downloaded from December 10, 2008, through August 18, 2009. Studies were divided into five categories based on whether there was a pharmaceutical component, either investigational or a marketed drug, and whether there was a psychosocial component, or a combination. Studies were reviewed for specific protocol-defined safety reporting strategies.

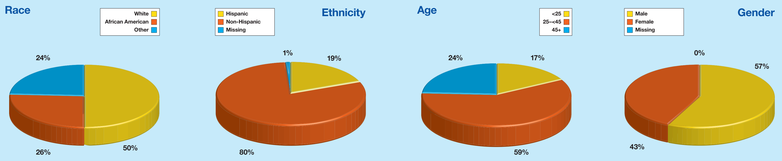
Outcome Measures

This review includes the extent of standardization of adverse event reporting across studies, the volume of reporting, and the impact of the reporting method on safety monitoring.

Results

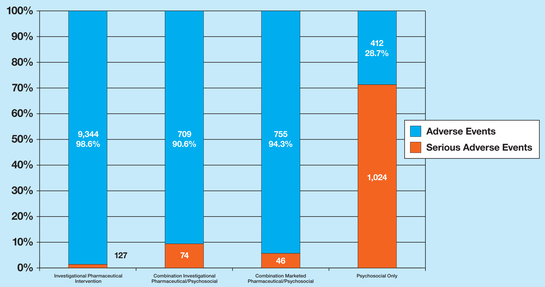
Number of Subjects	Total Number of Events (% unrelated)	Number of Adverse Events	Number of Serious Adverse Events	Number of Subjects with Reported Adverse Events (%)	Number of Subjects with Reported Serious Adverse Events (%)
6,737	12,492 (87%)	11,220	1,272	1,255 (19%)	700 (10%)

Demographics



Adverse Events/Serious Adverse Events Reported

AEs *N* = 11,220 SAEs *N* = 1,272



Pharmaceutical Intervention Studies

- There was consistent reporting of AEs and SAEs.
- On average, 2% of reported events were SAEs.
- The safety reporting burden was high.
- Results were consistent with investigational/marketed pharmaceuticals trials in new patient populations.

Psychosocial Trials

- Studies contained highly variable AE/SAE reporting that followed SAE reporting standards for pharmaceutical interventions.
- On average, 71% of reported events were SAEs.
- AEs were captured on logs in some studies, but information was not part of final data/ analysis sets.
- Many studies reported only SAEs, expanding the definition to nonmedical events such as criminal activity in adolescents.
- Many studies reported additional events as SAEs and created SAE reporting inflation (e.g., relapse of drug use, emotional distress, and suicidal ideation).
- These results created a safety reporting burden.
- Attempts were made to reduce the AE reporting burden by reporting only SAEs in many studies.

All studies conducted maintained appropriate safety monitoring.

New Strategy Developed for Safety Reporting

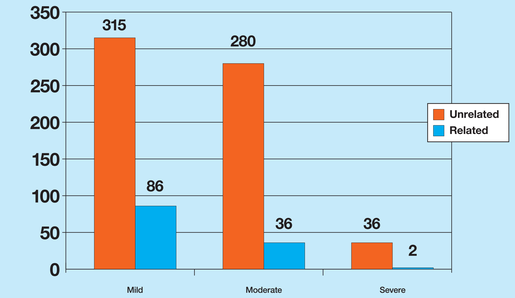
Since 2004 and the establishment of a single safety office, as well as a central database, new studies were assessed for possible participant risk based on the intervention, and safety reporting was tailored to that risk. This process is built on experience across all the previous studies and reflects the interest of the CTN to consolidate and streamline implementation of its clinical trials while maintaining appropriate safety oversight.

1. Standardize safety definitions and specifications based on good clinical practice (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 frequent training.
5. Continue Medical Dictionary for Regulatory Activities (MedDRA) coding.

New Strategy Applied Retrospectively

(Do not report grade 1 and 2 unrelated events)
Combination Marketed Pharmaceutical/Psychosocial Trial

1 study, 225 subjects enrolled, 755 AEs reported



- Would diminish reporting burden by 79%
- Would not negatively impact the safety review

New Strategy Applied Prospectively

A 6-month trial with HIV testing and a psychosocial intervention enrolled 1,281 participants using targeted safety reporting.

Results

Six SAEs and a single related AE over a 6-month reporting period. No safety concerns were raised by the Data and Safety Monitoring Board (DSMB).

Safety Review

The sponsor, the Institutional Review Board, and the DSMB have accepted this strategy for safety reporting. The U.S. Food and Drug Administration has accepted similar strategies in other clinical trial networks.

Limitations

Not all studies used the same strategies or same definitions for reporting adverse events or serious adverse events. Some psychosocial trials used local adverse event logs to record adverse events without entering them into a central data system. Adverse event definitions and forms were developed at each site, reported locally, and then transferred to a central data repository.

Notes

Visit www.nida.nih.gov/CTN for information about the CTN, www.ctndatashare.org for information about the CTN Data Share, and http://ctndisseminationlibrary.org to access the CTN Dissemination Library.

This project has been funded in whole or in part with Federal funds from the National Institute on Drug Abuse, National Institutes of Health, U.S. Department of Health and Human Services, under Contract No. HHSN271200522081C.