Strategies for Safety Reporting in Substance Abuse Trials

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\textbf{Background:} Reporting all adverse events (AEs) and serious adverse events (SAEs) in substance use disorder (SUD) clinical trials has yielded limited relevant safety information and has been burdensome to research sites. \textbf{Objective:} This article describes a new strategy utilizing standard data elements for AE and SAEs that defines a threshold to reduce unnecessary safety reporting burden in SUD clinical trials and describes retrospective review and prospective preliminary data on the strategy’s safety reporting impact. \textbf{Methods:} We developed a new strategy to standardize safety reporting and tailor reporting to the trial intervention risk. Protocols and safety data from 17 SUD clinical trials were reviewed. Retrospective analysis of five of these studies and prospective application to new studies is described. \textbf{Results:} Across the 17 previously completed trials, a total of 11,220 AEs and 1330 SAEs were reported in the 6737 participants. Wide variability in AE and SAE reporting rates were noted based on trial type and inconsistent reporting strategies. Application of the new, tailored safety strategy retrospectively and prospectively reduces reporting burden of irrelevant safety events. \textbf{Conclusion:} Comparison of the previous reporting strategies used in SUD trials to the new strategy demonstrates a more consistent safety system with a reduction in safety reporting burden while maintaining appropriate safety monitoring. \textbf{Scientific Significance:} Safety assessments should be tailored to the participant risks based on the trial intervention. The current strategies could be applied to safety assessments across all clinical trials in SUDs.

\textbf{Keywords:} safety reporting, substance use disorder, serious adverse events, adverse events, behavioral intervention, participant safety

1. \textbf{INTRODUCTION}

Clinical trials evaluate safety and efficacy/effectiveness. Safety has typically been evaluated through adverse event (AE) reporting. The collection and reporting of AEs has been inconsistent across clinical trials (1–4). In addition, there are challenges associated with safety reporting in general (5–8) including lack of harmonization from multiple oversight bodies such as institutional review boards (IRBs) (9–11), data safety monitoring boards (DSMBs) (12,13), and health regulatory agencies. Using different terms like AEs versus unanticipated problems (9–13) increases the challenges. Specifically, in trials that utilize only a psychosocial intervention, reporting of all AEs and serious adverse events (SAEs) has not revealed treatment group differences of significance but has added to the research sites reporting burden (14,15).

The National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trial Network (CTN) (16) has conducted a variety of both behavioral and pharmacological interventional clinical trials for substance use disorders (SUDs) and related conditions. The results have been published (17) and are available to the public via the CTN dissemination library (ctndissemationlibrary.org). Published reports from these CTN clinical trials describe different approaches aimed at reducing safety reporting burden and increasing reporting relevance. Variable definitions of AEs and persistent reporting burdens are noted (14,15,18).

This article presents a new safety reporting strategy, in SUD clinical trials, that standardizes AE reporting definitions and tailors safety reporting to the risk of the intervention in order to remove variability, decrease reporting burden, and maintain appropriate safety assessments. We examine safety reporting rates across trials conducted in the CTN, before and after implementation of the new strategy.
2. MATERIALS AND METHODS

All clinical trials conducted by the CTN obtained IRB approval and all participants signed written informed consent prior to participating in the research.

Trials were monitored by an independent NIDA-appointed DSMB. The DSMB reviewed the protocols, the data safety monitoring plan, ongoing enrollment, overall performance, and all reported AEs and SAEs. In addition, numerous site visits were conducted to monitor data quality (19) and staff were provided training regarding safety assessment and reporting procedures.

From 1999 to 2004, multiple data centers were used to collect clinical trial data and these data, including AE data, were transferred to a central repository (20). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). In 2005, contracts were awarded to a single data and statistical center and a clinical coordinating center with an experienced centralized safety monitoring program.

Protocols, case report forms (CRFs), and safety datasets from the 17 posted CTN protocols were obtained from the CTN Data Share website, http://www.ctndatashare.org, and were downloaded from 10 December 2008 to 18 August 2009 for review. The datasets had all protected health information removed and a unique indirect study identifier assigned. Studies were reviewed for specific protocol-defined safety reporting procedures and strategies. Although all 17 studies contributed to this review, only 5 of the 17 posted studies had complete AE/SAE reporting and the remaining 12 studies used a variety of strategies and definitions to address safety reporting.

We examined the AEs and SAEs reported and the number of AEs and SAEs per participant enrolled (PE) in each trial.

In 2007, the centralized safety office, based on extensive safety monitoring experience, developed a new strategy comprised of components designed to maintain safety for the PEs in the clinical trials and to streamline and diminish the burden of safety reporting at clinical sites. These components included:

- Standard safety definitions and specifications based on good clinical practices (GCP) definitions (21,22) (Table 1)
- Tailored safety event data reporting based on intervention risk using severity and/or relationship to therapy criteria
- Standard safety reporting section for protocols, specifying procedures, and measures for safety reporting
- Frequent and comprehensive safety reporting training
- MedDRA coding of the AE database

2.1. Standard Safety Definitions and Specifications Based on GCP Definitions

Clinical trial definitions for AEs and SAEs are based on GCP and investigational new drug (IND) definitions (Table 1) (21–23). All trials now identify and characterize AEs in a manner similar to all other types of interventional clinical trials.

2.2. Tailored Safety Event Data Reporting Based on Intervention Risk Using Severity and/or Relationship to Therapy Criteria

Safety reporting is tailored to the risk of the trial intervention. Risk is determined by the study population and the type of intervention proposed (IND-unmarketed drug, IND-marketed drug but for a different indication or population, non–IND-marketed drug using the labeled indication; behavioral intervention alone; or a combination of these). Thresholds are based on using relationship to the intervention and/or severity grading. Additionally, safety events that are considered outcomes (such as admission to a detoxification unit) are captured on a standard CRF and not additionally reported on an AE CRF consistent with FDA guidelines on safety reporting (23). Protocols were reviewed by IRBs and the NIDA-appointed DSMB without alterations to the reporting strategies.

2.3. Standardized Safety Reporting Section for Protocols, Specifying Procedures, and Measures for Safety Reporting

All trials now use an established protocol safety section template that describes the standard definitions for AEs and SAEs and clearly delineates the threshold at which safety events are required to be reported.

2.4. Frequent and Comprehensive Safety Training

Training occurs at trial initiation and continues throughout the clinical trial using web-based technology, on-site monitoring, and national clinical conference calls.

2.5. MedDRA Coding the Adverse Event Database

MedDRA coding continues to enhance the standardization of the safety database and facilitates comparison of AEs across diverse types of clinical trials.

The new tailored safety reporting strategy has been applied prospectively to five studies, only one of which has completed data collection and the others are actively enrolling. The completed trial is a behavioral HIV-risk-reduction intervention (Metsch et al., submitted for publication). We also applied the strategy retrospectively to the five previously completed trials on the CTN Data Share where complete AE reporting was performed. The number of AEs and SAEs reported and frequency of AE and SAE per subject were calculated.

3. RESULTS

3.1. AE and SAE Reporting Rates across Previously Completed CTN Trials

Results from the review of the 17 protocols listed on the public CTN Data Share revealed several strategies for reporting AEs and SAEs that included (1) reporting all AE/SAEs; (2) using AE logs to capture clinically insignificant AEs, and reporting only the related AE/SAEs; (3) reporting only SAEs; and (4) reporting only related AEs/SAEs. Table 2
The table below summarizes the safety reporting overall and the five trials where all AEs and SAEs were reported. The 17 clinical trials reported 11,220 AEs and 1330 SAEs in 6737 participants. Of note, 87% of these reported events were considered unrelated to the trial intervention. This resulted in an overall average of 1.7 AEs per PE (individual trial range 21–0 AEs/PE) and .19 SAEs per PE (range .5–.1 SAE/PE). This variability resulted in a 21-fold difference in the rate of AE reporting and a 5-fold difference in SAE reporting between the trials.

<table>
<thead>
<tr>
<th>Safety term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Adverse event</td>
<td>Any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related or not.</td>
</tr>
<tr>
<td>Suspected adverse reaction</td>
<td>Any adverse event for which there is a reasonable possibility that the drug caused the adverse event (IND Regulations – 28 March 2011).</td>
</tr>
<tr>
<td>Adverse reaction</td>
<td>Any adverse event caused by the drug (IND Regulations – 28 March 2011).</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>Life-threatening AE. (Life threatening means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred.)</td>
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<td></td>
<td>Inpatient hospitalization or prolongation of existing hospitalization.</td>
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<td></td>
<td>Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.</td>
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<tr>
<td></td>
<td>Congenital abnormality or birth defect.</td>
</tr>
<tr>
<td></td>
<td>Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of SAE.</td>
</tr>
<tr>
<td>Severity grading</td>
<td>Grade 1 – Mild</td>
</tr>
<tr>
<td></td>
<td>Grade 2 – Moderate</td>
</tr>
<tr>
<td></td>
<td>Grade 3 – Severe</td>
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<td></td>
<td>Grade 4 – Life threatening</td>
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<tr>
<td></td>
<td>Grade 5 – Fatal</td>
</tr>
<tr>
<td>Relationship to study therapy</td>
<td>Related – a reasonable possibility that the experience may have been caused by the product and/or therapy.</td>
</tr>
<tr>
<td></td>
<td>Subcategories: definitely related probably related possibly related</td>
</tr>
<tr>
<td></td>
<td>Unrelated – sufficient information exists to indicate that the etiology is not related to the study product and/or therapy.</td>
</tr>
<tr>
<td></td>
<td>Subcategories: unrelated</td>
</tr>
<tr>
<td>Unexpected event</td>
<td>Any adverse event, the specificity or severity of which is not consistent with the current package insert or investigator brochure, and if not available, the protocol, or informed consent.</td>
</tr>
<tr>
<td>MedDRA</td>
<td>MedDRA – the Medical Dictionary for Regulatory Activities: a dictionary of medical terminology used to code and classify adverse events.</td>
</tr>
<tr>
<td>Expedited safety report</td>
<td>An event that is serious, related to the intervention and unexpected, all using the definitions listed above.</td>
</tr>
<tr>
<td>Unanticipated problem</td>
<td>Unanticipated problem involving risks to subjects or others: any incident, experience, or outcome that meets all of the following criteria: (1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the subject population being studied; (2) related or possibly related to a subject’s participation in the research; and (3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.</td>
</tr>
</tbody>
</table>
TABLE 2. Safety reporting burden: cumulative and 5 of the 17 studies where complete AE and SAE information was reported.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Randomized N</th>
<th>Reported AE</th>
<th>AEs/participant enrolled</th>
<th>Reported SAE</th>
<th>SAEs/participant enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>All protocols</td>
<td>6737</td>
<td>11,220</td>
<td>1.7</td>
<td>1330</td>
<td>.19</td>
</tr>
<tr>
<td>Five studies with complete AE/SAE reporting used for retrospective review</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTN-0001 (24): Buprenorphine/naloxone versus clonidine for inpatient opiate detoxification (under IND, combined publication)</td>
<td>113</td>
<td>2363</td>
<td>21</td>
<td>13</td>
<td>.1</td>
</tr>
<tr>
<td>CTN-00002 (24): Buprenorphine/naloxone versus clonidine for outpatient opiate detoxification (under IND, combined publication)</td>
<td>230</td>
<td>1721</td>
<td>7.5</td>
<td>23</td>
<td>.1</td>
</tr>
<tr>
<td>CTN-00003 (25): Suboxone (buprenorphine/naloxone) taper: a comparison of two schedules (under IND)</td>
<td>516</td>
<td>5274</td>
<td>10.2</td>
<td>91</td>
<td>.2</td>
</tr>
<tr>
<td>CTN-0009 (26): Smoking cessation treatment with transdermal nicotine replacement therapy in substance abuse rehabilitation programs</td>
<td>225</td>
<td>755</td>
<td>3.4</td>
<td>46</td>
<td>.2</td>
</tr>
<tr>
<td>CTN-0010 (27): Buprenorphine/naloxone-facilitated rehabilitation for opioid-dependent adolescents/young adults (under IND)</td>
<td>154</td>
<td>709</td>
<td>4.6</td>
<td>74</td>
<td>.5</td>
</tr>
</tbody>
</table>

Note: CTN, Clinical Trial Network; SAE, serious adverse event; AE, adverse event.

3.2. AE and SAE Reporting Using the New Safety Reporting Strategy

We applied the new safety reporting strategy retrospectively to five trials (Tables 2 and 3) using the risk criteria described above. Those trials conducted under IND with an unmarketed drug would have no reduction in AE reporting during the drug development phase. The greatest reduction would occur in a more typical non-IND CTN trial targeting smoking cessation (Table 2 CTN-0009 (26)). This study used a nicotine patch, combined with cognitive behavioral counseling, and is considered a low-risk trial using an approved medication as labeled. This trial enrolled 225 subjects and reported 755 AEs of which 595 were mild or moderate unrelated events. Because of the low risk of the trial (marketed drug for a labeled indication), the new strategy would not report mild or moderate unrelated AEs (Table 1) and the safety reporting burden on the trial would have been decreased by 79%. Events excluded from reporting by this strategy would have included “knee pain,” “sore throat,” and “hurt arm” irrelevant to the use of a nicotine patch in a SUD population and a significant time burden for the research site.

A recently completed low-risk trial of a one-session HIV rapid testing and counseling intervention and its impact on HIV risk behavior enrolled 1281 participants. AE reporting was restricted to AEs and SAEs related to the trial intervention and all deaths throughout the trial. This resulted in a safety reporting burden of one related AE and six SAEs (deaths) for the entire 6-month trial (Metsch et al., submitted for publication). The IRBs and DSMB monitored this trial for safety and found no issues with the strategy employed or the resulting safety information. Four other CTN trials currently enrolled with ongoing IRB and DSMB review have also reduced the reporting burden and the degree is dependent on the type of trial. DSMB review also includes safety events that were captured as outcomes (such as admission to detoxification units, drug withdrawal symptoms, suicidal ideation, vital signs) in addition to the standard AE and SAE data evaluation. The four enrolled trials and four new clinical trials under development are also using this strategy and all eight trials will be reported when they are completed.

4. DISCUSSION

From 1999 to 2004, multiple investigators and data centers developed protocols and collected the safety data. This led to inconsistent strategies to report safety events and a 21-fold difference in the number of AEs reported and a 5-fold difference in SAE reported per PE. This resulted in inconsistent and undue reporting burden on the research sites. The increased reporting burden did not lead to an appreciable increase in participant safety, as monitored by IRBs and the DSMB. The four safety papers have been published by CTN investigators. Petry et al. reported four clinical trials that only captured SAEs, using standard definitions. In 1687 participants, 260 SAEs (estimated to be 520 hours of work) were reported; none were considered trial related and no treatment group differences were noted (14). Killeen et al. reported on a
single clinical trial that recorded AEs considered “clinically insignificant” on an AE log without entering them into a central database, while all related AEs and all SAEs were entered into a central database. In 353 PEs, 38% reported an AE (190 total events) and 9% reported an SAE (35 total events). They found no differences in reported events between the intervention and the control group (15). Horigian et al. described unique strategies for safety reporting in a family therapy-oriented trial for adolescents and did not rely on standard safety reporting definitions. For example, they captured (a) arrest, (b) school suspension and drop out, (c) runaway, (d) kicked out of home, and (e) violence as AEs. There were 954 events reported and only 1% related to participation in the trial (18). These data are not comparable to the other clinical trials because of these unique definitions.

Retrospective application of the new safety reporting strategy would have reduced safety reporting burden by as much as 79% and prospective application resulted in a markedly reduced safety reporting burden in a large but very low-risk HIV testing protocol.

Establishing a risk assessment and the threshold for reporting AEs based on relationship and/or severity grading are the critical components to mitigate safety reporting burden on research sites while maintaining appropriate safety monitoring. Any clinical trial that includes drug development would inherently have a greater safety reporting burdens.

These data are limited by presenting reporting burden as the number of events per PE. Data are not broken down by the type of events reported. The authors are planning to continue data analysis and report this information in a future publication.

Limitations to the newly developed safety reporting strategy include variability associated with determination of relationship or severity grading between clinicians. This has been reported previously (4); however, with appropriate training, using the assessment of relationship and severity are currently the best threshold determinants. The potential of missing a safety signal is also of concern. It is unlikely that this type of risk will be significant in trials using a marketed drug or in a behavioral trial, the most common CTN trials. Those trials exploring drug development would not have reduced safety reporting burden, commensurate with the risk. Additionally, the newly developed safety reporting system uses a broad-based review of safety information with a medical monitor, the sponsor, DSMB, and IRBs as the final adjudicators of safety. Safety reporting burden is also measured by a surrogate marker based on the number of events reported per PE. Petry et al. (14) conservatively reported 2 hours of research site time per SAE report, but there is no similar time estimate for AEs. Additionally, investigators and IRBs despite recent guidance documents from OHRP and FDA (9–11) and DSMBs have their own experiences with safety reporting. Lack of harmonization between the various review groups can further increase safety reporting burden. Open dialogs with IRBs and DSMBs are needed. A clear AE/SAE reporting plan specified in the protocol and justified based on the risks of the given intervention facilitates IRBs assessing and accepting new safety reporting strategies.

In summary, we present a newly developed, comprehensive approach to safety reporting tailored to the risks of a specific trial and its interventions. Preliminary data examined suggest this strategy reduces safety reporting burden on research site staff while maintaining a high level of vigilance toward the protection of the enrolled SUD study population. It is hoped that this approach may be of use across a range of trials of behavioral or pharmacological interventions, reducing burden, improving quality and relevance of safety data collected, and promoting comparability of safety data gathered across similar types of trials. Future research is needed to examine the extent to which this and other safety reporting strategies realize these goals.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.
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