Reporting adverse events in a surgical trial for complex congenital heart disease: The Pediatric Heart Network experience

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Objective: The purpose of this analysis was to evaluate a novel strategy for reporting adverse events in the Pediatric Heart Network's randomized surgical trial of systemic–pulmonary artery shunt versus right ventricle–pulmonary artery conduit in infants with hypoplastic left heart syndrome. The strategy was developed to align the reporting process with the needs of a surgical trial while maintaining participant safety.

Methods: Adverse event reporting was analyzed for 2 groups of study subjects: those randomized to a trial arm during a period in which a standard adverse event reporting system was used (period 1) and those randomized after institution of a system that focused serious adverse event reporting on 6 sentinel events (period 2). The analysis encompassed the period from randomization (Norwood surgery) to hospital discharge from stage II surgery. Adverse event rates were compared using a Poisson regression model for the number of events per subject.

Results: From period 1 to period 2, the rate of serious adverse events requiring expedited reporting decreased as expected (0.42 vs 0.14/subject/month of follow-up; $P < .001$). Subjects with a serious (sentinel) adverse event in period 2 had a significantly higher rate of death and cardiac transplantation.

Conclusions: The new adverse event reporting system successfully targeted subjects at highest risk, while decreasing the administrative burden associated with adverse event reports. This methodology may be of benefit in trials evaluating surgical or device-based interventions and in critically ill populations where many common clinical events would qualify as serious adverse events in the context of a drug trial. (J Thorac Cardiovasc Surg 2011;142:531-7)

Little has been published on adverse event (AE) reporting in pediatric research. There is even less experience with AE reporting in clinical trials in congenital heart disease research, and there is no regulatory guidance specific to conducting clinical research in critically ill children. Recent publications have standardized the definitions of a number of complications and AEs for patients undergoing treatment for congenital and pediatric heart diseases,[1,2] but few, if any, publications examine strategies for reporting and grading the severity of these complications and AEs in pediatric cardiac surgical trials.

The Pediatric Heart Network (PHN) was established by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), in 2001 to conduct multicenter studies in children with congenital and acquired heart disease.[3] Early PHN protocols[4,5] effectively used standard principles for reporting AEs that adhered to the criteria for defining serious AEs (Table 1). These general principles are established by the International Conference on Harmonisation, a body of clinical trial guidance derived from the collaborative efforts of the United States, European Union, and Japan and implemented by the federal Office of Human Research Protections and the Food and Drug Administration.[6,7] Coding dictionaries or classification systems are used to augment this guidance and provide a standardized approach to reporting AEs in clinical studies. The PHN used the Common Terminology Criteria for Adverse

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For the Pediatric Heart Network Investigators, see Appendix 1.

Supported by U01 grants from the National Heart, Lung, and Blood Institute (HL068269, HL068270, HL068279, HL068281, HL068285, HL068292, HL068290, HL068288, HL085057).

ClinicalTrials.gov number, NCT00115934.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Sept 16, 2010; revisions received Sept 16, 2010; accepted for publication Nov 26, 2010; available ahead of print March 14, 2011.

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0022-5223/$0.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2010.11.052

Abbreviations and Acronyms

AE = adverse event
CTCAE = Common Terminology Criteria for Adverse Events
DCC = Data Coordinating Center
DSMB = Data and Safety Monitoring Board
IRB = institutional review board
NHLBI = National Heart, Lung, and Blood Institute
NIH = National Institutes of Health
PHN = Pediatric Heart Network
SAE = serious adverse event
SVR = Single Ventricle Reconstruction trial

Events (CTCAE), version 3.0, developed by the National Cancer Institute, NIH. These principles and tools provided standard definitions of AEs and serious adverse events (SAEs), a system of severity scoring, and reporting guidelines, designed particularly for drug trials.

The limitations of the standard AE reporting approaches became apparent during the PHN's Infant Single Ventricle Trial, which compared treatment with enalapril to placebo in critically ill infants with single ventricle physiology.[8,9] There were not enough appropriate pediatric CTCAE codes to cover the complexity of this trial population, and the CTCAE severity scale was not developed for trials in critically ill infants. Discussions, training, and close monitoring for the duration of the trial were implemented to refine our approach to AE reporting.

Then in May 2005, the PHN launched the Single Ventricle Reconstruction (SVR) Trial, a randomized trial comparing a systemic–pulmonary artery shunt versus a right ventricle–pulmonary artery conduit in infants with hypoplastic left heart syndrome undergoing initial surgical palliation.[10,11] The SVR trial began with a standard AE reporting framework modified on the basis of lessons learned in the Infant Single Ventricle Trial, but it soon became clear that an AE reporting system based on the standard strategy for drug studies was inappropriate for this surgical trial. The specific challenge was that many clinical events that are common in the postoperative period qualify as serious AEs in the context of a drug trial; thus the standard reporting paradigm resulted in excessive reporting while providing a disproportionately small amount of useful safety information. Moreover, the large number of reports generated considerable administrative workload for individual investigators, study coordinators, and institutional review boards (IRBs)/research ethics boards as well as the NIH, the data coordinating center, the medical monitor, and the Data and Safety Monitoring Board (DSMB).

To enhance the ability to recognize clinically meaningful events, PHN investigators turned to the sentinel event concept. A sentinel event, as defined by the Joint Commission on Accreditation of Healthcare Organizations, is an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof, that signals the need for immediate investigation and response.[12] In a research context, sentinel perinatal events have been identified that predict patterns of brain injury.[13]

The purpose of this analysis was to compare two AE reporting methods used in the SVR trial to assess the accuracy of predicting the most severe adverse outcomes in the study population and the associated changes in reporting burden.

PATIENTS AND METHODS

Patient Population

The design of the SVR trial has been described[8] and the main results reported.[9] Neonates with hypoplastic left heart syndrome and other single right ventricle malformations were enrolled at 8 main PHN clinical sites and 7 SVR auxiliary sites. Subjects were randomized to receive a Norwood procedure with either a modified right Blalock–Taussig shunt or right ventricle–pulmonary artery conduit to provide pulmonary blood flow. The primary end point was death or transplant at 12 months. The protocol for the SVR trial was approved by each center's IRB, and written informed consent was obtained from a parent or guardian.

Safety Monitoring and AE Reporting Processes

The SVR trial protocol underwent review by an independent DSMB appointed by NHLBI to oversee all PHN studies and was subsequently approved by the IRBs at all sites, including the PHN Data Coordinating Center (DCC). AEs were recorded and submitted by the site team via a secure, web-based electronic data capture system to the DCC, with immediate reporting of SAEs to the DCC, NHLBI, and the independent PHN medical monitor, a pediatric cardiologist with expertise in cardiac critical care. Sites reported AEs/SAEs to their IRBs as dictated by local requirements. The DSMB reviewed study data every 6 months, and a summary of this review was sent to the local IRB to ensure that all participating centers were informed of any pertinent safety findings.

SAEs were initially defined in the SVR trial as events that met the criteria in Table 1. In this phase of the SVR trial, May 2005 to January 2007, referred to here as period 1, each AE and SAE was recorded and submitted to the DCC. The events were categorized in standard fashion as to the degree of relatedness to the trial intervention. The site investigator categorized the response to the AE as surgical or catheter intervention, medical therapy, or none; the clinical outcome was characterized as resolved or stabilized.

A revised approach, developed by the SVR Adverse Events Subcommittee, was implemented from February 2007 to trial end in October 2009 (period 2). The SVR AE subcommittee included congenital heart surgeons, pediatric cardiologists and cardiac intensivists, study coordinators, the AE coordinator from the DCC, and NHLBI staff. The subcommittee reviewed the limited published literature and obtained information from pediatric investigators who had been involved in previous operative and perioperative surgical trials.[14-16] An AE framework was established consistent with the concept of the sentinel event in patient safety literature.

Six "sentinel" SAEs, considered sufficiently serious for the SVR trial population, were identified (Table 2) and triggered expedited reporting. The frequency of these events was known from published retrospective outcome reports on neonates with hypoplastic left heart syndrome after Norwood palliation,[17-19] so there was a precedent for determining the number of reported events. Following standard practice, in addition to