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Serious adverse events of older adults in nursing home and community intervention trials

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ABSTRACT

Background/Aims: Clinical trials of older adults are increasingly common, but risks of serious adverse events (SAE) may vary. We describe the incidence of SAE in two randomized trials, one community-based and one nursing home-based.

Methods: We performed a secondary data analysis from two randomized clinical trials at one academic health center and 21 nursing homes involving 200 sedentary community dwellers aged 70–89 years and 185 female nursing home residents aged 65 years or older. Interventions included structured physical activity to reduce mobility disability in the Lifestyle Interventions and Independence for Elders (LIFE) study and oral cranberry capsules to reduce bacteriuria plus pyuria in nursing home residents (CRANNY) trial. We measured SAE incidence per 100 person-years and incidence of protocol-related unanticipated SAE per 100 person-years in LIFE and CRANNY trials.

Results: Mean age and proportion of patients with dementia in LIFE and CRANNY trials were 79.3 years and 86.4 years and 0% and 78%, respectively. There were 179 total SAE in LIFE including 8 (4%) deaths, and 116 total SAE in CRANNY including 33 (28%) deaths. SAE incidence was 33.7 (95% CI 27.2, 41.8) events per 100 person-years in LIFE and 69.4 (95% CI 49.1, 98.1) events per 100 person-years in CRANNY. No protocol-related unanticipated SAE occurred in either trial.

Conclusions: The frequency and severity of SAE vary in older adults. While SAE are common in nursing home residents, protocol-related, unanticipated SAE are rare in nursing home residents and community dwellers. This finding can inform trial monitoring protocols.

Trial registration: ClinicalTrials.gov identifiers: NCT01072500 and NCT01691430.

1. Introduction

Diseases of aging require continued study with intervention trials to reduce disease severity and prevent disability. Inherent in all intervention trials is the need to monitor and report adverse events. The vast majority of adverse events are anticipated, and only unanticipated problems as defined by the U.S. Department of Health and Human Services that are protocol-related warrant reporting (Fig. 1) [1]. Current National Institute on Aging (NIA) guidelines on adverse event surveillance require documentation of all adverse events with expedited reporting (within 48 h of Principal Investigator notification) of all serious adverse events (SAE) to the Data and Safety Monitoring Board and NIA irrespective of protocol relationship [2].

Resources required to meet NIA reporting guidelines may be prohibitive for intervention trials of older adults. Typically, personnel record adverse event data on paper forms including the nature and time of the event, associated hospitalizations, when the Principal Investigator was notified, and whether the event is ongoing or warrants reporting to external entities or study participants. This process may be labor-intensive for older adults that have differing susceptibilities to

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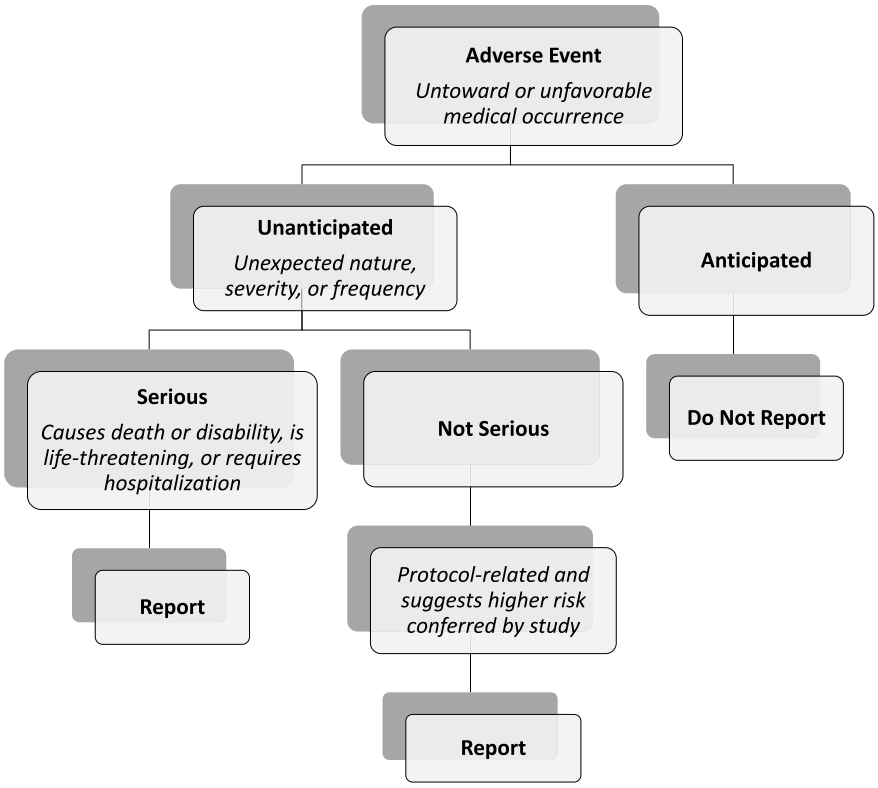

Fig. 1. Adapted from current adverse event reporting guidelines under Department of Health and Human Services Code of Federal Regulations Title 45 Part 46.

SAE. Specifically, nursing home residents may be high-risk for SAE by virtue of functional disabilities, grouped quarter living hazards (e.g., exposure to infectious disease outbreaks) and greater comorbidities compared to highly functional older community dwellers. Thus, high-risk nursing home residents are more likely than older community dwellers to meet SAE definitions during participation in intervention trials. However, data regarding SAE occurrence in low-risk intervention trials of older adults are lacking [3–5]. Quantifying SAE incidence in low-risk intervention trials of older adults may inform trial monitoring protocols and resource allocation for clinical personnel. For example, if expected SAE incidence is low, Principal Investigators may consider assigning less personnel time and effort towards SAE surveillance.

As investigators from two older adult clinical trials, one among a cohort of community dwellers (i.e., lifestyle interventions and independence for elders [LIFE] trial) and one among a cohort of nursing home residents (i.e., CRANberry capsules for prevention of urinary tract infection in Nursing home residents at Yale [CRANNY]), we are uniquely positioned to describe SAE using primary data from two distinct older adult populations. This study aimed to describe the incidence of SAE per participant-month of surveillance in LIFE (including only participants at the Yale site) and CRANNY and to describe the incidence of protocol-related, unanticipated SAE among participants in LIFE and CRANNY to inform resource allocation for SAE monitoring and reporting.

2. Methods

2.1. Participants

This study consisted of 200 participants enrolled in the LIFE trial at the Yale site, and 185 participants enrolled in the CRANNY trial. Only the Yale participants in LIFE were included to allow for comparable samples sizes and geographic distribution between both clinical trials. Participants in LIFE were sedentary older men and women with functional limitations randomized to a physical activity intervention or a successful aging health education intervention targeting prevention of major mobility disability. Participants in CRANNY were women nursing home residents age 65 or older who were randomized to cranberry capsules versus placebo capsules for reduction or prevention of bacteriuria plus pyuria. Further details of these participants have been reported elsewhere [6,7]. The Yale Human Investigation Committee approved this study.

2.2. Data collection

Baseline demographic and SAE data collected through the parent clinical trials have been reported previously [6,7]. In LIFE, SAE included death, a life-threatening event, persistent disability/incapacity, hospitalizations, and clinically significant laboratory and clinical test results. In CRANNY, because of the significant baseline frailty of the population, SAE included deaths and hospitalizations. NIA guidelines for adverse event monitoring and reporting were followed in both trials over the participant surveillance period [8].

Anticipated SAE were outlined in each IRB protocol. Unanticipated SAE included those that were unexpected, in terms of nature, severity, or frequency given (a) the research procedures described in the protocol-related documents (e.g., IRB protocol, informed consent document); and (b) the characteristics of the study population. Protocol-relatedness of the SAE was defined as a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in research. SAE categorization as anticipated and/or protocol-related was made by study personnel.

2.3. Statistical analysis

Means and standard deviations and counts and percentages are reported for characteristics of LIFE and CRANNY study participants. Tests of significance for differences between the two cohorts are not provided because of multiform distribution differences and lack of measurement standardization between the two study samples. Observed counts and rates are reported for SAE for both cohorts. Generalized linear models with Poisson distributions using natural logarithms for time at risk