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The Utility of the National Death Index in Identifying Deaths in a Clinic-based, Multi-site Cohort: The Experience of the Pediatric HIV/AIDS Cohort Study

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Introduction

Loss to follow-up (LTFU) is a serious concern in longitudinal research studies. High LTFU rates can bias study results¹, particularly if the reasons for the losses are related to the outcomes under investigation. When the death of a study participant goes unrecognized or unreported, a crucial endpoint goes undocumented while research staff may continue efforts to pursue contact, leading to the unnecessary use of study resources.

The Pediatric HIV/AIDS Cohort Study (PHACS) is a multi-site cohort study of the effects of human immunodeficiency virus (HIV) infection and antiretroviral medication use in youth and young adults born with HIV or uninfected but exposed to HIV at birth^{2,3}. PHACS opened to enrollment in 2007 at 24 study sites in the United States (U.S.). In 2015, a search of the National Death Index (NDI) was implemented to identify previously-unreported deaths among LTFU participants among the 4,207 participants enrolled in two PHACS youth cohorts. Given that death is a primary outcome measure in PHACS, it is important to determine whether the reason that contact ceased is due to a participant's death.

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Methods

The NDI is a centralized database of death record information on file in U.S. state vital statistics offices. It is maintained by the National Center for Health Statistics for the purpose of research. It is widely used to obtain outcome data in mortality studies; the NDI webpage provides a reference list of 658 peer-reviewed articles from studies using NDI data⁴.

Permission to conduct an NDI search is obtained by completing a 23-page application. Confidentiality agreements, institutional signatures, IRB approval letters, and other supporting documents must be provided on behalf of all individuals who will have access to the search results. PHACS is a collaboration between nine NIH institutes and close to 30 academic and research institutions, including study sites, two leadership centers based at Harvard and Tulane Universities, a contract research organization (CRO), and a data management center (DMC). In order to reduce the effort required to complete the application the submission process was delegated to the CRO. The handling of the output files produced by the search were limited to the CRO, the DMC, and the leadership center at Harvard. Nonetheless, the information and supporting documentation required for the application was substantially greater than for studies for which a single applicant could handle both the application and the output files produced from the search.

The compilation of the user records, which contain the identifying information necessary to conduct a search, required coordination among staff from all study sites. In order to facilitate the task of identifying LTFU participants, the DMC used information from the study database to create lists for review by sites of participants meeting the study's LTFU definition of "no contact for two consecutive study visit windows, or approximately 2.5 years." Because participants are identified by randomly-generated Participant Identifiers in the study database, once staff confirmed that a participant was indeed LTFU (versus missing two study visits but still in contact with the site), they needed to take the additional step of replacing the Participant Identifier with his/her name in order for CRO staff to create user records to submit for the search.

Across all sites, LTFU status was confirmed for 231 of 4,218 participants (5.5%). User records were created pursuant to the NDI User's Guide for specific data coding and specifications and included first and last names, sex, and dates and states of birth

Results

Possible matches were produced for 95 of the 231 user records. PHACS investigators reviewed the output and concluded that only one record was a true match, and a death certificate was obtained for confirmation. Using the NDI, PHACS was able to document one previously-unidentified death among the 231 LTFU study participants (0.4%).

Discussion

The process of completing the application to conduct the NDI search, collecting the required information from the clinical sites to create the user records, and handling and interpreting the output files proved complicated and time-consuming for a multi-site research network

like PHACS. The PHACS investigators concluded that the additional data gained from the search did not justify the resources invested to complete the application, compile the user submission records, and review the search results. Subsequent searches are unlikely to be pursued.

It is unclear whether the search produced only one true match because there were additional, actual deaths that were not identified or because there was indeed only one death among the LTFU participants. There are several factors that may support the conclusion that there may be actual deaths that the search did not identify. The likelihood of receiving a match increases according to the level of personal information that can be provided. In an HIV study, where confidentiality is of paramount importance, research staff are sensitive to the desire to limit the collection of personally identifying information. Published studies documenting the utility of the NDI in establishing deaths among study cohorts were typically able to provide social security numbers^{5,6}, which PHACS does not collect from study participants. Also, NDI records are limited to deaths occurring within the United States. PHACS study sites serve a diverse patient population. Although the large majority (>99%) of participants enrolled in the two youth cohorts for which the NDI search was conducted were born in the U.S., 32% of caregivers of participants in the perinatally exposed, uninfected cohort and 28% of caregivers of participants in the perinatally HIV infected cohort were born outside of the United States. Site staff report that it is not unusual for youth participants to move frequently between the area where the study site is located and their primary caregivers' country of birth, increasing the likelihood that a death may take place outside of the country. Given these circumstances, an NDI search may be a more worthwhile investment of resources for studies that can provide more personally identifying information or have a less diverse, more geographically stable cohort.

There is also evidence to support the conclusion that the single, true match was indeed the only death occurring among the LTFU group. PHACS is a clinic-based study for which participants give permission to access their medical records, and often the clinic is also a direct health care provider to the participants. As a result, study staff may be more likely to learn of participant deaths as they occur, reducing the likelihood that there are unidentified deaths. In addition, the average age of PHACS LTFU participants was 10 years. While the NDI has been used with success to document mortality among HIV cohorts^{7,8}, the younger age of the PHACS cohort, advances in HIV care in the United States, and better engagement with care among youth versus adults may reduce the risk of mortality in this pediatric cohort^{9,10}. Among the 3,986 participants not LTFU, there have been 27 participant deaths (<1%) since PHACS opened to enrollment ten years prior to the initiation of the search. It may be reasonable to conclude that the observation of one death among the 241 LTFU participants is valid when considered within this context. Moreover, most PHACS participants were born to women infected with HIV but are not infected themselves and thus may not be subject to the same mortality risk as participants in other HIV cohort studies. An NDI search may be a more productive effort for studies of cohorts with a higher mean age or which anticipate higher mortality rates based on the health status of their study participants.

The NDI offered limited utility in identifying previously-unrecognized participant deaths in this clinic-based, multi-site pediatric study. Although it was a benefit to the study to be able

to identify even one previously unknown death, given that death is the most serious outcome that can be documented, the resources required to conduct an NDI search lead us to conclude that it may not be a time- or cost-effective approach to obtaining mortality data for studies with a design or cohort characteristics similar to PHACS. We recommend the application process be streamlined to reduce the time, effort, and resources required to complete an application to conduct an NDI search for a multi-institution study.

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