Statement B for

Tissue and Organ Donor Epidemiology Study (TODES)

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B. Statistical Methods

B.1. Respondent Universe and Sampling Methods

With guidance from the project/s Working Group, RTI decided to select a purposeful sample of OPOs to participate in TODES. RTI selected Twenty-four (24) Organ Procurement Organizations (OPOs) and eye banks with a mix of donation volume and geography to represent areas with higher and lower rates of the infectious disease markers of interest and included at least one OPO from each of the 11 Organ Procurement Transplantation Network (OPTN) – defined regions. The U.S. is divided into these regions to facilitate communication and transparency of policy development related to organ procurement and transplantation. The population of the total catchment areas for the OPOs invited to participate in TODES is greater than 150 million which represents about 50% of the U.S. population. RTI also worked with the American Association of Tissue Banks (AATB) to develop a strategy for soliciting participation by tissue banks. After discussion with several of the large tissue processors, it was determined that the most efficient method for collection of data from tissue donors is to target the same OPOs that plan to provide organ data which represents about 50% of all tissue donors recovered.

For ocular donors, RTI worked with the Eye Bank Association of America (EBAA) to identify the seven eye banks with the highest volume of donors. These eye banks are included in the TODES Participation Plan of 24 facilities. RTI will be able to determine reliability by comparing the study results from the eye banks with reports produced by the EBAA for the years represented in the study: 2009-2013.

RTI will obtain data directly from the United Network for Organ Sharing (UNOS) and invite the targeted OPOs and eye banks to participate in TODES by extracting and providing non-identifying donor-specific retrospective data from their donor records for calendar years 2009-2013. RTI had held initial communications with the 24 donor facilities to describe TODES. We do not expect all of them to participate. There may be donor facilities that do not participate and RTI may obtain data from another donor facility as a replacement. It is expected that 24 facilities, total, will participate in TODES.

Specifically, the 24 facilities have been recruited to provide demographic, organ, tissue, and eye donation information as well as infectious disease test results for deceased donors and referrals entered into the organizational databases between 2009 and 2013. TODES requires participating organizations to extract the relevant data from their existing records of deceased donors and potential donors (referrals). Therefore, the burden will rest on the participating organizations and not individual members of the public associated with the data. It is important to note that although the basic unit of analysis is a donor, the basic unit of study participation is the responding organ procurement or eye bank organization. It is estimated that each participating

organization will contribute, on average, 1000 records per year from authorized donors and referrals with infectious disease test results.

As this is not a survey, but an early investigation into infection rates in a poorly-studied population, sample size and power calculations for a priori hypothesis testing is less of a concern. However, with each organization submitting, on average, 5000 records, we expect the aggregate study database to contain between 200 and 120,000 records for each infectious disease test. In order to understand the expected widths for 95% confidence intervals of prevalence using the Clopper-Pearson method, simulations involving 10,000 replications were used to calculate the average 95% confidence interval width for a variety of samples sizes and proportions, Table 1. Table 1 shows that for any test that has at least 10,000 records, as long as the prevalence is less than 0.3, the expected width will be less than 2 percentage points. Similarly, for a prevalence estimate as low as 0.001, the expected 95% CI will be 2 percentage points for a test that only contained 200 records. Table 1 illustrates that the present study will collect sufficient data to estimate initial prevalence estimates with a sufficiently tight 95% CI for infectious disease tests that contribute at least 1000 records.

Table 1: Expected Clopper-Pearson Confidence Interval width

Average 95% CI Width		Observed Prevalence							
		0	**0.0001**	**0.001**	**0.01**	**0.05**	**0.1**	**0.2**	**0.3**
Sample Size	**200**	0.018	0.018	0.027	0.045	0.076	0.096	0.122	0.135
	1000	0.004	0.004	0.007	0.016	0.030	0.040	0.052	0.059
	10000	0.0004	0.0007	0.0016	0.0042	0.0089	0.0121	0.0159	0.0182
	20000	0.0002	0.0005	0.0011	0.0029	0.0062	0.0085	0.0112	0.0128
	50000	0.00007	0.00025	0.00062	0.00181	0.00388	0.00532	0.00706	0.00807
	75000	0.00005	0.00019	0.00050	0.00147	0.00316	0.00433	0.00576	0.00659
	100000	0.00004	0.00016	0.00043	0.00127	0.00273	0.00375	0.00498	0.00570

B.2. Procedures for the Collection of Information

This study will engage in secondary analyses of extant data from organ procurement organizations and eye banks. The extant data were collected at the time that the deceased organ and/or tissue donor was identified by these organizations. The data requested by TODES will not be identifiable to any individual person; rather, all organs and tissues are assigned an ID code(s) allowing tracking of multiple tissues and organs from one facility to another along with information about the donor relevant to eligibility and donation status. The data that will be extracted from existing donor records at participating organizations for TODES will not permit RTI or HHS to link information back to individual persons either as donors or recipients of transplanted organs and tissues. The sharing of data for research purposes under TODES will be covered by Data Use Agreements executed between each participating organization and RTI.

The specific data to be obtained from the participating organizations include the following categories of information:

1. Donor demographics and death information;

2. Donor infectious disease test results for HIV, HBV, and HCV; including serological assays and nucleic acid testing when available; and

3. Basic donation and disposition information regarding organs, tissues, and/or eyes.

The participating organizations will extract the relevant data from their existing donor records for calendar years 2009 – 2013 and the data will be transmitted securely to RTI as line data (one record per donor). Data requested for TODES will not require additional processing, mathematical manipulations, or summarization on the part of the participating organizations.

The infection rates calculated from the selected OPOs will not be generalizable to all OPOs but will provide a valuable estimate of the prevalence ranges for the viral markers of interest. RTI will analyze trends over time, as well as the rates based on antibody screening, screening plus confirmatory testing, and nucleic acid testing (NAT) where available. The data and additional (verbal) information resulting from TODES will allow better characterization of these facilities by describing the data systems utilized, both manual and electronic, the extent of data collection and data storage, as well as the level of detail that is captured for organ, tissue, and eye donors and referrals; an understanding of the referral and screening process including reasons for elimination of potential donors and the order of screening steps during the referral process; and use of the testing results to estimate risk of infection associated with organ and tissue transplantation. This study will lay the groundwork for conducting future, prospective epidemiologic studies of organ and tissue donors that could inform policy decisions related to donor eligibility and qualification, and potentially, increase the donor pool.

B.3. Methods to Maximize Response Rates and Deal with Nonresponse

OPOs and eye banks were selected for inclusion in the study based on geographic region, donor volume, and infectious disease prevalence estimates for their catchment areas. To maximize participation, RTI conducted initial teleconferences with the United Network for Organ Sharing (UNOS), selected OPOs, the American Association of Tissue Banks, and the Eye Bank Association of America to better understand donor referral and screening processes, the various data management systems used by organ, tissue, and eye banking organizations, and the variations in data collection procedures between organizations. Basic information was shared regarding geographic region, service area, population size, referrals, donation volume, data systems/features/resources, and willingness to participate. The OPOs involved in these initial discussions were identified in collaboration with HHS and the TODES Working Group, which included OPO representation, Federal partners, and clinical advisors. The Working Group also

provided input on the study aims and data variables of interest. These discussions provided RTI with a better understanding of the donor selection process, as well as the resulting data records generated and stored by organ, tissue, and eye donor organizations.

In March of 2014, RTI held an in-person meeting with representatives of four regional OPOs to review the study objectives and discuss the data variables under consideration. This face-to-face discussion informed the final data variables list, and, due to direct OPO participation, will encourage study participation. The extensive planning discussions, the involvement of UNOS, and additional technical assistance and support to the participants will greatly reduce the burden of data extraction on the participants. TODES will directly obtain some of the organ donor/donation data from the United Network for Organ Sharing (UNOS) which operates a centralized national Organ Procurement and Transplantation Network (OPTN) for the purpose of managing the nation's organ transplantation system under contract with the U.S. Department of Health and Human Services. This will further reduce the burden on the participating organizations and result in a high degree of study cooperation and completion among those organizations that agreed to participate in the study.

B.4. Test of Procedures or Methods to be Undertaken

Viral Prevalence

Serological assay results will be used to calculate unadjusted prevalence estimates for HIV, as well as the prevalence of HBV and HCV seropositivity. Serological results will be available for all donors, and some OPOs will provide nucleic acid test (NAT) results.

In addition to estimating prevalence, the PROC FREQ procedure in SAS™ (Cary, NC) and the Clopper-Pearson method will be used to calculate exact confidence intervals for the prevalence. If the observed prevalence is zero, then an upper limit will be estimated and the lower limit will be set to 0. The target Type I error for the exact confidence intervals will be 0.05.

Fisher's exact test will be used to compare prevalence by binary variables such as sex or high risk status. Logistic regression models will be used to model prevalence as a function of multiple donor characteristics such as sex, high risk, age at death, cause of death, etc. Where possible, these logistic models will be estimated using exact methods available in PROC LOGISTIC.

Viral Incidence

Because the data available for this study are cross-sectional, direct incidence estimation is not possible; however, the method of Zou et al (2004) will be used to indirectly estimate viral incidence. The method used by Zou estimated the incidence of HBV, HCV, HIV, and HTLV by applying estimates of age- and sex-specific incidence rates for first-time blood donors to tissue donors. The incidence rates in blood donors were adjusted to tissue donors using the ratio of the prevalence rates in blood and tissue donors. We will use a similar approach by utilizing

prevalence and incidence data from blood donors obtained from an appropriate existing blood donor database. In addition to the indirect estimate of viral incidence, we will utilize NAT-yield results to estimate incidence to the extent possible, and compare the results of both methods.

B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Members of the research team are quantitative data experts, epidemiologists and biostatisticians. We have consulted with UNOS, OPOs, AATB, and eye transplant specialists, as well as received input from the TODES Working Group (Attachment 4) regarding study design, protocol development, and data collection and management. Data analysis will be performed by the biostatistical staff at RTI International.

REFERENCES

Zou S, Dodd RY, Stramer SL, Strong DM. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. NEJM. 2004;351:751–9.