Supporting Statement B for
National Tissue Recovery through Utilization Survey (NTRUS)

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PART B – STATISTICAL METHODS

1. Respondent Universe and Sampling Methods

Regulation outlining "Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments" [1] includes recognition by the federal government of a distinct group of tissue types used for transplantation. The term 'conventional tissue' is used often and is described as a wide range of human tissue that includes pericardium, dura mater, heart valves, skin allograft, bone allograft, fascia, tendons, and ligaments. The preamble to the regulation describes the Food and Drug Administration's (FDA's) survey of relevant clinical literature indicates 'conventional tissue' presents a different potential for communicable disease transmission risk and graft failure, and thus different levels of potential benefits from improved processing procedures and quality assurance steps used when manufacturing tissue. Operational and financial impacts of the regulation on 'conventional tissue banks' are also thoroughly described.

The respondent universe for NTRUS comprises tissue banks registered with FDA from this unique sector of all human cell, tissue, and cellular and tissue-based product (HCT/P) establishments. Of these FDA registered tissue banks, about 83 percent are accredited by the American Association of Tissue Banks (AATB).FDA concluded that 75 to 80% of conventional tissue banks in the United States voluntarily follow AATB Standards. These tissue banks handle donor referrals, obtain informed consent or authorization to recover or acquire tissue, and they perform manufacturing functions that include donor screening and testing, and tissue recovery, processing, storage, and distribution. These functions are managed by an overarching quality program (e.g., audits of activities, investigation of adverse reaction reports) and operations are subject to periodic inspections by external agencies. These tissue banking and tissue manufacturing steps equate to the section topics that comprise NTRUS.

In addition, all AATB-accredited transplant tissue banks must fully cooperate with and complete AATB-sanctioned surveys [2]. To achieve the most accurate estimation of tissue donation activity, the tissue banks not accredited by the AATB engaged in donor screening and recovery of conventional tissue will be contacted to participate in sections of NTRUS relevant to their activities. These tissue banks are registered with FDA and comprise about 25 percent of this category. This approach was taken previously and the goal of NTRUS is a 100% response rate to match the response rate experienced for a similar survey conducted by AATB when gathering data for 2007.

Due to the very high saturation of the involvement of conventional tissue banks accredited by the AATB as NTRUS respondents, use of a statistical sampling method to identify and select survey respondents is not indicated.

2. Procedures for the Collection of Information

NTRUS will use a mix of open and closed questions developed by AATB with consultation from subject matter experts at tissue banks and AATB, officials from the

Office of the Assistant Secretary for Health (OASH), the Center for Biologics Evaluation and Research (CBER) at FDA, and the Centers for Disease Control & Prevention (CDC), with ultimate approval by the U.S. Department of Health and Human Services (HHS).

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

1. Tissue bank inspections;
2. Donor referrals, consent/authorization, ineligibility screening ;
3. Basic donor demographics, quantities and types of tissue recovered
4. Quantities and types of tissue processed, methods to eliminate microorganisms and preserve tissue, processing tissue from non-U.S. sources
5. Storage of unprocessed and processed tissue
6. Quantities and types of tissue distributed, ability to meet demand for certain tissue types; tissue distributed outside the U.S. and countries
7. Donor test results for communicable diseases
8. Adverse outcome reports

The participating organizations will extract the relevant data from their existing donor records for calendar years 2012 and 2015

Using an online survey tool, AATB and an approved subcontractor, In-Touch Insight Systems (http://www.intouchinsight.com), will ensure the structure and flow of questions to maximize response rates as well as the quality of response data. In-Touch Insight Systems (I-TIS) was selected because they have a notable history that spans more than thirty years working with private and public sector clients to track performance using surveys that provide practical, affordable and strategic insights to organizations. I-TIS was the survey company AATB enlisted to perform the survey that captured 2007's data. The subcontractor's team includes program managers, analysts, and developers who have years of experience in the design, development and operation of survey and associated reporting solutions. I-TIS will strive to: improve the survey's design and analysis; accelerate time to results; reduce complexity and risk; leverage proven technology; and, provide live real time dashboard reporting.

Using communication by phone and email, a responsible person at each tissue bank will be established as the primary contact to oversee their data entry and completion of the survey. An email invitation from AATB will follow that explains NTRUS, the importance of the submission of accurate data, deadlines for data entry, expected compliance to AATB's accreditation policies (where applicable), and it will contain a unique, secure link to the online survey instrument.

When the link in their email is accessed, the respondent will be taken into the survey and will see a 'task list' of only the sections their tissue bank will complete. Each section may be completed directly into a computer or it can be printed allowing the responding tissue bank to gather the information they need offline, and submit the responses to that

section online in one sitting. To accommodate those tissue banks involved in many tissue banking functions, the sections of the survey can be completed one section at a time. Using the unique link in the email, respondents will be able to return to their 'task list' to complete subsequent sections of the survey. For storage and future reference, each tissue bank will have the ability to save and/or print their own information once they have completed the survey.

The final data will be downloaded and held on secure servers. At the end of the survey period, the survey will be taken offline. All data is archived for a period of 2 years after the survey ends.

3. Methods to Maximize Response Rates and Deal with Nonresponse

The AATB manager assigned to NTRUS will be given a unique login and password that provides unlimited access to aggregate results data, as well as for each individual tissue bank. Online reporting will be updated on a daily basis and a comprehensive online dashboard and analytical reporting will be available to the AATB manager. A unique dashboard will be created for HHS to be able to monitor progress but all data will be de-identified in regard to which tissue banks have submitted data. This access is 24x7, web-based, and will be completely customized to capture frequency of access by survey participants and entry of survey data.

In an effort to maximize response rates, progress will be monitored continuously by I-TIS. A reminder email will be sent and, when necessary, phone calls will be made to survey respondents. Response rates will continue to be monitored through to completion of the survey. To accommodate busy work schedules and reduce burden for respondents, tissue banks will be given one month to enter data for activity that occurred during 2012, and will be provided another month to enter data for activity that occurred during 2015.

The goal is a 100% response rate to match the response rate experienced for a similar survey conducted by AATB when gathering data for 2007. The response rate can only be reduced if participation is lacking from any of the few tissue banks that recover conventional tissue that are not accredited by the AATB.

4. Tests of Procedures or Methods to be Undertaken

To evaluate and refine the survey instrument, a pilot test will occur consisting of not less than 6 and not more than 9 conventional tissue bank respondents. Although a similar survey tool was used to gather data covering activity in 2007, new questions have been added for NTRUS and cognitive evaluation should occur prior to launch. New question topics include expansion of data gathering that includes:

1. conventional tissues acquired from living donors, such as birth tissue (e.g., amniotic membrane, chorionic membrane, amniotic fluid, umbilical cord tissue, and umbilical veins);
2. new communicable diseases tests to screen donors have been introduced since 2007's survey, and some previous tests are no longer used;
3. seeking data regarding handling of tissue designated by FDA as a device, a drug, or a biological product because some conventional tissue banks have developed such

products;
4. more information is being sought in regard to the extent of international distribution of conventional tissues; and
5. data surrounding reports received of adverse reactions potentially caused by conventional tissue allografts and subsequent investigation outcomes.

To facilitate comprehension of survey terms and questions, an "NTRUS Definitions of Terms" document has been developed and will be readily available and referenced throughout the survey. A majority of the terms/definitions are familiar to conventional tissue banks because they are garnered from the current edition of AATB's Standards for Tissue Banking.

If the results of the pilot test culminate in substantive changes to the survey instrument or procedures, OMB will be informed as quickly as possible before NTRUS data collection begins.

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

The following individuals were consulted on statistical aspects of the survey design. Scott Brubaker, NTRUS Project Manager for AATB, consulted with select subject matter experts from tissue banks. In addition, the CDC/NCEZID/DHQP, Office of Blood, Organ and other Tissue Safety; FDA/CBER/OCTGT, Division of Human Tissue; FDA/CBER, Office of Biostatistics Epidemiology; and OASH/OHAIDP, Division of Blood and Tissue Safety and Availability, were consulted about the survey design.

In-Touch Insight Systems (I-TIS), see Section 2 above, was selected to build the online version of the survey instrument, collect the data, monitor respondent participation, and provide an initial technical analysis for a report. The following key personnel at I-TIS will be involved:

1) Patrick Leckey - Director of Engineering
2) Nancy McFetridge - Project Manager
3) Caryn Suuronen - Client Manager
4) Alan Gervais - Senior Software Developer
5) Dominik Rymsza - Lead, User Experience

Relevant addresses and phone numbers include:

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References:

1. Food and Drug Administration. Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement; Final Rule. November 24, 2004. Accessible at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ActsRulesRegulations/TissueProposedFinalRules/default.htm.
2. AATB Accreditation Policies for Transplant Tissue Banks, March 30, 2016. See Section II, Required Elements B, Additional Compliance. Accessible at: http://www.aatb.org/Accreditation-Policies.