

**Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry**

**National Amyotrophic Lateral
Sclerosis (ALS) Biorepository Governance**



**February 12, 2013
Summary Report**

Acronyms

Acronym	Expansion
ALS	Amyotrophic Lateral Sclerosis
ALSA	Amyotrophic Lateral Sclerosis Association
ATSDR	Agency for Toxic Substances and Disease Registry
BAC	Biospecimen Access Committee
BD-STEPS	Birth Defects Study to Evaluate Pregnancy exposureS
CASPIR	CDC/ATSDR Specimen Packaging, Inventory and Repository
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare and Medicaid Services
CRADA	Cooperative Research and Development Agreement
CSF	Cerebrospinal Fluid
CV	Coefficient of Variation
CV	<i>Curriculum Vitae</i>
dbGAP	Database of Genotypes and Phenotypes
FDA	Food and Drug Administration
FTP	File Transfer Protocol
HIPAA	Health Insurance Portability and Accountability Act
ID	Identification
IOM	Institute of Medicine
IRB	Institutional Review Board
IT	Information Technology
LCL	Lymphoblastoid Cell Lines
MDA	Muscular Dystrophy Association
MRC	Medical Research Council
MTA	Material Transfer Agreement
NBDPS	National Birth Defects Prevention Study
NCBDDD	National Center on Birth Defects and Developmental Disabilities
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NDRI	National Disease Research Interchange
NEALS	Northeast Amyotrophic Lateral Sclerosis Consortium
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OMB	Office of Management and Budget
PHI	Protected Health Information
PHS	Public Health Service
PI	Principal Investigator
PSI	Phlebotomy Services International
QA	Quality Assessment
QC	Quality Control
SAVAHCS	Southern Arizona VA Healthcare System
SNP	Single Nucleotide Polymorphisms
US	United States
VA	(United States Department of) Veterans Affairs
VAB	United States Department of Veterans Affairs Biorepository
VABBB	VA Biorepository Brain Bank
VABHS	VA Boston Healthcare System
VACO	VA Central Office
VBA	Veterans Benefits Administration
VHA	Veterans Health Administration

**Centers for Disease Control and Prevention (CDC)
Agency for Toxic Substances and Disease Registry (ATSDR)
National ALS Biorepository Governance**

**Minutes of the Meeting
February 12, 2013**

Purpose

Purpose: Discuss current governance practices with federal biorepositories and provide comments on proposed governance policies and procedures for the National ALS Biorepository.

Welcome and Introductions

**Wendy Kaye, PhD
Senior Epidemiologist, McKing Consulting Corporation
National ALS Registry Program
Agency for Toxic Substances & Disease Registry**

Dr. Kaye greeted participants, and requested that those present introduce themselves. A list of meeting attendees is provided with this document as Attachment 1. Following the introductions, she presented housekeeping information and reviewed the day's agenda.

National ALS Biorepository Pilot Study

**Wendy Kaye, PhD
Senior Epidemiologist, McKing Consulting Corporation
National ALS Registry Program
Agency for Toxic Substances & Disease Registry**

Dr. Kaye reported that the law to enact the National Amyotrophic Lateral Sclerosis (ALS) Registry was passed in October of 2008. Under the law, the Centers for Disease Control and Prevention (CDC) and Agency for Toxic Substances & Disease Registry (ATSDR) are charged with establishing and maintaining a population-based ALS registry for the United States (US). However, the law does not make ALS a reportable disease. The legislation specifies that the purposes of the ALS Registry are to describe the incidence and prevalence of ALS; describe the demographics of ALS patients; and examine risk factors for the disease.

ATSDR has adopted a two-pronged approach for capturing ALS cases. Existing national databases and an algorithm developed in a pilot study are used to identify true cases of ALS. The databases include the Veterans Benefits Administration (VBA), Veterans Health Administration (VHA), Medicare, and Medicaid. The algorithm takes into consideration such elements as visits to a neurologist and a prescription for RILUTEK®. The algorithm also identifies "potential ALS patients" in the national databases. These persons are not included in

the National ALS Registry, and additional data are needed in order to determine whether they are true ALS patients. ATSDR also created an Internet-based self-registration portal. The portal captures patients who may not be in national databases, and allows participants to provide epidemiological data through surveys.

No single study or database can answer all of the questions about ALS. The registry aims to answer the following questions:

- How many people actually have ALS?
- What are the underlying genetic and environmental causes of ALS?
- How can understanding these causes lead to prevention and treatment?
- What biomarkers are useful for predicting disease progression and treatment responses?

This information is assembled by integrating epidemiological data, clinical data, and basic research findings.

A biorepository is a collection of biological specimens for future use. The specimens can be applied to gene associations and environmental causes. In the future, they could validate biomarkers and possibly lead to the discovery of underlying pathobiology.

Several biorepositories are available for ALS researchers. The Northeast ALS Consortium (NEALS), the National Institute of Neurological Disorders and Stroke (NINDS), the United States Department of Veterans Affairs (VA) Biorepository (VAB), the VA Brain Bank, and the Medical Research Council (MRC) Brain Bank for Neurodegenerative Diseases in London are examples of these resources.

The National ALS Registry is currently in operation and a biorepository could enhance it by:

- Correlating biomarkers with the extensive epidemiologic data collected by the National ALS Registry;
- Enrolling a nationally representative, population-based sample of participants who are not selected by geographic area, exposure, or clinical characteristics; and
- Increasing the number of biological specimens available for research on ALS.

The goal of the National ALS Biorepository Pilot Study is to pilot methods for collecting and banking biological specimens from participants in the National ALS Registry. Further, the pilot study will assess the potential for developing a comprehensive, national research resource that could be maintained in the long term. The study's objectives are to maximize scientific potential, given Registry parameters; maximize cost-efficiency; make recommendations for long-term sustainability; and recommend a process for providing access to the specimens to researchers.

In March 2012, experts in ALS, biorepositories, and biomarkers convened at the National ALS Biorepository Expert Panel Meeting. The group provided input regarding the draft ALS Biorepository Pilot Study protocol. Among the discussion points were sample size and follow-up, specimens to be collected by the biorepository, and the biorepository's potential research uses. The group suggested that the biospecimens collected from participants should complement the epidemiologic data in the National ALS Registry; allow comparisons with other studies; maximize scientific utility within Registry constraints; and be "future-proof;" that is, ensure that specimens are amenable to emerging technologies and research priorities.

The National ALS Biorepository Pilot Study will collect specimens in participants' homes and will enroll 300 participants for in-home collection. Participants must be enrolled in the National ALS Registry and will be geographically diverse. Specimens of blood, urine, hair, and nails will be collected at two time periods, six months apart. Saliva will be collected if the blood draw fails. The order in which the blood specimens are to be drawn was determined by the constraints of the various sample requirements, and is depicted in the following table:

The National ALS Registry Biorepository Pilot Study: in-home collection



Priority	Sample preservative	# tubes	ml / tube	Fractions	Potential analyses (examples)
Blood					
1	K ₂ EDTA	1	10	White cells, red cells, plasma	DNA, proteins, red cell lipids
2	K ₂ EDTA	1	4	Whole blood	Lead, other metals
3	Plain	1	10	Serum	Clinical biochemistries, metabolic products, other small molecules
4	PAXgene RNA	2	2.5	RNA-stabilized whole blood	Intracellular RNA
Urine			9	--	Electrolytes, environmental chemicals, metabolic products, gut microbiome
Nail clippings			--	--	Metals
Hair clippings			--	--	Metals
Saliva*			2	--	DNA

*saliva samples will be self-collected only when blood collection fails.

The study will also enroll 30 participants for post-mortem collection. As noted, these participants must be members of the National ALS Registry. Their eligibility for the post-mortem collection must be confirmed by a treating neurologist, and they must be cognitively able to consent to participate in the study. Further, they must not plan to be on a life support system, and their family members should be supportive of their participation in the study. Because of the limited time frame of the study, persons with slow-progressing disease will not be eligible for post-mortem collection. All materials must be retrieved by the end of the two-year study period, September 2015. Post-mortem collection will include brain and spinal cord tissue, cerebrospinal fluid (CSF), muscle, and bone. This aspect of the study will be conducted in collaboration with the Boston University Alzheimer's Disease Brain Bank.

The study protocol has received scientific clearance through ATSDR. Dr. Rebecca Pentz, Professor of Research Ethics at Emory University School of Medicine, conducted an ethics review of the protocol and materials, especially for the post-mortem collection. The Office of Management and Budget (OMB) granted a Clinical Exemption for data collection. The protocol is undergoing Institutional Review Board (IRB) review. Study staff are being hired, and participants will be recruited into the study beginning in mid-April 2013. ATSDR is exploring the

option of adding skin to the post-mortem collection. If skin is added, a separate laboratory will be utilized to transform the skin cells into cell lines.

Discussion Points

- Dr. Kasarskis asked about consent issues associated with post-mortem collection. In most states, the next of kin is legally responsible after a person dies.
- Dr. Kaye responded that the pilot study will ask potential participants to indicate their understanding and interest in participating. A family member will be asked to sign a “pledge” to agree to participate. If the next of kin is not willing to participate, then the study will not retrieve the specimen.
- Dr. Kowall reported that the Alzheimer’s Center at Boston University takes a similar approach. The participant indicates intent to donate, and the family must be supportive.
- Dr. Sorenson noted that participants will be self-identified and asked about plans if interest is significant and more people volunteer to participate than the 300 the study can accommodate.
- Dr. Kaye answered that when people join the National ALS Registry, they have the option to check a box indicating their interest in studies for which they may be eligible. The National ALS Biorepository Pilot Study will invite potential participants from that group for the in-home collection, and will ensure a geographically diverse population. The selection algorithm will also allow for diversity among rural and urban areas. The in-home collection will include Hawaii and Alaska, but the post-mortem collection will take place in the contiguous 48 states because of the 48-hour time limit for retrieving specimens. There will be a notice on the ATSDR website when the pilot study opens, and there is potential for high interest.
- Dr. Brooks emphasized that conducting the biorepository pilot project will “breathe great energy” into the National ALS Registry. The method for rolling out the pilot study will be important. Many ALS patients are likely to view the study as a much-needed and epic opportunity. The advertisement of the project should emphasize the positive aspects of the study that will help the registry and should make the selection process clear.
- Dr. Jenkins asked whether the same laboratory would be used for all of the in-home collections.
- Dr. Kaye replied that Fisher BioServices will process and store all of the samples. The same kit will be sent to all participants and used by the in-home nurse.
- Dr. Kasarskis said that the process of obtaining in-home specimens worked well for the VAB. The approach was convenient for patients, and there was a high acceptance rate. Their only struggle was in contracting national nursing entities with the proper research certifications.
- Dr. Kaye said that the pilot study will utilize Phlebotomy Services International (PSI), a company that conducts studies for the National Institutes of Health (NIH) and other federally-funded agencies. The company collects specimens all over the country and has strict requirements for their nurses and phlebotomists. There will be ample time for the company to schedule the visits.

- Dr. Horton agreed that the pilot study is a marketing opportunity for the National ALS Registry. It is important that ATSDR and CDC make the most of this opportunity. Physicians and neurologists are also important communicators about the Registry, and the effort is collective.
- Dr. Marcus asked about the enrollment and coverage of the National ALS Registry.
- Dr. Kaye indicated that enrollment in the registry is strong. Over half of the people who join the registry also complete surveys. Dr. Horton added that the registry includes participants from all 50 states and US territories.
- Given that the pilot study will not consent more than 30 participants for the post-mortem study, Dr. Bowser pointed out that they could potentially have zero post-mortem specimens. He asked about “fallback” plans, such as working with other organizations that collect tissue. It is likely that the next-of-kin will want to participate and will want to contribute tissue.
- Dr. Kaye said that if the study period ends before all of the consented specimens are collected, they will provide lists of other banks that are interested in taking specimens, thereby creating linkages with patients and next-of-kin. In creating the study protocol, they discussed at length the ethical considerations associated with consenting a person to participate and then not accepting specimens after September 2015.
- Dr. Brady asked about the next steps beyond the pilot study, such as what will happen to the specimens if funding is not available to continue the National ALS Biorepository.
- Dr. Kaye answered that the specimens will belong to ATSDR. One of the study deliverables is to advise ATSDR on where the specimens should be stored. ATSDR will maintain and distribute the specimens from the pilot study even if they cannot continue collecting specimens after the pilot phase.
- Dr. Horton added that while future funding is not clear, there is good Congressional support for the National ALS Registry. They are in a good position to conduct the pilot and determine the feasibility of a National ALS Biorepository.
- Dr. Kaye said that in the future, the biorepository could be integrated into the National ALS Registry so that participants in the registry could indicate their willingness to contribute specimens up-front.
- Dr. Kowall asked about disclosure to participants and contingency plans regarding the post-mortem collection aspect of the study and noted that people will need to be recruited early in the study process. In his experience, the length of illness can be longer than expected.
- Dr. Kaye agreed and said that potential post-mortem participants will be recruited from persons who have been in the National ALS Registry for a longer period. Further, the study will exclude slow-progressors and will incorporate consultations with the treating neurologist.
- Dr. Marcus asked how the study will respond to potential volunteers for the post-mortem collection who are not likely to die within the study period.

- Dr. Kaye answered that those persons will be told that they are ineligible for that aspect of the study. Persons who indicate interest will sign a Health Insurance Portability and Accountability Act (HIPAA) waiver to allow for consultation with their neurologist. A person could be ineligible for the post-mortem collection for several reasons, such as an indication of lack of family agreement.
- Ms. Bledsoe said that if the specimens will potentially be transferred in the future, it is important that the HIPAA authorizations and informed consent forms are appropriately broad while remaining meaningful. Some of these forms contain specific language about where specimens are stored, for instance.
- Dr. Kaye said that the informed consent process stipulates that the specimens must be used for ALS research; there is no discussion of where they will be stored. The specimens will also be de-identified when sent to researchers.
- Dr. Lonsdale asked whether the informed consent process acknowledges the risk of identification through genotyping in the future.
- Dr. Kaye replied that the possibility is not addressed. The probability is low, because while DNA is a unique piece of information, it is not an identifier.
- Dr. Pentz agreed that DNA is not an identifier at this point, as databases are not available to link genetic sequencing with individuals. It could, however, be possible in the future.
- Dr. Lonsdale indicated that sequences can be identified to the individual level.
- Ms. Bledsoe added that there are arguments for including explicit statements in the informed consent package indicating that privacy cannot be guaranteed.
- Dr. Lonsdale said that such language is included in the consent process for a National Cancer Institute (NCI) study. The study will minimize the risk of identification, but the risk is present.
- Dr. McQuillan said that an upcoming Institute of Medicine (IOM) workshop will address these questions as the science moves in this direction.
- Dr. Boylan asked about criteria, such as length of disease, which may be applied to selecting participants for the in-home collection.
- Dr. Kaye said that the criteria apply to ensuring that the group is diverse in age, geography, gender, and urban and rural locations. That demographic information is available in the National ALS Registry. RILUTEK[®] use is not a factor, as the data are not available in the Registry.

Governance of Existing Federal Biorepositories

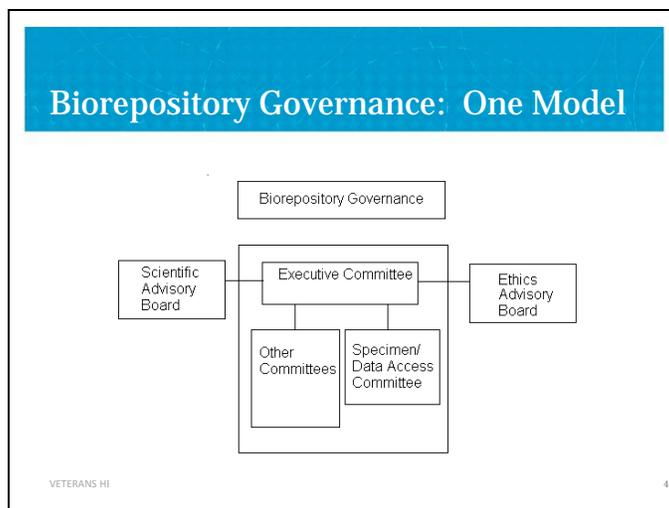
Department of Veterans Affairs Biorepository and Brain Bank

Marianne Bledsoe, MA
Senior Program Manager for Biorepositories and Biobanking
Biomedical Laboratory Research and Development
Office of Research and Development
United States Department of Veterans Affairs

Ms. Bledsoe presented an overview of governance, data access, and distribution policies. She reported that in their paper “Biobank Governance in the Post-genomic Age,” Gottweiss and Lauss define biobank governance broadly, focusing on the regulations of relationships between individual citizens, society, and biobanks. Issues of consent, privacy, ownership, access, and benefit sharing are critical to governance. Governance serves as a system of oversight. Good governance is about responsible stewardship of valuable resources and ensuring that specimens are used for good science. Legal and ethical issues are addressed to maintain the trust of participants and the public.

Specimen and data access and distribution policies are elements of governance. External governance mechanisms include factors that are generally not controllable, such as existing legislation and regulations, socio-cultural norms, funder requirements, scientific peer review, and ethics and privacy review. Internal governance mechanisms can be controlled and include public engagement; scientific advisory and oversight committees and mechanisms; ethics advisory and oversight mechanisms; specimen and data storage and laboratory practices, which ensure quality; and specimen and data access.

There are many models for biorepository governance. One model includes a scientific advisory board that advises on the overall scientific direction of the project. An executive or steering committee may manage the day-to-day operations and decision-making of the bank. An IRB may be included, and a separate ethics advisory board could provide advice. Other committees on biosafety, data safety, and other issues could be created. Often, a specimen and data access committee makes decisions about how samples and data are used.



A biobank should document its access requirements as well as its review and dissemination policies thoroughly. These requirements should address policies and procedures for determining what constitutes appropriate research uses of the specimens and data, both scientifically and ethically. They should also address policies and procedures for prioritizing requests for access. For example, some biorepositories give first priority to private researchers, second priority to unfunded pilot projects, and lower priority to for-profit entities. Requirements for access to data may be less stringent than requirements for access to specimens because specimens are non-renewable resources with a finite lifespan. These requirements will vary by biorepository and by specimen type.

The process for access should be transparent, equitable, and free from conflicts of interest in the decision-making process. The process should be published for the scientific community and for the research participants. The rigor of the access requirements will vary according to the kind of biorepository. Generally, the more scarce the resources, the more stringent the access requirements. Good policies should be in place to ensure responsible access, and the policies should balance with the potential benefits and risks to participants and society. Good review processes often improve the science.

A number of considerations apply to reviewing requests for access. Scientific considerations include the appropriateness of the proposed research use based on the purpose, nature, characteristics, limitations, and strengths of the repository. These factors are seldom included in the review of a grant application, but they play an important role in reviewing access to biorepository specimens. Other considerations include scientific merit and the potential impact of the proposed research; adequacy of the research design, particularly statistical issues; availability of funding for the research; experience and qualifications of the investigators; and adequacy of the research environment.

A number of ethical considerations inform the appropriate use of specimens. Benefits and risks to participants, populations, and society at large, are especially important. Some of these issues are addressed by the IRB, but some issues may need to be reviewed as part of the request for access, especially regarding whether the proposed research use is consistent with informed consent. In some cases, the research using the specimen will not be considered human subjects research, and there may be no requirement for IRB review. Many repositories ask for documentation from the IRB that a proposed project is exempt from review. When this review is required, regulatory approvals should be documented.

When specimens and associated data are distributed, researchers should receive no identifying information. Some information may be needed in some cases and should be addressed in the consent and authorization forms. A strong Material Transfer Agreement (MTA), Cooperative Research and Development Agreement (CRADA), or other contractual agreement is extremely important to define the conditions of the use of the material.

MTAs, CRADAs, and other contractual agreements may stipulate that the recipient of the specimens will not attempt to identify subjects; will abide by relevant regulations; will not sell or share the specimens and/or data with third parties; will only use the specimens and/or data for the proposed research use; will not use specimens for testing in humans; will follow appropriate biohazard precautions for handling specimens; will acknowledge the biorepository in publications, which helps the repository document its contributions and ultimately to get funding; will indemnify the biorepository; will abide by any collaborative agreements in place; will return research data to the biorepository if required; and will abide by any other conditions specified by the biorepository.

The agreements may also include requirements for disposition of unused specimens or destruction of specimens and/or data at the end of the research period. They may stipulate any intellectual property and publication rights of the providers of the specimens and/or data and the recipient researcher and/or institution.

Ms. Bledsoe shared observations and experiences from the VA Biorepository Brain Bank (VABBB) ALS Bank. The bank was established in 2006 and was recently opened for requests for access. A number of issues were identified after one round of review, which included approximately 16 applications. The VABBB assessed these concerns so that future requests for access will have a better chance of success. Investigators whose applications were not approved were encouraged to reapply.

Applications were frequently incomplete. To address this problem, the VABBB triages the applications and clearly states on its website that incomplete applications will be delayed for review. Many applicants described sample sizes that were too small and did not fully justify the sample size. The VABBB now indicates in its processes that applications should provide justifications for the sample size and suggests that a biostatistician should be consulted as the application is created. In some cases, the researchers lacked experience. Some applications did not include sufficient detail regarding the proposed study. The VABBB enhanced the application to address these problems. Researchers in ALS frequently obtain samples from multiple sources, and some of the applications to the VABBB were not clear regarding the sources of additional samples and whether the samples would be available.

Ms. Bledsoe shared the following “lessons learned” from the VABBB experience:

- Make sure policies and procedures are well-established before entertaining tissue requests.
- The biorepository should work closely with researchers in refining their requests before requests are submitted and evaluated.
- If there has been preliminary data in human specimens, it should be included in tissue request applications.
- Manage researcher expectations by explaining the policies and processes clearly.
- Education and marketing are essential.
- It may be necessary and desirable to refine policies and procedures based on experience and/or changes in science and ethical norms.
- There is a “delicate balance” between ensuring that specimens are used appropriately and ensuring that they are used at all. Finding the right balance can be difficult, especially with a scarce resource.

**Christopher Brady, PhD
Director, Scientific Operations
VA Biorepository
VA Boston Healthcare System
United States Department of Veterans Affairs**

Dr. Brady presented an overview of the VABBB, which is a multi-site brain bank. Many of the bank operations, including clinical data collection and management, enrollment, coordination of tissue recovery, and diagnostic neuropathology, occur at VA Boston Healthcare System (VABHS). Tissue is analyzed, processed, and stored at the Southern Arizona VA Healthcare System (SAVAHCS) in Tucson, Arizona. The physical biorepository is located there as well. SAVAHCS coordinates tissue releases to investigators. Tissue and data releases from the VABBB are ongoing.

In designing its governance, VABBB wanted a transparent and understandable application and release process. The governance design process included how reviews would be conducted and how the expert committee would be convened. Finalizing the MTA was challenging because the VABBB has multiple sites that must sign off on the transfers. Materials in support of committee functions, such as conflicts of interest, the charge to the committee, and review forms, were developed. The process is a work in progress.

The VABBB Tissue Access Committee includes a standing committee, comprised of *ex officio* members, that oversees the day-to-day work of conducting reviews. The Access Committee also includes a number of subject matter experts who vote on the tissue requests. The reviews are conducted via telephone in a manner similar to a grant review. Many of the applicants to the VABBB have already been reviewed by NIH or another funding entity. The VABBB committee does not serve as a second-level scientific review, but they are mindful of the amount of tissue that is being requested, given the limited resources in the bank. There is frequent communication with the applicants after the review, whether the request is approved or disapproved. The VABBB Tissue Access Committee is coordinated by the VA Central Office (VACO).

After a request is approved, VABBB identifies the cases in the Tucson facility that will be selected for release, the clinical data that will be released, and archives of previous data collected by the National ALS Registry at the Durham, North Carolina VA facility. VABBB also incorporates Quality Assessment (QA) into the process, sending a Tissue Quality Form with the samples.

Discussion Points

- Dr. Horton asked about the turnaround time from receipt of the application to shipping samples to the investigator.
- Dr. Brady answered that the elapsed time depends upon the nature of the request. The request is reviewed and receives approval or disapproval. The VABBB then works with the investigator to coordinate transfer of the tissue. If a case is simple and involves relatively few samples, it could be turned around within a month. Some cases are more involved. For instance, the VABBB has a process by which all genotyping data are returned to the biorepository, and those cases require more time and negotiation. The VABBB does not need to involve the IRB.

- Dr. Bruijn asked how many applicants were granted tissue samples, and about information regarding the projects that utilize the samples, publications, and any data sharing plans.
- Ms. Bledsoe replied that they have not listed their researchers on their website. The process has just begun, but VABBB expects to be notified of publications from the use of its specimens. Because investigators do not always inform biorepositories about publications, some biorepositories ask for the information on a regular basis or search PubMed and other resources for information and then ask the investigator for verification.
- Dr. Bowser co-chairs the NEALS biorepository and commented on similar issues that NEALS has experienced. He and the other co-chair of the committee vet applications and work with the applicants to ensure that no information is missing. NEALS includes biofluids and requires that applicants provide Quality Control (QC) information and reproducibility data, such as coefficient of variation (CV) values, for their chosen assays. If applicants do not have these data, NEALS provides them with approximately 30 blinded samples to determine how well the assay performs. If the assay performs well, then the applicant will receive samples; if not, NEALS provides the information to the applicant so that the assay can be improved. Occasionally, investigators approach NEALS when they are submitting a grant application for a project that will utilize their samples. In these cases, NEALS will provide the investigator with a letter of support that does not promise samples, but outlines the process for sample release.
- Dr. Pentz said that in the future, results of research and publications should be expressed in lay terms so that participants in biorepositories and their family members can have access to them.
- Ms. Bledsoe agreed and said that the VABBB newsletter summarizes projects that were approved.
- Dr. Muravov noted that when the VABBB receives a specimen, it freezes half of the specimen for the future and reserves the other half for release. He asked about the point at which the frozen part of the specimen would be used.
- Dr. Brady confirmed that half of the specimen is frozen, and half is fixed. The fixed half is analyzed at the Boston facility and is archived in Tucson. The VABBB has the ability to distribute fixed or frozen tissue, depending on the request.

National Institute of Neurological Disorders and Stroke
The NINDS Repository: Policies to Facilitate Resource Sharing

Roderick A. Corriveau, PhD (via telephone)
Program Director, Extramural Research Program
National Institutes of Health
National Institute of Neurological Disorders and Stroke

Dr. Corriveau explained that the mission of the NINDS repository is to accelerate discovery of causes and risks for neurological disease by sharing samples and data. The repository was created in 2002, and many changes have occurred since then in policy as well as in a shift from renewable resources to non-renewable resources.

NINDS placed a notice regarding the repository's goals, use, and access. Notice Number: NOT-NS-12-003 is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-NS-12-003.html>.

Important policy issues for consideration include the following:

- Access to samples, including submission of samples
- Order evaluation and prioritization of orders
- Material Transfer Agreements
- Synergy through returned results and receiving information about samples
- Sharing phenotypic and genotypic data
- Lessons learned / looking forward

With some exceptions, NINDS-funded investigators typically submit samples and data to the NINDS repository. Terms and conditions of grant awards from NINDS may require sharing. Over time, they have learned to address consent issues early in the terms and conditions of the award and before IRB approval at the site. This approach ensures sharing. NINDS provides suggested and required consent language. The repository institutes certain benefits for submitters, such as access to free or discounted samples.

NINDS's policy has been that samples and unidentified data are available to researchers at hospitals, universities, and commercial organizations. When samples are distributed to commercial organizations, the MTA stipulates that the organizations may use the samples for their own internal research to generate knowledge. That knowledge may be used to generate profit, but the samples and biological materials derived from them cannot be used for profit.

The repository has traditionally housed mostly renewable resources, such as lymphoblastoid cell lines (LCLs) and DNA from LCLs. Order evaluation and prioritization is relatively straightforward for these resources, and legitimate orders are filled. As the repository has evolved to include more limited resources and questions have arisen regarding the utility of DNA from LCLs, the policies have changed. A Biospecimen Access Committee (BAC) now evaluates applications for limited resources. Some limited resources, such as DNA from whole blood, represent intermediate ground. In these cases, a threshold has been established for the distribution to be evaluated by the BAC.

In order to establish that the request is legitimate, the Principal Investigator (PI) and an institutional official authorized to make legal binding agreements must sign the MTA. The PI must complete a statement of research intent. For requests for renewable resources, this statement is a brief overview to indicate that the research is legitimate. The MTA also addresses issues such as the destruction of samples after use, a promise not to attempt to identify the individuals from whom the samples were collected, and a prohibition of use of samples for human experimentation. The MTA stipulates that materials will be used only for research, not for direct profit, and that secondary distribution must be approved by the NINDS. Secondary distribution has been an issue with induced pluripotent stem cells.

NINDS works to achieve synergy through returned results to the repository. Recipients are encouraged to report genotypic information to the repository so that the information can be listed with the samples and increase their value. It is not easy to achieve this synergy, but benefits such as free or reduced-cost samples have been helpful.

The NINDS repository was conceived to support genome-wide association studies. When the repository was created, the Database of Genotypes and Phenotypes (dbGAP) did not exist, and there were few resources for sharing single nucleotide polymorphisms (SNP) data. As studies were conducted with samples from the NINDS repository and SNP data became available, the repository created a SNP database. The database was publicly accessible to investigators who applied for it through the Coriell database. When the resource was available, 761 investigators registered for information from it, and at least 27 publications resulted from use of the data. The publications focused almost exclusively on creating computational tools. The SNP database was discontinued due to concerns about identification risks, and the information was shifted to dbGAP. Data are still shared through dbGAP.

In addition to SNP data, the NINDS repository has a strong history of sharing phenotypic data. The repository captures relatively few clinical data elements, but they are shared via the NINDS repository website. A minimal clinical data set is available for all subjects in the repository. They are careful to maintain and monitor this resource as they balance a desire to make resources available and useful with a desire to respect the subjects in the repository and not to put them at unnecessary risk.

To evaluate the impact of the resource, it is important to provide model acknowledgement language that investigators can use in their publications. There can be a lack of leverage regarding acknowledging the resource and reporting publications. Investigators should be reminded to provide information about publication, but it is also important to conduct ongoing literature searches for new papers or citations. For obtaining data from investigators, time is of the essence to collect and share meaningful clinical data.

“On demand” work for distribution can become a bottleneck. For instance, if the repository waits for orders before aliquoting and performing QC, then the process can be quite slow. Other major issues for a repository regard how to address the risk of de-identification and whether to return medically actionable genetic information.

Discussion Points

- Dr. Horton asked about administrative fees for disseminating samples.
- Dr. Corriveau answered that the NINDS repository does charge a fee, depending upon the sample type, which helps with cost recovery. The cost also depends on whether a submitter asks for an embargo and whether the investigator will return high-value results to the repository. The fee is minimal, and they may not charge a fee on future collections, such as biomarker discovery samples.
- Dr. Brady answered that VABBB does not charge fees. Ms. Bledsoe added that there are some constraints associated with a federal agency collecting fees.
- Dr. Cwik asked about reporting requirements at the end of the project for which the samples were used, especially since many results may not be published.
- Dr. Corriveau said that the MTA from the NINDS repository requires that unused samples are returned. There is not an explicit requirement for a report on a project if there is no publication.

- Dr. Brady said that the VABBB approach is similar. They do not ask for formal progress reports, but they have discussed the idea. Ms. Bledsoe said that some repositories send annual inquiries to investigators who have received tissue. The inquiry asks for updates on research results and publications, as well as data about the investigators' satisfaction with the resource. This annual information collection is a broader opportunity for feedback on the samples than the questionnaire that is initially sent with the samples.
- Dr. Lonsdale added that the National Disease Research Interchange (NDRI) serves approximately 600 investigators per year. They send a QA form with each shipment and conduct an annual, web-based QA to get information about the samples as well as publications and conferences.

National Center for Birth Defects and Developmental Disabilities **National Birth Defects Prevention Study Biorepository Governance**

Mary Jenkins, PhD

National Birth Defects Prevention Study Biologics Coordinator
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

Dr. Jenkins reported that in 1996, Congress mandated the establishment of Centers for Birth Defects Research and Prevention. CDC funded these centers through cooperative agreements in five-year cycles. All of the centers collaborate on the National Birth Defects Prevention Study (NBDPS). There have been 10 centers over time in geographically diverse areas.

The NBDPS is a population-based, case-control study of approximately 30 major structural birth defects. The study focuses on defects with unknown etiology and includes infants born between October 1997 and December 2011. The three main components of the study are case ascertainment, maternal interview, and DNA collection.

After mothers are interviewed, they receive a cheek cell collection kit. The study collects buccal cells using two cytobrushes each from the mother, father, and infant. One of the cytobrushes remains with the local center, and the other brush is returned to the repository.

The DNA collection has changed over the years of the study. From 1997-2003, each center conducted its own DNA extraction and QC. They sent the aliquots to the repository, which was at CDC at CDC/ATSDR Specimen Packaging, Inventory and Repository (CASPIR). In 2003, the study shifted to the NBDPS Central lab at CDC, which has helped with the standardization of samples that are sent to the repository. In 2011, the study outgrew CASPIR and experienced a freezer failure, so the samples were moved from CASPIR to Fisher BioServices.

Most of the samples at the NBDPS Biorepository are available for distribution, but some are unavailable because they failed QC. Samples are only released to NBDPS researchers at one of the 10 center laboratories. Aliquots may also be shipped out of the biorepository to center laboratories because the family has become ineligible or to the NBDPS Central lab for subaliquoting. Aliquots may be destroyed if they become ineligible or re-labeled if a control infant is later diagnosed with a birth defect.

NBDPS has a Coordinating Council, which is composed of each center's PIs. The council is the decision-making body that oversees the entire study. A Data Sharing Committee is composed of two members per center. This body reviews letters of intent and proposals requesting

specimens and data. The brief letters of intent must be approved before the detailed proposal is submitted. The Data Sharing Committee also reviews abstracts and manuscripts resulting from analyses of non-genetic and genetic data from the NBDPS. Other bodies include the Biologics Committee and the Genetic Analysis Working Group, which provide information for the Data Sharing Guidelines and support for requests for DNA analysis.

The application process for samples from the NBDPS Biorepository is relatively closed. Investigators from outside the NBDPS must collaborate with a sponsoring PI from one of the centers. Each center PI is responsible for confidentiality and data use oaths. Letters of intent and proposals are submitted to the Data Sharing Committee for review. The Data Sharing Committee evaluates all project proposals according to the same criteria, which include whether the analyses are reasonable, power calculations, plans for biologics and other expertise, and conflicts with existing proposals. The Data Sharing Guidelines include requirements for project approval.

Proposals involving DNA analysis must undergo an additional review. Those projects are reviewed for the following aspects:

- Provision of relevant preliminary data
- Laboratories that will analyze the DNA specimens must pass an external QA
- Overlap with other projects
- Review of genes by the IRB

The external QA of the laboratories utilizes pre-characterized samples. The laboratories apply the proposed methods to the samples and return them to CDC. Matrices are maintained to limit overlap of projects.

When the NBDPS was established, it was impossible to know which genes would be studied. The IRB approved submission of “gene one-pager” forms. The form addresses whether disease-causing allelic variants of the gene are known, and whether the proposed test will identify them. If so, the test must be completed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory so that the results can be reported to individuals.

Following approval of a proposal by the Data Sharing Committee and approval of gene one-pagers by the CDC IRB, investigators submit a “Request for Biorepository Samples” form. The form verifies a sponsoring PI and other relevant information. Investigators must review the interview status to ensure that they have useful information. Each of the aliquots is allotted to one of the centers, so they must confirm that the center has not previously requested all of their allotted samples. Investigators confirm that samples from their own center have not been requested.

The agreement, which must be signed by the requesting investigator and sponsoring PI, states that the DNA will be stored securely by the center. Results of the project will be transmitted within two months to the genotyping database, and the study must be completed within three years of requesting the samples.

CDC cooperative agreements do not fund genetic analysis; they only fund collection of samples. Therefore, each center obtains its own funding for analysis. Because the group is of limited size, prioritization for sample requests has been on a first-come first-served basis. The process can be modified based on timelines of funding agency requirements.

Before samples are distributed, sample requests are reviewed and verified at CDC. If specimens need to be aliquoted, the central laboratory performs the sub-aliquoting and sends the specimens back to the repository for distribution. A list of available aliquots is created and shared with the lead investigator via a Secure Data Network. Only CDC Data Curators can request samples from the repository. Final requests are submitted to the repository via a secure File Transfer Protocol (FTP) site. The aliquots are shipped directly to the laboratory designated by the requesting center.

Typically, results are transmitted to the genotyping database after the publication is released. This approach eliminates any embargo period. Data submission and publications are tracked through annual data sharing updates. Lead investigators update their projects annually. If they do not update the project, then it can be terminated and another investigator can lead it. Data will be released annually to NBDPS collaborators.

Among the lessons learned by the NBDPS is the importance of centralizing sample processing. It is also important to choose the repository carefully and ensure that the following are in place: equipment QC, contingency plans and back-up storage space, data QC and inventory management, and responsiveness.

Creating two aliquots per specimen saves storage space. Separate small freezer units are preferable to a single large unit. Data management is also important, and their process includes monthly snapshots of inventory and monthly review of shipping, re-labeling, and destruction reports.

The NBDPS is ending, and a new case-control birth defects study, the Birth Defects Study to Evaluate Pregnancy exposureS (BD-STEPS), is beginning. The new study will not collect samples via cytobrush, but will collect saliva instead. The new study will use repository-only aliquots, and they hope to utilize a single IRB. Broad data sharing will be included in the consent form. Data have not yet been submitted to dbGaP, but the sharing of aggregate data is likely in the future.

Discussion Points

- Dr. Antao asked who CDC Curators are. Dr. Jenkins answered that only she and the PI of the study can request samples for other people.
- Ms. Bledsoe asked about the policy regarding returning individual research results to participants, particularly with regard to how samples are verified. There is a great deal of debate on this topic.
- Dr. Jenkins said that the study has not yet returned results, as no clinically significant studies have been completed. Because of the potential for clinically significant variants, a process is in place. Aggregate results will be reported via an annual newsletter. If participants want their individual information, they can request it. A clinical geneticist at each center will report results to participants. Any studies that are determined to be clinically significant must be completed in a CLIA-certified laboratory. Participants are informed that any results should be verified with their healthcare providers.
- Dr. Marcus asked how studies are determined to be clinically significant.

- Dr. Jenkins said that in one proposed study, investigators plan to study a chromosome deletion that is known to be clinically significant. Many people would have been diagnosed with the deletion before the study was complete. If they have not been diagnosed, how important is it for them to know it? This deletion is potentially significant for reproductive reasons, so it is a clear-cut decision. Other decisions are less clear. For instance, a gene may have disease-causing variants, but the proposed study may not identify them. The gene one-pager allows for assessment of the information on a case-by-case basis. The process for determining whether information should be returned includes several layers of review, including review by clinical geneticists at the center.
- Ms. Bledsoe noted a paper describing the experiences of NBDPS would be a great addition to the field. Dr. Jenkins hoped that those “lessons learned” would be part of the literature generated as the NBDPS comes to an end.

National Health and Nutrition Examination Survey **The NHANES Biorepository Program**

Geraldine McQuillan, PhD
Senior Infectious Disease Epidemiologist
Division of Health and Nutrition Examination Surveys
National Center for Health Statistics
Centers for Disease Control and Prevention

Dr. McQuillan presented an overview of the National Health and Nutrition Examination Survey (NHANES) Biorepository Program. NHANES is a probability sample of the US population, with 5000 US residents per year sampled from a variety of households in 15 counties in the US. When persons are selected, they are asked to sign a separate consent for the collection and storage of blood and urine for use in future studies. They are also asked to consent to the collection of DNA for genetic studies if they are 20 years old or older.

Blood is collected at a mobile examination center. Some of the blood is stored at CDC in CASPIR. These samples are pristine. They have never been frozen or thawed. CASPIR includes samples from NHANES 3, which was conducted from 1988 through 1994, and samples from 1999 through 2013. NHANES became a continuous survey in 1999. Over two million samples are stored in CASPIR. Unfortunately, CASPIR has no more space to receive additional samples, so other repositories are needed.

Other blood samples from the NHANES mobile examination centers are sent to one of CDC's 28 laboratories. Surplus sera that are returned are stored in a residual bank in Frederick, Maryland. Over 300,000 samples from 1999 through 2010 that have been previously thawed are stored in this bank. They are an excellent resource for future studies.

Researchers may submit proposals to use NHANES specimens on a rolling basis. Proposal guidelines are on the Web at http://www.cdc.gov/nchs/nhanes/genetics/stored_specimens.htm. The review process includes a technical review panel and IRB review. Samples are released only after a study is approved at a cost per vial of \$8.50.

Proposals are emailed to Dr. McQuillan, who forwards them to the Stored Specimen Technical Panel. The panel includes a clinical pathologist, a pediatrician/epidemiologist, a survey analyst with a nutrition and laboratory background, a university professor with laboratory background, a statistician, and other subject matter experts as needed. Because proposals are accepted on a rolling basis, protocols are not prioritized. It is important to public health to be responsive to requests. If the research is considered worthwhile, it is accepted.

The criteria for accepting proposals include the following:

- Specific aims are stated, with the hypotheses to be tested.
- Background and public health significance are clearly stated, and are supported by existing literature.
- Research design and methods are included that demonstrate a working knowledge of procedures required for laboratory assays, and assays are state-of-the-art and validated.
- An acceptable analytical plan demonstrates knowledge of the NHANES design and weighting issues. NHANES is a complex design that over-samples various populations in order to provide more precise estimates for minority groups, and many proposals do not include sufficient analytic processes.
- Appropriate experience and qualifications of the investigators are included.

Dr. McQuillan creates a summary statement based on the evaluations from the technical panel. The statement addresses the proposal's major strengths and weaknesses as expressed by the reviewers. The investigators are asked to respond to the identified weaknesses, and the responses are returned to the technical panel. If the panel concludes that the investigators have addressed the weaknesses satisfactorily, then the protocol is approved. Dr. McQuillan sends a packet of information, including the summary statement and protocol, to the Associate Director for Science for review. The package is also reviewed by the Confidentiality Officer and the IRB. CDC's IRB approval is necessary for the shipment of specimens.

Upon approval, the investigator chooses samples by looking at the public-use files. The investigator then sends an Excel spreadsheet to the National Center for Health Statistics (NCHS) with the sequence identifications (IDs) of the corresponding vials of serum. Samples are available for those aged six and up. This spreadsheet is matched to the consent file to ensure that the individual has provided appropriate consent. The in-house IDs are matched to the inventory from the contract repository or CASPIR. A final "pull" file is created, and the samples are pulled and sent with only the in-house ID.

An Interagency Agreement or an invoice is sent to cover the cost of pulling the specimens. An MTA is signed by the PI and the director of the laboratory who is handling the specimen. The MTA addresses the use of the specimens.

All results from research from a stored specimen project are returned to NCHS. The investigator only has the in-house ID, so the materials must be returned to be linked to the public-use sequence number in order to conduct analysis. The investigator then has 60 days for QC. The data cannot be presented or published until the QC period has been completed

and the data has been released to the public. The time period has been sufficient, and investigators have not complained about the process.

Dr. McQuillan shared the following “lessons learned” from the NHANES Biorepository:

- Careful consideration should be given to the test results from future research studies that should be reported back to participants and how this will be done.
- Make sure investigators, especially technicians, do not change labels when they run your samples. An investigator removed the NHANES label on a set of samples, making the re-linking the samples to the public-use sequence a nightmare.
- Investigators can greatly add to the value of NHANES by using stored specimens. They can take advantage of future technology, respond to new outbreaks, and define the pre- and post-prevalence of an infection. They can evaluate the efficacy of a vaccine program because NHANES is nationally representative and they can look at new environmental toxins.

Discussion Points

- Dr. Horton asked how soon applicants can receive samples from the NHANES Biorepository.
- Dr. McQuillan answered that proposals are accepted on a rolling basis. She vets them first, and if the applications are complete, she sends them to the technical panel immediately. The panel has two weeks to review the applications. If the proposal is approved, the samples could be released in approximately one to two months.
- Dr. Brooks asked how many proposals per year are approved.
- Dr. McQuillan said that NHANES is limited because the projects conducted with NHANES data cannot be actionable, as results are not returned. Therefore, the types of research that are conducted are narrow and not clinically relevant. Approximately 10 to 15 proposals per year are approved, and many more would be possible without that limitation. Further, NHANES does not advertise very well. She and one programmer are the only staff devoted to the biorepository. She would like to see 20 to 30 proposals approved per year, but the increase in volume would require more staff and more advertising.
- Dr. Horton asked whether it was difficult to collect fees for the samples.
- Dr. McQuillan answered that they had no difficulties, as they publicize the fees and justify them. She created a table to illustrate the costs associated with preparing the samples, the vials, and costs to the repository. She has not experienced any issues with the fees or with increasing them when necessary.
- Mr. Hixon said that BioFisher supports various models for cost reimbursement, from cost recovery to the cost of shipping.

Presentation of Governance for National ALS Biorepository Pilot Study

Marta Gwinn, MD, MPH
Senior Consultant for Epidemiology
McKing Consulting Corporation
Centers for Disease Control and Prevention

Dr. Gwinn thanked the group for attending and participating in the discussion. She presented the current draft governance for the National ALS Biorepository Pilot Study, explaining that the goal of the National ALS Biorepository is to provide a resource for research that will contribute to better prevention and treatment of ALS. The resource should be population-based and nationally representative, like the National ALS Registry; integrated with epidemiologic information collected by the National ALS Registry; based on informed consent by research participants; and publicly available to ALS researchers.

The purpose of the pilot study is to develop and test procedures for enrolling participants, collecting specimens, and storing samples in the biorepositories. In-home collections will occur of blood, urine, hair, and nails. A separate program will collect brain and spinal cord, CSF, muscle, and bone post-mortem. The pilot study will also propose guidelines for the release and use of samples for research; however, the pilot study does not include implementing and testing the guidelines; calling for and reviewing research proposals; or distributing samples for research.

The goals of the guidelines are to encourage use of the biorepository for relevant research; assure and facilitate researcher access to the samples and registry data; assure that public presentations of findings are accurate and objective; establish guidelines for authorship and acknowledgement of the resource; and maintain a record of proposed and published research.

Dr. Gwinn described the proposed National ALS Biorepository Research Committee, or “Core Committee,” which is based on ATSDR’s draft guidelines for use of the National ALS Registry data. The National ALS Registry Research Committee governs the use of registry data for epidemiologic analysis and for recruiting participants for other studies such as surveys or clinical trials. The committee members are appointed by ATSDR to serve two-year terms. A committee chair is elected by members.

The Core Committee consists of three researchers or clinical care providers, one lay patient advocate, one ethicist, two members of ATSDR’s ALS program, the Associate Director for Science of the ATSDR Division that houses the registry, and an additional person appointed by that division’s director. The Associate Director and person that he or she appoints are not voting members of the committee.

The proposed Biorepository Research Committee structure adds two supplementary voting members: one laboratory-based ALS researcher and one laboratory scientist with knowledge of laboratory procedures and QC. The Biorepository Research Committee will be supported by ATSDR and an Executive Secretary. It is proposed that the committee review research proposals twice annually, following announcements in the *Federal Register*.

The research application will require the investigator's contact information and a brief summary of the proposed research. It will include the funding source, potential conflicts of interest, and an IRB determination. Researchers requesting samples and data will also be asked to provide a cover letter explaining the nature of the research, a biosketch or *curriculum vitae* (CV) of the PI, a copy of the full study protocol, documentation of IRB approval or exception, and a sample request sheet. These materials can be submitted online via an ATSDR portal.

Before the committee meets, the Executive Secretary will review the submitted applications for completeness. The Executive Secretary will complete a Review and Score Sheet and will document other information, such as whether the investigator has applied previously. The Executive Secretary will assign full review of the application to two voting committee members, including at least one of the laboratory scientist supplementary members. Application materials will be distributed to all members of the Biorepository Research Committee. The committee members will read each application, and the reviewers will complete Section 2 of the Review and Score Sheet, which includes the score criteria.

The research proposal review criteria are as follows:

- Is the protocol scientifically valid?
- Will the study add to existing scientific information on ALS?
- Do the investigators demonstrate capacity to complete the proposed research?
- Does the protocol include adequate protections of confidentiality?

Approval of a proposal requires a score of at least 3 on each criterion. When the committee meets, either virtually or in person, the assigned reviewers will present the application and lead the subsequent discussion. Voting committee members will vote to approve or deny the application and will agree on the final score. The committee chair will submit the Committee decisions and scores to ATSDR.

ATSDR will make its determination and respond to the PIs. The PIs will be notified regarding whether their project is approved and whether it is high priority. If so, they will receive a project number and will complete the Confidentiality and Data Use Agreement and MTA. If the project is denied, the PI may resubmit it one time. The PIs are also responsible for an annual Project Update.

The Confidentiality and Data Use Agreement includes the following provisions:

- Protect confidentiality by not linking biorepository records with identifiable data such as medical records and by restricting and tracking access to samples and data within the facility.
- Respect ATSDR control of samples and data, acknowledging that ATSDR must approve all uses of the materials. PIs will not share samples or data with other investigators and will delete data files when the project is completed.
- Abstracts and manuscripts will be submitted ATSDR for review. Abstracts should be submitted two weeks in advance of presentation, and manuscripts should be submitted four weeks in advance of submission.

The MTA is standard to the Public Health Service (PHS). It details that materials cannot be used in humans or commercialized; materials can be used only for the specified project without sharing; the recipient (investigator) of the materials retains patent and intellectual property rights; the provider (ATSDR) must be acknowledged in presentations and publications; and endorsement by the government may not be implied.

All projects must provide an annual update. The update should indicate any changes in investigators and report on the status of the project. Completion or termination of the project will lead to questions regarding return of the samples and data. The update also asks for a list of publications and presentations. There is also a provision for terminating the project if the update is not provided by a specified date.

ATSDR is responsible for announcing availability of samples from the biorepository in the *Federal Register*. ATSDR is also responsible for administering the review committee and prioritizing applications after the scores are submitted. ATSDR releases the samples and data and monitors research progress and products.

The investigator obligations include agreeing to the Data Use and Confidentiality and MTA requirements. The investigator will also agree to send abstracts and manuscripts to ATSDR for review; to submit annual progress reports; and to report publications. The investigator is also responsible for returning residual samples and deleting files at the end of the project.

Additional investigator activities could include releasing research data to the biorepository to build synergy and the knowledge base associated with each sample. Additional ATSDR activities could include sharing information about active and completed projects online or sharing research data with other investigators.

Dr. Gwinn thanked Dr. Vinicius Antao, Dr. Mary Jenkins, Dr. Rod Corriveau, and Dr. Geraldine McQuillan for their contributions.

Discussion Points

- Dr. Bruijn commented that the guidelines include a requirement that data will not be shared with other researchers until 12 months after the original publication, which seems like a long time. Dr. Gwinn agreed and noted that the NHANES requirement is only 60 days.
- Dr. McQuillan asked about any human subjects concerns that should be addressed. Dr. Kaye answered that IRB and human subjects considerations are part of the specimen collection, but not sample distribution, as the samples will be de-identified. ATSDR will be able to link the specimens, but as long as the linkage is not provided to recipients of the samples, there are no IRB issues.
- Dr. McQuillan cautioned that human subjects considerations may need to be revisited, since ATSDR can link the information to individuals.
- Stressing that it is important to be upfront about the process and the possible outcomes, Dr. Gubitz asked what it means when an application is scored as “low priority.” Do the investigators have to wait longer for samples, or do they receive fewer samples?

- Mr. Handsfield recommended that ATSDR consider whether deleting data at the end of the study may violate the Federal Records Act and its requirements pertaining to funding and data maintenance. Data retention requirements can be up to 20 years. Ms. Bledsoe said that NIH and the Food and Drug Administration (FDA) have data retention requirements of 3 years.

Discussion of National ALS Biorepository Governance

Wendy Kaye, PhD
Senior Epidemiologist, McKing Consulting Corporation
National ALS Registry Program
Agency for Toxic Substances & Disease Registry

The group discussed a series of questions pertaining to the National ALS Biorepository and its governance. Detailed discussion points are documented following the question within which they were raised:

Who Should Be Allowed to Request Specimens from the Biorepository?

- Ms. Bledsoe suggested that any qualified ALS researcher, from academia or industry, should be allowed to request specimens.
- Dr. Bruijn said that they may not want to limit access to ALS researchers alone, but that an ALS researcher should be a collaborator or partner on the project. For instance, a marker that overlaps Parkinson's Disease and ALS could bring value to the field.
- Dr. Kowall said that not restricting applicants to researchers with "a track record in ALS" could encourage pilot studies and new ideas.
- Dr. Sorenson added that any proposal that addresses ALS is, by default, from an ALS researcher.
- Dr. Marcus noted that Dr. Corriveau's presentation addressed the question of consent and whether limiting the release of specimens to ALS research may be too narrow. For example, a research project on neurodegenerative disease from an expert in Parkinson's Disease could incorporate a hypothesis about common pathways. She encouraged a broad view of what is relevant to ALS.
- Dr. Kaye clarified that the Registry is Congressionally mandated to conduct work specific to ALS. It will be important to understand whether specimens collected under this mandate could be used for research other than ALS research.
- Dr. Kasarskis said that the guidelines for the review panel could address this question so that the review panel will keep the priorities of the bioregistry on track. ATSDR will have the final say regarding who will receive specimens.
- Dr. Horton asked the group whether American researchers should have priority over European researchers who request specimens.

- Dr. Bruijn felt that the biorepository should be international. Researchers from different countries collaborate on many initiatives and programs.
- Ms. Bledsoe added that many other sources of ALS specimens come from researchers outside the US, so it is important that those researchers are allowed access to the National ALS Biorepository samples.
- Dr. Cwik agreed and added that because ALS is a rare disease, it is important to have as many samples as possible and to give as many researchers as possible access to them.
- Mr. Handsfield asked whether the biorepository should be open for surveillance work, given that according to federal rules, surveillance is not research and surveillance systems do not require IRB review.
- Dr. Kowall said that if a surveillance-related project would advance the science of ALS, then it could be considered.

What Type of Analyses Can Be Done?

- Dr. Gwinn asked about governance regarding the ways that the samples could be used, which will impact the types of scientists that might apply for them. Other biorepositories require that applicants requesting samples provide data on the performance of their chosen assays. Research to develop assays for ALS would be relevant and state-of-the-art. She wondered how to balance the value of the National ALS Biorepository samples as another source to be combined with other samples with its intrinsic value as a population-based, nationally representative sample.
- Dr. Bruijn recommended that the governance should not be too proscriptive. The scientific review will determine whether the proposals are the best use of the biorepository samples.
- Dr. Kasarskis agreed. Science and technology move fast, and the governance should leave it open, allowing the scientific panel determine the merit of the proposals.
- Dr. Bowser agreed, but noted that the review committee might consider sending test samples to evaluate performance when proposed assays look promising but have not been validated. The test is a form of QC that ensures that the samples will not be wasted.
- Ms. Bledsoe said that the negotiations with the researchers could incorporate this approach. The review committee could approve a pilot study with a few test samples, and then the investigators could return the data in order to get more samples.

When Can Samples Be Requested?

- Dr. Bruijn supported a process for reviewing requests on an ongoing basis as they are submitted. Specific time periods are too restrictive. Reviews can be conducted via email and telephone, and the process can be flexible.
- Ms. Bledsoe mentioned the need to let the collection “mature.” At what time will there be sufficient numbers of cases with sufficient data?

- Dr. Kowall said that a flexible review process will be important for funded investigators for whom “the clock is ticking.” Review committees can meet via phone or via virtual conferences on the Internet.
- Dr. Boylan added that a restrictive review process may discourage investigators. If there is a long lag time, investigators may bypass this resource.

When Will The Samples Be Available?

- Dr. Cwik noted that distributing samples is not part of the pilot study protocol and asked when the samples will be available.
- Dr. Kaye answered that the contract ends in September 2015, at which point all specimens will be collected.
- Dr. Horton said that prior to the end of the contract; ATSDR will decide whether a full-fledged biorepository is possible. If so, it is likely that another group will be contracted to administer it. It may be possible to use the pilot samples to populate the full biorepository. They will need a sufficient amount of samples in order to move forward, and a plan will be in place before the end of the contract.
- Dr. McQuillan indicated that she is the only person who handles the distribution of the NHANES samples.
- Dr. Kaye reminded everyone that the 300 blood specimens would be representative of the National ALS Repository, and agreed that there could be problems if samples are distributed before the collection is complete and fully representative.
- Dr. Gubitza recommended that when the collection phase is complete, ATSDR should announce the contents and availability of the biorepository. The announcement should also explain the process for requesting samples.
- Dr. Brady suggested that if there is a possibility that the samples will be transferred after they are collected, the informed consent form should take that possibility into account.
- Dr. Kaye said that the location of the samples will not be specified. ATSDR will own the samples and can store them at a CDC facility or a contract facility.
- Dr. Kasarskis reinforced the need to manage the expectations of the research community, emphasizing the importance of not over-promising and then not being able to deliver on those promises. Over-promising could result in the research community becoming disenchanted. The research community will be eager to utilize the samples, but this pilot study is elaborate and broad, encompassing many issues and methods regarding data management, processing, consent, and collection.
- Dr. Kaye stressed that the pilot study also aims to collect specimens that will be useful even if ATSDR does not go forward with the biorepository for some reason.

How to Request Samples

- Dr. Kaye reminded the group that the preliminary process for requesting samples includes a 7000-character project summary, the IRB-approved protocol, proof of IRB review, investigators' CVs, and issues related to conflicts of interest. She asked whether applicants should provide additional information.
- Ms. Bledsoe wondered whether a full study protocol is needed. In many cases, a peer review of the project will already have been conducted. A summary, or a slightly-expanded summary, of the project may be sufficient for evaluation.
- Dr. Lonsdale agreed and added that NDRI does not require the full study protocol. Investigators provide a technical summary as well as a lay summary, which is provided to the source of the tissue and the family.
- Ms. Bledsoe said that the VA requests information such as preliminary data, statistical analysis, and support for the tissue that is being requested.
- Dr. Bruijn suggested that comments from the peer review could be submitted.
- Dr. Lonsdale reported that NDRI collects that information for NIH awards when it is appropriate.
- Dr. Gubitz indicated that when NIH awards are made, the information (investigator name, institution, grant abstract, etc.) becomes publicly available at the "NIH RePORTER" website.
- Dr. Bruijn pointed out that many foundations are funding research. The system should ensure that ATSDR is comfortable with the review of the proposed project.
- Ms. Bledsoe said that if the peer review is pending on a project request, the VA follows up with the investigators to ensure that funding will be available.
- Dr. Marcus said that in order to obtain NIH funding, an investigator must prove that there is access to specimens. She asked about a process for providing letters of support for proposals, and whether a pre-review system was needed.
- Dr. Bowser said that many investigators have requested letters of support from NEALS so that their grant applications can state that they have access to specimens from NEALS. There is an abbreviated review by co-chairs of the review committee.
- Dr. Sorenson clarified that the letter of support is qualified. It does not state that the investigators have guaranteed access to samples. Instead, it indicates that if the project is reviewed successfully, there will be access.
- Ms. Bledsoe noted that other repositories provide letters of support indicating that the kinds of specimens requested by the investigators are available and describing the process for acquiring samples. Typically, reviewers want to ensure that the applicants have thought about the types of samples that they will need and where to find them. Dr. Bowser added that reviewers also want to ensure that enough samples are available.

- Dr. Lonsdale indicated that the NDRI process for letters of support is similar. They determine whether the procurement is technically feasible and whether the tissues are available. They do not make guarantees.
- Dr. Bowser said that NEALS evaluates the proposed methodology. Some applicants have not been willing to disclose the specific protein or gene that will be studied. Applicants from academia and industry were concerned that the review committee might use that information for their own purposes. NEALS created non-disclosure statements that review committee members sign for every application.
- Dr. Horton asked for clarification about CDC IRB reviews of proposals.
- Dr. Kaye said that because the biorepository is approved and because the data sent to investigators are de-identified, the projects will not need CDC IRB approval. Applicants will indicate whether their institution has reviewed and approved the project or reviewed it and determined it not to be Human Subjects research.
- The group discussed aspects of using a website or electronic system to submit applications. Dr. Kaye said that the National ALS Registry uses an electronic system to receive applications to notify Registry participants about a study. The biorepository could be integrated into this system, but there are potential issues with viruses, so only .pdf files can be used.
- Ms. Bledsoe suggested that in its communications, ATSDR could describe reasonable amounts and types of tissues. It is likely that the applications will be better if the investigators understand the realm of possibilities at the outset.
- Dr. Horton asked about limiting quantities for researchers. Dr. Lonsdale said that NDRI does not limit quantities; they judge each application on its own merits. Dr. Kaye noted that the volume of tissue requested could factor into the prioritization protocol.
- Mr. Handsfield said that often, the number of samples requested will depend on the kind of analysis. A protocol with a rigorous analysis will require more samples than a descriptive study. He encouraged that anyone requesting samples should have a statistician on the investigative team at the outset.
- Dr. Kaye added that the summary should provide justification for the types and numbers of samples requested.

Conditions for Release of Samples

- Ms. Steinberg commented that the proposed requirement to send abstracts and manuscripts to ATSDR sounded controlling. Dr. McQuillan noted that NHANES does not make that requirement.
- Dr. Kaye said that ATSDR is Congressionally mandated to submit research results to an external peer review prior to submitting it to a journal. Projects that result from the biorepository may fall under that rule as well.

- Dr. Sorenson hoped that they could avoid requiring that anyone who publishes research results based on samples from the National ALS Biorepository would be required to send the manuscripts through ASTDR.
- Ms. Bledsoe said that if that requirement is made, ATSDR should decide what to do with the manuscripts. It may make more sense to require that manuscripts be shared with ATSDR after they are accepted for publication.
- Dr. Gubitzi indicated that intramural NIH investigators and other NIH employees go through a clearance process at NIH.
- Dr. Kasarskis asked whether the intent of this requirement was to ensure that the National ALS Biorepository is attributed in the paper. If that is the case, ATSDR only needs to require the author page and acknowledgements. This approach will not require the proposed two-week timeline for abstracts and four-week timeline for manuscripts.
- Dr. Marcus agreed with asking for the manuscript when it is accepted. The paper can serve as a record for how the specimens are used. She did not think that the paper should be subject to review, but it is appropriate to require the investigators to return the publication and a lay summary to ATSDR.
- Dr. Bruijn agreed, noting that it is important to remember that the biorepository is a partnership with the ALS community. Lay summaries can serve to promote the biorepository. Researchers will likely welcome that opportunity.
- Dr. Gubitzi added that the website could list the publications that have resulted from work with the samples. Dr. Horton said that ATSDR is maintaining a list of papers that resulted from the pilot phase of the registry. He envisioned a similar record of papers from the biorepository.
- Mr. Handsfield suggested that this information could be required as part of the annual project update.
- Dr. Gwinn hoped that they could streamline the redundant requirements in the documents so that they are not burdensome on the investigators. For instance, some elements in the MTA are repeated in the Data Use Agreement. She asked about preferences for placement and timing of the requirements.
- Ms. Bledsoe suggested that the MTA and the Data Use Agreement could be combined, and also suggested requiring an institutional official to sign off on the agreements.

Follow Up on Findings

- The group agreed that it is reasonable to expect an annual update on research progress. The yearly update could also ask for details about presentations and meetings as well as abstracts and articles.
- Mr. Handsfield asked about the time span for the Data Use Agreement, and whether there is a time span for renewal or a limit on the number of times that it could be renewed.

- Dr. Jenkins said that the NBDPS Data Use Agreement includes an annual data sharing update and requires investigators to resign the agreement annually.
- Mr. Handsfield said that the Centers for Medicare and Medicaid Services (CMS) agreement is for five years. After five years, the agreement is renewed annually and can be renewed indefinitely.
- Ms. Bledsoe said that many Data Use Agreements are for the life of the project and do not have defined endpoints.
- Dr. Kaye clarified that the intent is to maintain control of the specimens and ensure that they are not used for purposes other than the approved project.
- Ms. Bledsoe thought that a time limit may be problematic, as investigators often do not know how long it will take for the project to be complete. As long as the terms in the MTA and Data Use Agreement are specific regarding how the specimens and data are used, an expiration date may not be necessary.
- Mr. Handsfield noted that a good research project is likely to ask more questions than it answers. A separate document may be needed to amend or extend the MTA and Data Use Agreement, or a completely new agreement may be needed if an investigator wants to do something new with specimens or data.
- Dr. Bowser described his experience with investigators who complete the approved project and then ask to conduct additional work with any remaining sample. NEALS requires that leftover material should be returned, so these investigators must complete a new application in order to use the material in a new way.
- Dr. McQuillan said that NHANES uses an amendment to the agreements in this case. They conduct a review of the new project.
- Ms. Bledsoe asked about the quality of the samples that are returned to NEALS. Dr. Bowser answered that the returned samples are not returned to the repository; rather, they are reclassified. They could be used for pilot assays, for instance. NEALS is determining whether to run QC on the samples. Ms. Bledsoe clarified that the returned samples may have limited utility, but the primary reason for requiring the return of samples is to prevent investigators from keeping the samples or giving them to someone else.
- Dr. Lonsdale said that NDRI does not require the return of samples. Investigators submit a Certificate of Destruction of unused samples.
- Dr. McQuillan indicated that NHANES has accepted returned samples and has not experienced problems.
- Dr. Gubitza noted that the quality of returned samples will depend on the type of sample, as some samples may be more fragile than others.
- Dr. Bowser agreed that the integrity of the sample will depend on what it is used for as well as its type. Because the samples are precious, NEALS asks for them to be returned, even though their quality is not assured. However, everyone does not comply with the requirement to return samples.

- Dr. Kaye pointed out that the Data Use Agreement includes the expectation that investigators will submit data from their projects to the registry so that the data are available for others to use. She asked about an appropriate embargo on the information, as the initial proposed time was one year, and NHANES has a 60-day time frame.
- Ms. Bledsoe and the group agreed that requiring investigators to return results is a good idea, as long as ATSDR is prepared to manage the data when they are submitted.
- Dr. Marcus did not feel that a year would be too long of an embargo, depending on the complexity of the research. NHANES does not release phenotypic information until the laboratory data are returned. That step prevents investigators from sharing data.
- Dr. Bruijn said that it usually does not take one year to publish, especially when researchers have been working intimately with data for a long time. Often, data from one group alone is not sufficient, so sharing data from these types of studies is important. She supported a shorter time frame and a collegial sense of sharing.
- Dr. Marcus noted that it takes a great deal of time to analyze, understand, and interpret phenotypic data. She suggested implementing a default time frame, such as six months, and giving researchers the option to request and justify a longer embargo period.
- Dr. Kowall said that it is becoming standard to post data sets rapidly to promote rapid access to primary data. There is a priority to publish as well as a responsibility to share.
- Mr. Handsfield pointed out that there are two general schools of statistics: the Bayesian School, which is more likely to work with data to “see what they can find,” and the Frequentist School, which tends to design statistical analysis based on the experimental design. Both schools of thought should be accommodated, but it should not take a year or more to complete either one.
- Dr. Gwinn commented on the difference between managing data and sharing data. The resources are greater to share data, which should be figured into the cost of managing and returning the data.
- Dr. Boylan asked whether an archive will be created and updated with research findings on individual de-identified samples.
- Dr. Kaye answered that results and information from each project may be stored as a data table, much like Dr. Corriveau’s NINDS resource. A website will describe ongoing studies, but it is not clear how the data will be published and maintained.
- Dr. Antao said that if multiple studies are conducted with the same sample, it may be complicated and challenging to append the data tables, especially if different measurements are used.
- Dr. Kasarskis suggested that ATSDR create a system for managing the data to build for the future and integrate across more extensive data sets. The uniqueness and added value of this biorepository comes from harmonizing it with phenotypic and geographic data from the National ALS Registry. Planning this system and its associated costs will be time well-spent as they build this “epidemiological treasure chest.”

- Dr. Brooks agreed and added that the biorepository should plan for the next level of harmonization with multiple resources.
- Dr. Gwinn commented that the process will involve more than information technology (IT). It will require curation by a person with subject matter knowledge and the skills needed to create a versatile database.
- Dr. Marcus said that if researchers are to be prevented from sharing data with each other, then each researcher should have a different set of IDs.
- Mr. Handsfield emphasized that a data management team will be needed, including subject matter experts, IT experts, a database administrator, and perhaps a web administrator. These costs should be taken into account. He cautioned that some researchers may consider their data to be proprietary.

Making Awards Public

- Dr. Kaye said that ideally, a website will share information about studies and the investigators. The website should be understandable to the public. She asked for suggestions about other efforts, such as actively sharing information with participants.
- Dr. McQuillan cautioned that investigators have not historically been successful at writing lay summaries of their work, and it may not be worth asking them to write them. The summaries should be written at the seventh grade level. Genetics projects are particularly difficult to express in simple language.
- Ms. Bledsoe asked about conflict of interest, suggesting that members of the review committee should disclose any conflicts. Investigators should disclose any conflicts that were declared to the IRB, but those issues may be best addressed at the institutional level.

Review Process / Committee Makeup

- In addition to the persons proposed for the review committee, Dr. Buijn suggested adding ad hoc representation from the Muscular Dystrophy Association (MDA) and the Amyotrophic Lateral Sclerosis Association (ALSA).
- Ms. Bledsoe proposed including a pathologist to review solid tissue in addition to the laboratory experts, given that the review will cover a wide range of specimens.
- Dr. Marcus suggested including more than one patient or family member on the committee. As they will be the only lay people on the committee, it is important that they will not feel intimidated and will feel comfortable speaking up.

Review Process

- Dr. Kaye explained that the review process will be similar to an IRB review. All members of the review committee will receive all of the application materials and rate the proposals. Two members of the review committee will be designated as primary and secondary reviewers. They will provide written comments and lead the discussion.
- Dr. Kasarskis suggested that the guidance should define what constitutes a quorum and the scoring metrics.
- Dr. Cwik asked for more information about “high priority” versus “low priority,” and what it means if a project is approved with low priority.
- Dr. Kaye answered that ATSDR will make the final determination about who receives specimens. The review committee will rank the applications based on the review criteria and ATSDR will accept proposals based on the review results and other factors, such as whether a proposed project may be duplicative of an ongoing project.
- Dr. Gwinn said that the process could be more transparent. For instance, publishing a list of ongoing projects may reduce duplicative proposals. Further, the proposals could be divided into three levels of priority. The second level could be pilot-type studies, and the third level could be commercially-oriented research. It is important that the criteria are clear.
- Ms. Bledsoe said that some banks provide a streamlined process for pilot projects. Investigators can go through this process to request a small number of samples to test an assay, for instance.

Overview of Discussion and Recommendations

Wendy Kaye, PhD
Senior Epidemiologist, McKing Consulting Corporation
National ALS Registry Program
Agency for Toxic Substances & Disease Registry

With input from the group, Dr. Kaye summarized the main points of the day’s deliberations:

Who Can Request Samples

- Research should be about ALS, but ALS should be broadly defined.
- Applicants can come from academia or industry, but the research must be for purposes of knowledge, not profit.
- Let the scientific review determine the applicability to ALS research.
- May not want to limit to ALS researchers, but a collaborator that is an ALS researcher should be part of the project. The review committee should determine whether the investigative team is qualified to conduct the research. Researchers who are new to ALS may come from other areas, such as immunology.
- There may be funding and mandate issues associated with using the specimens for research other than ALS.

- The consent form may need revision to accommodate broader research and to not promise confidentiality.
- Samples should be available to the international research community as well as to researchers from the United States. The shipping costs may need to be considered.

Type of Analyses That Can Be Done

- Do not be too prescriptive regarding what should and should not be done, as these issues will emerge in the scientific review process. It is not possible to mandate what future advances may be.
- As part of the negotiations with the investigator, the review committee may consider requiring pilot projects or QC on samples. Returned specimens could be used for this activity.

When Can Samples Be Requested?

- Conduct reviews as frequently as possible, on an ongoing or monthly basis, and assess proposals in the environment at the time of review. Researchers may have funder-imposed timelines and may be discouraged from using the biorepository if reviews are infrequent.
- It may be advisable to let the collection mature so that there are sufficient samples and sufficient data about them.
- ATSDR should manage researcher expectations, for instance by announcing when samples will be available and whether ongoing samples will be available. It is likely that the samples will be available in September 2015, at the end of the pilot study contract.

How To Request Samples

- The full study protocol is unnecessary; a detailed summary and information from the peer review should be sufficient.
- If the peer review from another agency is pending, then ATSDR should follow up with the Principal Investigator to see if there is a change of status to ensure that the funding is available. The follow-up could be more prescriptive about what the investigator should include in the summary.
- IRB approval or exemption should be provided.
- The summary should include preliminary data related to laboratory assays and/or available statistical data.
- ATSDR can create a process for supplying investigators with a letter of support to show access to specimens. The letter can indicate that the specimens are available but will not guarantee that the investigator will have access to them. An abbreviated review of the project to ensure that it is appropriate will be necessary to release a letter of support.
- Applicants will not need CDC IRB review and approval, but they should submit certification that the institution where the research will be conducted has reviewed it appropriately. The IRB is not required to be accredited.
- Investigators can utilize an electronic system for submitting applications. The system will include information on the types of specimens that are available and the sizes of the aliquots so that researchers will understand what is available. The specimens will be aliquoted to avoid freezing and thawing the specimens. The website will also outline the timeframe for distributing samples and data to approved investigators.

Conditions for Release of Samples

- ATSDR does not need to review abstracts and manuscripts prior to publication. Investigators should, however, provide proof that acknowledgement of the sample source is included in the manuscript prior to publication. ATSDR could provide sample language for the acknowledgments. There is little that ATSDR can do other than not provide samples in the future, if investigators do not comply with this requirement. Acknowledging the resource builds support for the resource, which the investigators should understand. These requirements and sample language could be included in the MTA and/or Data Use Agreement.
- Investigators could provide citations, presentations, and publications in their annual report.
- A legal determination on the applicability of ATSDR Peer Review process is needed.
- Lay summaries of study results will be published on the website.
- The Data Use Agreement and MTA can be combined into one document, and an institutional official and the Principal Investigator should sign it. The agreements should not have an expiration date, but there may be a requirement for renewal or re-signing them. This re-signing could be part of the annual review.
- Amendments to projects will require a review and an update to the Data Use Agreement and MTA.

Follow-Up Findings

- Samples must be returned to the biorepository at the conclusion of projects.
- Results will also be returned to the biorepository. There will be an embargo, perhaps of six months, on sharing the information with other investigators so that the researchers have time to publish their results. If justified, researchers can request additional time. It is important that the data community has rapid access to the data.
- The data returned from researchers will probably not require a new Certificate of Assurance, depending on the system and the level of access. The information is only accessible by a very few people; only aggregate data will be available widely.
- Questions remain regarding data return and sharing, including how to store and curate the data. Managing the data will be a full-time job, especially since multiple data on the same patient can be complicated.
- ATSDR should develop a concept and systems of how to manage data. The development process will need someone with subject matter understanding, and the database team should include IT and web administration expertise.
- To prevent researchers from sharing data with each other, each should have a different set of IDs.

Making Awards Public

- ATSDR's website for the National ALS Registry will expand to include information about the projects from the biorepository and their results. The explanations will be in simple language.
- There was discussion regarding whether ATSDR should require investigators to disclose conflicts of interest, or whether that matter should be left to the IRB of the institution that houses the research. There should be a system for reviewers to declare conflicts of interest.

Review Process / Committee Makeup

- The review committee will be comprised of the current ATSDR committee, plus a statistician. Additionally, a pathologist could be included for review of solid tissue requests, as well as an additional lay member and representation from MDA and ALSA.
- "Quorum" and the scoring metrics will be defined, as well as the prioritization scale. The criteria will be clearly stated.
- A streamlined process for pilot projects will be considered.

Final Comments

At the conclusion of the meeting, the floor was opened for final comments, which were as follows:

- Issues related to costs to distribute samples will be addressed in a future meeting focusing on feasibility. Dr. Kaye asked the group whether there might be problems associated with charging a fee for pulling and shipping the specimens.
- Dr. Kasarskis felt that the fee would not be a problem, since the samples are not available any other way.
- Ms. Bledsoe added that charging for samples may lead applicants to think critically about what they are asking for and may improve the science. There are also costs associated with collecting fees. Cost models are available for these issues.
- Mr. Handsfield added that there could also be costs associated with shipping data with the samples, such as the costs of data extraction and media.
- Dr. Horton asked whether the fees are flat per sample, or whether they vary according to the sample type.
- Dr. Bowser said that NEALS charges a flat fee, but they do not charge a fee to sites that collect samples and participate in the repository. They charge more for industry.
- Mr. Thomas emphasized that it is not legal to buy and sell tissue, so any fees charged are for cost recovery, including shipment, processing, and preservation.
- Ms. Bledsoe said that recent changes to the HIPAA Privacy Rule include requirements pertaining to selling data. Authorization from the patient is required if there will be a sale of protected health information (PHI). There are exceptions for public health and for research. The research exception allows costs to be recovered for preparing the data.
- Dr. Kaye said that extracting data is costly and time-consuming, so it will be possible to determine a price to defray that cost.
- Mr. Hixon said the party responsible for recovering the money should be identified. The sponsor or the repository can collect money, depending on the project and the sponsor's needs.

- Dr. Cwik said that funding agencies want to keep costs as low as possible, and while they would probably not object to fees associated with samples, the costs should be kept reasonable.
- Mr. Thomas recalled the group's discussion of feedback from researchers about the quality of the resource. There should also be quality indicators for procurement, including an assessment of whether environments were maintained and recovery targets were met. The project should be standardized so that it can maintain its goals.
- Dr. Boylan said that one way of ensuring that the sample set is mature is to collect a critical mass of samples before they are distributed. It would be helpful for researchers to know if ATSDR has hopes for the types of projects that these samples will be used for, such as longitudinal studies that will require both collected time points.
- Dr. Kaye said that the information could be included in the announcement that the specimens are available. The announcement would be on the ATSDR and perhaps in the *Federal Register*.

With no further business posed or questions raised, Dr. Kaye thanked the meeting participants and officially adjourned the meeting.

Participant Roster**National ALS Biorepository Governance
Expert Panel****February 12, 2013
Atlanta, Georgia****Participant List****Vinicius Antao, MD**

National ALS Registry Program
Agency for Toxic Substances & Disease Registry
Division of Health Studies
Atlanta, GA

Marianna Bledsoe, MA

Senior Program Manager for Biorepositories
and Biobanking
Biomedical Laboratory, R&D
Office of Research and Development
Department of Veterans Affairs (10P9B)
Washington, D.C.

Robert Bowser, PhD

Director, Gregory W. Fulton ALS and
Neuromuscular Research Center
Professor, Divisions of Neurology and Neurobiology
Barrow Neurological Institute & St. Joseph's Hospital
and Medical Center
Phoenix, Arizona

Kevin Boylan, MD

Director, ALS Center
Department of Neurology
Mayo Clinic
Jacksonville, FL

Christopher "Kit" Brady, PhD

Director, Scientific Operations
VA Biorepository (151C)
VA Boston Healthcare System
U.S. Department of Veterans Affairs
Boston, MA

Benjamin Rix Brooks, MD

Director, Carolinas Neuromuscular/ALS-MDA
Center
Department of Neurology, Carolinas Medical Center
Adjunct Professor of Neurology, University of North
Carolina School of Medicine
Charlotte, NC

Lucie Bruijn, PhD

Chief Scientist
The Amyotrophic Lateral Sclerosis Association
Washington, DC

Roderick A. Corriveau, PhD

Program Director, Extramural Research Program
National Institutes of Health
National Institute of Neurological Disorders and
Stroke
Bethesda, MD

Valerie Cwik, MD

Interim President/Research and Medical Director
Muscular Dystrophy Association
Tucson, AZ

Ariel Davis

Research Assistant
McKing Consulting Corporation
Atlanta, GA

Margaret "Peg" Gallagher, PhD

Lead Microbiologist
Centers for Disease Control and Prevention
Atlanta, GA

Amelie Gubitz, PhD

Program Director, Neurodegeneration
National Institute of Neurological Disorders and
Stroke
National Institutes of Health
Bethesda, MD

Marta Gwinn, MD, MPH

Senior Consultant for Epidemiology
McKing Consulting Corporation
Centers for Disease Control and Prevention
Atlanta, GA

Jim Handsfield, MPH

Atlanta, GA

Scott Hixon

Associate Director, Technical Services
Fisher BioServices
Rockville, MD

Kevin Horton, DrPH, MSPH

Chief, Surveillance and Registries Branch
Agency for Toxic Substances & Disease Registry
Division of Health Studies
Atlanta, GA

Mary Jenkins, PhD

Health Scientist
Centers for Disease Control and Prevention
National Center on Birth Defects and Developmental
Disabilities
Atlanta, GA

Vikas Kapil, DO, MPH, FACOEM

Chief Medical Officer/Associate Director for Science
National Center for Environmental Health/ Agency
for Toxic Substances and Disease Registry
Atlanta, GA

Edward Kasarskis, MD, PhD

Co-Principal Investigator
Cynthia Shaw Crispen Chair for ALS Research
Department of Neurology
University of Kentucky
Lexington, KY

Wendy Kaye, PhD

Senior Epidemiologist
McKing Consulting Corporation
National ALS Registry Program
Agency for Toxic Substances & Disease Registry
Atlanta, GA

Neil Kowall, MD

Professor, Neurology
Bedford VA Medical Center
Boston University
Boston, MA

John Lonsdale, PhD

Vice President, research
National Disease Research Interchange
Philadelphia, PA

Michele Marcus, MPH, PhD

Assistant Director, Kaiser Permanente Center for
Health Research Southeast
Professor, Rollins School of Public Health
Emory University
Atlanta, Georgia

Heather Marshall Traino, PhD

Assistant Professor
Virginia Commonwealth University
Richmond, VA

Geraldine McQuillan, PhD

Senior Infectious Disease Epidemiologist
Centers for Disease Control and Prevention
National Center for Health Statistics
Division of Health and Nutrition Examination
Surveys
Hyattsville, MD

Oleg Muravov, MD, PhD

National ALS Registry Program
Agency for Toxic Substances & Disease Registry
Atlanta, GA

Rebecca Pentz, PhD

Professor of Research Ethics
Emory University School of Medicine
Atlanta, GA

Maggie Ritsick, MPH

Vice President/Project Manager
McKing Consulting Corporation
Atlanta, GA

Judith Smith

National ALS Registry Program
Agency for Toxic Substances & Disease Registry
Atlanta, GA

Eric Sorenson, MD

Neurologist
Mayo Clinic
Rochester, MN

Shari Steinberg, MPH

Health Scientist
Centers for Disease Control and Prevention
Atlanta, GA

Jeff Thomas

Director of Donor Services
National Disease Research Interchange
Philadelphia, PA

Deborah Tress, JD

Attorney
Centers for Disease Control and Prevention
Office of General Council
Atlanta, GA

Laurie Wagner, MPH

Research Associate/Pilot Coordinator
McKing Consulting Corporation
Atlanta, GA

Marlena Wald, MPH, MLS

Training Specialist
CACI
Agency for Toxic Substances & Disease Registry
Atlanta, GA