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ADRC Best Practices (2021)

In 2020-2021, the National Institute on Aging convened a working group (Contributors) to update the guidance on best practices for the ADRCs in the acquisition, preparation, and storage of biospecimens. These updated documents are included below by topic. The recommendations for annual ADRC External Advisory Committee meetings, which also may be of assistance in preparing ADRC Progress Reports, were developed in 2017.

These best practices are intended to be a resource for new Centers and for Centers who may be embarking on a new line of research. Of importance, they should not be construed as requirements for Center activities.

We appreciate that many of these areas are rapidly evolving and as such, we envision these guidelines as dynamic and will be re-evaluated periodically to determine if further updates are needed. Please email Dr. Krista Moulder (moulderk@wustl.edu) if you have suggestions for new topics or for sections that may be outdated.

Note: We are following DOI Best Practices for a collection of documents.

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

BRAIN GUIDELINES

All laboratories should review current consensus-based recommendations for tissue collection, processing, storage, retrieval, and dissemination as well as for histologic methods and any other tissue-based assays. A relevant document with broader recommendations has been developed by NCI at: https://biospecimens.cancer.gov/bestpractices/.

The following guidelines represent current best practices for establishing and maintaining standard operating procedures (SOPs) for a research brain bank focused on Alzheimer's disease (AD) and related neurodegenerative and cerebrovascular diseases.

I. Infrastructure requirements

A. Autopsy considerations

i. Usual practice for research brain banks is brain autopsy only; however, to the extent possible, including spinal cord or full autopsy should be considered and requested, albeit recognizing that additional resources may be required.

ii. Staffing of a 24/7 on call autopsy coordinator, autopsy technician(s), and tissue bank technician(s) is recommended so that collection can occur as rapidly as possible after death.

B. Data management

iii. Autopsy related data are essential to maximize the research usefulness of brain donations.

- For each case, minimal recommended documentation includes time of death, post-mortem interval, and if available information related to agonal state (e.g., fever, days on ventilator)
- Additional relevant parameters include study participant's sex, race, ethnicity, *APOE* genotype (if the individual is consented for genotyping), age at death, relevant family history, medication history, diagnosis(es) of brain diseases, other diagnoses, duration of illness(es). Most of these variables should be previously collected through ADRC clinical cores.

iv. Responsibility for obtaining additional information is commonly carried out independently of brain banking operations; no matter where it is housed, proper database linkages to other ADRC cores (Clinical, Imaging, Biomarker, etc.) should be in place and overseen by the Data Management and Statistics core. Databasing this information may also occur within the brain bank operation, or some other component of the research group. Corroborating data that include biomarker results and genetic data (if available) should be able to be cross-referenced. For all these reasons, having regular meetings between NP core workers and representatives of other ADRC cores is strongly encouraged, because such data may inform the neuropathologic diagnosis. See also **Section IV. B.**, below.

v. For more on databases, sample storage, and sample tracking infrastructure, see **Section III.**, below.

C. Freezer management

i. Freezers should be located in designated rooms with independent, high-quality HVAC systems that are relatively safe from potential natural or human-made disasters.

ii. HVAC units should be placed on outlets with access to a backup generator.

iii. Freezers, HVAC units, and ambient temperatures should be monitored by a central monitoring system.

iv. Alarm notifications should be sent to the biobank coordinator via email and phone call, 24/7.

v. Back-up personnel should be in place for instances when the biobank coordinator is unavailable.

vi. Back-up, independent monitors should be in place in freezer rooms.

vii. Routine maintenance is required on freezers to clear ice, clean filter, and condenser. Freezers should be shut down periodically to defrost.

viii. Maintain a minimum of two back-up freezers for emergencies and yearly shutdowns. Freezers generally have lives of 6-15 years in duration. For a long-term biobank that expands over time, this means that there needs to be resources set aside for freezer replacement and maintenance.

ix. Measures should be taken to protect the biospecimens' security—controlled access to the building, the rooms, and/or the freezers. (See **Section IV. E.**, below).

x. When needed, freezers should be able to be relocated to places with comparable infrastructure regarding monitoring, power management, and controlled access.

II. At time of autopsy

A. Safety and regulatory issues

i. Autopsies must be performed according to local approved IRB protocols (with valid consent protocols), as well as in compliance with all hospital, municipal, state, and federal laws and regulations.
ii. Explicit permission for genomic studies as part of the autopsy consent (See Best Practices document on Consent and Confidentiality) is encouraged to ensure broad utility of collected materials. Since many of the cases will have pathological diagnoses other than AD per se, it is important to acknowledge non-AD dementias and controls are incorporated as valid study participants.
iii. Always use at least universal precautions when handling human tissue or body fluids (Administrative and engineering controls should be used in addition to personnel protective equipment).
iv. If prion disease is a consideration, then follow protocols published by the National Prion Disease Pathology Surveillance Center. (http://www.cjdsurveillance.com). This procedure may be reserved for cases of short-duration dementia or those clinically suspected of harboring prion disease. Some centers may use this protocol for all dementia cases because of the possibility that any case may have unsuspected CJD. Alternatively, some centers refer cases where prion disease is suspected to the National Prion Disease Pathology Surveillance Center.
v. For COVID-19, institutional, state, and federal recommendations should be followed. Implementing COVID-19 screening questions (i.e. about agonal cough and fever, a COVID-19 test proximal to death, COVID-19 exposure, etc.) on intake forms is recommended but definitely imperfect in terms of predicting infection status. Workflows should be established through discussions with all stakeholders (autopsy technicians, coordinators, study PIs, neuropathologists, etc.), minimizing exposure to all, but especially, at-risk staff.

B. Autopsy protocol

i. Minimal data should be gathered as described in **Section I.D**., above.
ii. Tissue block sampling should follow current NIA-AA guidelines (*1, 2*). Paraffin-embedded tissue blocks should be archived and stored in a temperature-regulated environment with safeguards against physical damage, temperature changes, severe weather, and natural disasters for as long as possible, but at minimum 10 years depending on research needs or regulations.
iii. Obtaining a portion of cerebellar hemisphere sufficient to fill a tissue cassette from every case and to store at -80^{o}C as quickly as possible is recommended for potential future DNA preparation (if the consent allows).
iv. Best practice is to establish protocols to dissect and freeze, as quickly as possible, selected brain regions for potential future biochemical and genomic analyses. A variety of methods can be used and the details depend on the desired use of the tissue. Examples are flash freezing tissue in liquid nitrogen, cold isopentane, or between blocks of dry ice. Freezing the brain intact (i.e. whole hemisphere) is not considered best practice because of difficulty in subsequent dissection.
v. Support of collaborative research is a best practice. Additional brain samples and additional methods for optimal stabilization for specific assays should follow documented protocols.
vi. Postmortem cerebrospinal fluid (CSF) may be collected usually from the ventricular system, if adequate resources are available. If it is, then best practice is to centrifuge, aliquot, and freeze at -80^{o}C in appropriate containers based on expected use (see CSF section) and to thaw only once for use. Furthermore, denoting any potential contamination (with blood) is recommended.

III. After autopsy

A. Tissue-relevant procedures and reporting

i. Histologic and immunohistochemical staining of standard tissue blocks should follow current NIA-AA guidelines (1, 2), which include proscribed sections for Aβ and phospho-tau immunohistochemical (IHC) evaluation.
ii. IHC workup should be performed routinely with recommendations to perform TDP-43 staging in amygdala, hippocampus, and middle frontal gyrus (3).
iii. α-Synuclein IHC workup should also be performed (4, 5) as stated in the NIA-AA guidelines.
iv. Assessing age-related tau astrogliopathy (ARTAG) using p-Tau IHC in amygdala and middle frontal gyrus is recommended but not obligatory (6).
v. Notably, at present there is not a list of specific antibodies that are required to be used for IHC on ADRC autopsies. Additional methods including thioflavin-S staining and silver impregnation remain useful for assessing lesion burden and distribution.
vi. Standard neuropathologic data for all ADRC study participants must be reported to the National Alzheimer Coordinating Center using the most recent Neuropathology Data Form (https://naccdata.org/data-collection/forms-documentation/np-11) in a timely manner. Integration with other ADRC cores (specifically those involved with databasing) to aid in this endeavor is encouraged.

B. Storage and inventory

i. All biospecimens should be stored in appropriately labeled containers with unique identifiers in compliance with HIPAA and in a regulated environment with safeguards against physical damage, temperature changes, severe weather, and natural disasters. Histologic slides used for diagnosis and paraffin-embedded blocks should be archived for as long as possible, but at minimum 10 years depending on research needs or regulations.
ii. It is best practice that all biospecimens are stored in a manner that meets universal precautions for human infectious material, IRB oversight, employee health safety regulations, permits further neuropathologic evaluation if needed, and optimizes future potential research use.
iii. Best practice is to **maintain an accurate and appropriately safeguarded inventory** of accrued biospecimens, distributed biospecimens, disposal, and available tissue and fluid resources. **For reporting purposes, tissue requests and sharing should be tracked and documented.** Collaboration with the Data Management and Statistics core is encouraged and allows for optimal linkage of this information to other data sources within the ADRC.
i. Biospecimen resource inventory should be linked with a database(s) that contains outcomes of neuropathologic evaluation, clinical information, and results from other investigations, *e.g.*, genetic information. This arrangement must be IRB compliant and meets the need for study participant's confidentiality, security, and informed consent provisions (see Informatics Guideline). Integration with other ADRC cores, such as Administrative and Data Management and Statistics cores are necessary.
ii. On an ongoing basis, some efforts should be made to audit the integrity of the biobank and the efficiency of storage.

C. Ethical considerations and tissue sharing

iii. In addition to scientific advisory committees for the research group, a brain bank should regularly convene a **Biospecimen Use Committee** for oversight of biospecimen requests and/or be involved in institutional committees focused on biospecimens. This may be subsumed as part of the ADRC Executive Committee.
iv. For specimen sharing, data use, and collaborative agreements should include proper acknowledgement of funders etc. for all persons receiving samples and/or data, including those within the same institution, and some efforts should be made to help clarify proper use of the samples/data. It is prudent to use material transfer agreements (MTAs) and/or data use agreements (DUAs), particularly when the biosamples/data are shared with outside institutions. When possible, **results should be returned to be connected with the rest of the data for those samples**.
v. Shipping of human biospecimens must be done with care, which factors in potential for spoilage, and use appropriate packaging, and in accordance to local and federal regulates. A description of some considerations is present here: https://biospecimens.cancer.gov/bestpractices.

IV. Long-term considerations

A. **Digitization of diagnostic slides** should be considered if resources are available. If digital pathology slides are shared, protected health information should be removed from the linked file name or as part of the microscope slide label. For further details on digital slide recommendations please see the Best Practices Digital Neuropathology document.

B. **Participating in the ADRC research volunteer community.** NP Core should integrate with Clinical and ORE Cores to convey the importance of brain autopsy and this may involve direct interactions with research study participants at ADRC conferences, health fairs, etc. In addition, the NP Core should also work with the Research and Education Component to provide opportunities for students and fellows. NIA has the following resources available to assist:
   a. Brain donation resources for ADRCs
   b. https://www.nia.nih.gov/health/brain-donation-gift-future-generations
   c. View the Brain Donation Social Media Toolkit
   d. ADORE brain donation items

C. **The ethics of cost recovery** (See Best Practices Cost Recovery document) needs to be critically assessed when disbursing human biospecimens. There is special potential for these issues to become ethically, and indeed legally, problematic when money changes hands. Acknowledging this, institutions, departments, and individuals will gain support for their biobanks using many different financial models. Within a given biobank, there can be differing protocols for how different subtypes of samples (as well as professional and technical services) are provided for academic and private end-users. There is not a "one-size-fits-all" solution for any of these contexts. Disbursals to private companies may be worthwhile, but attention should be paid to data integrity as biobanks often have access to data from their own samples. Consideration of an on-site collaborator who is granted such access may help to facilitate. The type of sharing of specimens (to non-profit and/or for profit etc.) should be clearly indicated within the autopsy consent. Given the lack of clear and proscriptive rules that apply in this area, biobanks should team with IRBs and oversight consulting groups (e.g., project-specific executive committee, formal advisory committee [internal or external], research subject advisory council, or other campus-specific consultative/oversight group) to ensure long-term compliance with broader ethical and legal standards.

D. **Procedures and processes to prevent catastrophic loss of stored specimens** are a key priority for repositories, and the best policy is a proactive one. In the event of a disaster, the most likely short-term peril is failure of electricity and/or freezers (See **Section I.C**., above), either individually or in a room- or building-wide electrical or HVAC failure. Floods, fires, and other sudden causes of damage are also possible. To prevent these events from happening requires a high level of vigilance (e.g., HVAC and freezers alarmed with 24/7 monitoring as described above) and financial backing. Other emergency possibilities include natural or human-made catastrophes such as computer failure or some other scenario of widespread chaos. To optimize outcomes in these situations requires pre-planned emergency SOPs and hardware redundancy (and automatic safe storage).

E. **Long-term biobank protection and optimization**
   i. Document control software can be used to generate and update SOPs and can be used for administrative (including IRB) requirements.
   ii. An organizational chart can be a significant tool in supporting existing governance structures through elucidation of roles, responsibilities, chain of command, and requisite reporting relationships.
      - See https://biospecimens.cancer.gov/bestpractices/
   iii. Biobank audits
      - Specimen tracking and inventory quality control (QC) should be built into the biobank plan and included in the IRB.
         - QC and inventory cross-referencing (with the database) can dovetail with sample disbursals
         - Ongoing random sampling can help evaluate and optimize inventory
      - Periodic deeper audits may be executed to verify tissue location and quality, and to optimize tissue allocation for best efficiency.
   iv. End of the biobank life-cycle (also see Best Practices Disseminating and Discarding document)

- Should a brain bank not have sufficient resources to continue and/or plans are underway to shut it down, the relevant NIH program officer should be consulted to facilitate dissemination of tissue to local and/or qualified ADRC brain banks or to NCRAD or Neurobiobank.
- Different biobanks have their own time windows but some are very long-lasting and plans should be made for eventually handing over control from one group of individuals to others.
- It is important to have it be well understood that the biobank is ultimately the property and responsibility of the parent institution, rather than any individual or department.
- Ethically (that is, to be consistent with the spirit and wording of the original participant consent language) and scientifically, it may be appropriate to move the biobank across institutions under rare and unusual circumstances. This is not a trivial endeavor, may have legal repercussions and should only be done following extensive and transparent consultations with all interested parties.
- It is easiest to integrate these concepts early in the biobank's life-cycle, and reconcile various components of the study design.
    - Involve IRB early in this process.
    - Consent form must reflect the ultimate governance is the University, not that of an individual.
    - Ensure there is a SOP for "unspecified further use" of the samples to the extent allowed by the IRB.

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Informed Consent, Confidentiality and Privacy Guidelines

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

INFORMED CONSENT, CONFIDENTIALITY AND PRIVACY GUIDELINES

I. General guidelines for informed consent, confidentiality and privacy related to biospecimens:

A. When possible, written informed consent should be obtained for the collection, storage, and research uses of biospecimens.

B. The updated Common Rule (2018 requirements; https://www.hhs.gov/ohrp/regulations-and-policy/regulations/finalized-revisions-common-rule/index.html) includes the expectation that, as part of the informed consent process, potential subjects will be provided with a concise and focused presentation of the key information that is most likely to assist them in understanding the reasons why one might or might not want to participate in the research.

C. The Common Rule clarifies that human subjects research includes obtaining biospecimens through intervention or interaction with living individuals, or obtains, uses, studies, analyzes, or generates identifiable biospecimens. An identifiable biospecimen is a biospecimen for which the identity of the person is or may readily be ascertained by the investigator or associated with the biospecimen. (This includes "coded" biospecimens.)

D. All research on biospecimens must comply with the applicable privacy and human subjects protections regulations (45CFR 46 – Common Rule, 21CFR 50 and 56 - FDA; 45CFR 160-164 – HIPAA)

E. An ADRC's institutional IRB must determine whether IRB review is required to collect, store, and/or use biospecimens, and if so, what at what level (e.g., full board review, expedited review, exempt review). The access and retention of private identifiable information associated with the biospecimens will inform the local IRB's determination of the appropriate level of review for the research, i.e. the possibility that identity of the subject is or may be ascertained by the investigator.

F. Brain autopsy consent is required as per local institutional or IRB guidelines – this research may be exempt from federal regulations since the subjects are decedents at the time of tissue collection. However, because brain autopsy is best accomplished through early educational initiatives with research volunteers and their loved ones, it is best practice to obtain informed consent from the people while they are still living.

G. When genetic research will or could be performed, the Genetic Information Nondiscrimination Act of 2009 (GINA) must be addressed. GINA's baseline level of protection against genetic discrimination can be addressed, but the limitations of GINA must be addressed as well (e.g., it does not apply to life, disability, or long-term care insurance; employment discrimination prohibitions do not apply to employers with fewer than 15 employees).

H. BANKING OF SPECIMENS FOR FUTURE USE

If residual biospecimens are used (e.g., leftover from clinical procedures or collection in a different research protocol), it is preferred to get informed consent from participants for the banking and subsequent use of their biospecimens.

I. DATA SHARING

II. Recommended components of the informed consent document and process:

A. The informed consent document should address the following:

a. Which biospecimens will be collected and the procedures performed and any physical risks associated with biospecimen collection
b. What information will be associated with the biospecimens and who will have access to direct identifiers
c. The risks related with breach of confidentiality, including risk of disclosure to other family members
d. The potential future uses of biospecimens, including unknown possible future uses (see II.C below)
e. How long biospecimens will be stored (e.g., indefinitely)
f. With whom the biospecimens will be shared
g. Whether the biospecimens may be used for commercial profit and whether the participant will share in this commercial profit
h. Whether clinically relevant research results generated from the analysis of biospecimens (including individual research results) will be disclosed to participants, and if so, under what conditions
i. Whether the research will (if known) or might include whole genome sequencing.
j. Whether the biospecimens can be withdrawn from the ADC bank, and the procedure for doing so.

B. Where appropriate, it is recommended to provide options for the research participants to choose whether to participate in some but not all aspects of the biospecimen project (*e.g.,* lumbar puncture, storage of DNA).

a. Recommend consent document provide yes/no checkboxes that clearly describe each option. For example, if subjects can opt to allow banking of data OR banking of biospecimens, provide separate checkboxes for the participant to complete.

C. When applicable to the project, it is recommended to build into consent forms both current and future uses of research on biospecimens.

a. If the study's primary purpose is to create a data or biospecimen repository, the details of the banking procedures should be laid out in the main body of the consent form.
b. If the study team does not plan on banking the samples, the plan for destroying the specimens should be described such as "The samples will be depleted when analyzed" or "The samples will be destroyed once analysis is complete."

c. If the study team plans on storing the samples after their research is complete (in order to possibly use for a future study), this is considered banking of the samples.

When describing banking for future research:

d. Clearly describe the biospecimens and/or data to be banked for future use (including data associated with biospecimens) and for other types of research.
e. Clearly describe how the biospecimens and/or data will be obtained (e.g. biospecimens left over from routine tests or procedures vs. biospecimens collected specifically for banking, data from medical records vs. data from questionnaires conducted specifically for research). Make clear if collecting the biospecimens/data involves additional procedures that subjects will undergo only if they agree to banking.
f. Make clear whether the banking of their data/biospecimens is required, or whether it is an optional part of the study. If banking is an optional study component, describe it in an "Optional Studies" section at the end of the consent document. **Note:** Mandatory banking is typically acceptable only if there is no prospect of direct benefit.
g. If there are research activities that will be performed only with banked data/biospecimens (e.g., genetic testing, creation of cell lines), describe these activities in this section.
h. Clearly state that you may share the data/biospecimens outside your research team and outside of your institution and describe the procedures for outside investigators to obtain those samples/data that will help protect the person's privacy. Explain why they will be shared outside of your team and institution.
i. Describe how the data/biospecimens will be coded or anonymized.
j. Describe risks related to banking of biospecimens and/or data. Loss of confidentiality should always be identified as a risk of banking. However, if the information being stored is sensitive (e.g. a breach could damage the participant's reputation, or pose legal risks), or if future research with banked biospecimens may generate sensitive data (e.g. identify predisposition to disease or other information that could affect the participant's well-being, relationships, insurability, employability, etc.), then describe these possible consequences of a breach of confidentiality.
k. If you are banking biospecimens, Commercial Products language may apply. (Example text: "Researchers may develop products from the samples and information you provide for this study. Some of these products may have commercial value. If the research team or others use your samples or information to develop products of commercial value, you will not receive any profits from products created from your samples or information.")

D. Given the progressive nature of Alzheimer's disease and its effects on cognitive abilities, it is recommended that consent processes **include a plan for determining when and how to assess decision-making capacity of those whose capacity to provide informed consent might be impaired**.

a. Determine which, if any, of the participants may have impaired decision-making capacity. For example, the consent plan may specify that people with dementia should undergo assessment of their decision-making capacity, whereas those with a diagnosis of mild cognitive impairment (MCI) would not. This would be justified based

on expected levels of impairment in day-to-day functional abilities for dementia and MCI.

b. The method used to assess capacity should be tailored for the level of risk posed to participants. Procedures may pose no physical risk (e.g. urine or saliva collection), could pose some physical risk (e.g., venipuncture for blood collection), or could pose a slight increase over minimal risk (e.g., lumbar puncture for CSF collection).
c. Capacity assessments can be tailored to compensate for a person's limitations, enhancing or maximizing their capacity. For example, an examiner can provide reminders to individuals who have memory impairment. (CITE THE ABA/APA document https://www.apa.org/pi/aging/programs/assessment/capacity-psychologist-handbook.pdf, see page 27)
d. The plan should address who is permitted to assess decision-making capacity, including whether and when clinical judgment is required.
e. To **assess decision making capacity**, measure the person's decisional abilities. There are four abilities: understanding, expressing a choice, appreciation, and reasoning. Among these, the core abilities are understanding and expressing a choice.
    I. The first term, **understanding**, describes a person's ability to know the meaning of facts, such as that they are being asked to participate in research, and to understand that they are participating in research. Another term for this is comprehension. A person's ability to understand a fact can be assessed by asking the person to paraphrase back information (for example, "Can you tell me in your own words what are the risks of this study?"). To compensate for their memory deficits, the examiner could provide background and ask the participant to acknowledge their understanding by saying back the information in their own words. For example, to assess whether the person understands that participation is voluntary, you can ask, "You are being asked to participate in research study. Do you have to participate in research?"
    II. The second term, **expressing a choice**, describes a person's ability to state their decision, such as their answer to "Do you want to enroll in this study?"
    III. The **ability to appreciate** taps into a person's values, and assuring that their choice is consistent with their values. To assess this ability, ask why the person is deciding to enroll in the study, especially when there is no direct benefit e.g., "What do you see as the benefits to you of joining this study?," or "You will not benefit directly from the study, how do you feel about participating?"
    IV. To evaluate a person's **ability to reason**, one could ask "How is joining this study better than not joining it?" or "You are taking some risks (repeat the study risks), to benefit science. Tell my how feel about this?"
    V. Most assessments of decisional abilities focus on the abilities to understand and then to express a choice.
f. Because the ADRC clinical cores are longitudinal projects, address whether those who lose decision-making capacity AFTER enrollment will be permitted to continue

their participation, and if so, whether any procedures will be curtailed, and **whether and when to reevaluate participants' decision-making capacity**. A potential signal for a reassessment is a change in a person's ability to participate in study procedures.

E. Electronic informed consent (eIC or eConsent; https://pubmed.ncbi.nlm.nih.gov/32175821/) is generally permissible and allows collection of informed consent without requiring the research participant to be present for a face-to-face process.

a. Method of contact for conducting eConsent
    I. Via telephone
    II. Videoconference/telemedicine software approved by your institution (e.g., Zoom)
b. Sending and receiving informed consent documents
    I. Use encrypted email to send and receive information from participant including complete PDF version of current IRB-approved ICF
    II. Use an eConsent software package that has passed IT security review and received IRB approval
c. Obtaining signature for eConsent
    I. Receive picture of wet signature in ICF signature page via email
    II. Electronic signature via approved software or apps (e.g., REDCap or DocuSign)
        i. Participants should be provided a copy of the complete eConsent including layered information, and any material accessed via hyperlinks should be maintained and accessible for the duration of the study
        ii. For FDA-regulated studies eSignatures must be CFR21 Part 11 compliant, including the ability to verify the identity of the person signing the eConsent
d. Documentation of consent
    I. Document the name of the individual who conducted informed consent discussion and when the discussion took place
    II. If unable to document the informed consent discussion contemporaneously (e.g., conducting discussion by phone and sending/receiving documents by email), include additional lines to indicate date and time when discussion took place as well as date and time form was signed by individual who conducted the informed consent discussion

F. It is recommended that intended data sharing include:
a. Whether the data you are sharing is identifiable or de-identified information.
b. If sending de-identified data/samples/images relay that any personal information that could identify them will be removed before the data/samples/images are shared.

c. If sending identifiable data/samples/images, describe the identifiable information that will be associated with the data.
    I. Explain the purpose of sending identifiable data
    II. If data are being shared with the sponsor or publisher and that data may be made available to other researchers with no limits on who might use these data or how the data may be used in the future.

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Cost Recovery Guidelines

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

COST RECOVERY GUIDELINES

General Comment/Justification:

Alzheimer's Disease Research Centers (ADRCs), with their cores, are funded to provide the infrastructure to support both Center-affiliated research projects and non-affiliated research projects. In general, ADRCs do not charge investigators for receiving biospecimens to the extent that NIH Center budgets cover these costs. However, there are exceptions to this general rule. In competing renewal applications, cores generate and justify their budgets according to their best estimates of the future demands for their resources. These expectations are based on future plans of the Center components (other cores and projects), planned affiliations and collaborations, and on past experience (e.g., autopsy rate for the last 5 years). Budgetary projections may not match reality of the demands placed on the Center. Biospecimen requests may be so large that an individual laboratory would be forced to abandon other Center activities in order to prepare the samples. In these situations it is appropriate, allowable, and recommended that Centers develop cost recovery policies to deal with demands when they exceed the budgeted support of the Center. A guiding principle is that no cost recovery program should diminish the essential goal of providing human biospecimens to fuel research into Alzheimer's disease. The best practice guidelines outlined here are intended to apply to ADRC specimens and not necessarily specimens collected through other mechanisms. The following recommendations may guide each Center's development of cost recovery policies.

Definitions:

Program Income is defined as **gross** income—earned by a recipient, a consortium participant, or a contractor under a grant—that was directly generated by the grant-supported activity or earned as a result of the award. Program income includes, but is not limited to, **income from fees for services performed, and charges for research resources**. The amount of program income earned and the amount expended must be reported on the annual financial report. Any costs associated with the generation of the gross amount of program income that are not charged to the grant should be deducted from the gross program income earned, and the net program income should be the amount reported.[1]

Cost recovery refers to the recovery of the expenses of the labor, supplies, and services required to operate biospecimen programs that are **not** already included in the Center budget (prepare, document, ship, etc.) biospecimens. Cost recovery does **not** refer to the sale of the specimen itself. There can be no overlap between specific expenses paid by the grant and paid through program income/cost recovery.

Program Income Alternatives**:** NIH allows four program income alternatives (additive, deductive, combination and matching). The NIA P30 and P20 Alzheimer Disease Research Center grant mechanisms dictate use of the Additional Costs Alternative in their Notice of Grant Award under the section titled: "Treatment of Program Income." Additional Costs Alternative is equivalent to the Additive Alternative as described in the NIH Grants Policy Statement. The Additive Alternative indicates that any program income is added to funds committed to the project or program and can be used to further eligible project or program objectives. Note that previously, P30 and P50 Alzheimer Disease Research Center grants used the combination alternative.

Recommendations for Best Practices:

Cost recovery policies are subject to scrutiny and should be developed in accordance with Office of Management and Budget (OMB) Circular A21 principles (see Note at end of section). All institutions should

work closely with their own Sponsored Projects Accounting offices and their NIH Grant Management Specialists in developing policies and procedures to comply with the NIH Grants Policy Statement.

Determining and Setting the charges for Biospecimen services:

1. Charges or fee schedules for biospecimen services should be based on fair estimates of the actual effort (salary and fringe benefits) and costs (supplies, shipping, etc.) associated with sharing the biospecimen. These charges should include all costs associated with the service that are not covered by the grant award and should be reviewed at least annually and revised to assure that charges are covering excess costs.
2. Sound cost accounting principles should be employed when setting charges. Personnel costs (salary and fringes), supplies, shipping, equipment rental, and other services (e.g., genome sequencing) are examples of costs that can be considered when setting charges.
3. Overhead can ONLY be included in cost recovery charges when applied to services provided to an external client (not to users within your institution).
4. Cost recovery may not be limited to the laboratory providing the specimen. Often the burden on data managers to identify appropriate samples based on inclusion-exclusion criteria is significant and cost recovery may also apply to the Data Management Core.
5. Cost recovery income should be directed toward support of the operations of the unit expending the effort, i.e., the income should not subsidize an unrelated function or laboratory.
6. A tiered system of charges may be considered. That is, the charge may depend on the funding source (federally funded, non-profit foundation or industry) of the research for which the biospecimens are requested. An example of such a system has been developed for the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD). This information is available on the NCRAD site listed as "price structure" under each study's available biospecimens.

Tracking and Reporting of Program Income

Perhaps the simplest method of tracking program income is creation of a program income fund where costs in excess of what the grant can cover (personnel, supplies, etc.) are charged and income from services rendered can be applied. The balance at the end of the budget year will determine which "alternative" is used: Additive or Deductive. The activity on this fund would be the basis of reporting program income on the institution's annual financial report to NIA. If an ADRC has more than one core laboratory generating program income or if a laboratory is funded for similar activities from multiple grants that stipulate different program income alternatives, tracking will be more complicated. The $25,000 limit on net income is for the entire grant

Reference

(1) NIH Grants Policy Statement (April 2021): Management Systems and Procedures, 8.3.2 Program Income.

Note: The Code of Federal Regulations (https://www.ecfr.gov/cgi-bin/text-idx?SID=bfb0b57d58de9add89103074281ea94a&mc=true&node=pt2.1.200&rgn=div5) establishes uniform cost principles and audit requirements for all Federal awards to non-Federal entities and administrative requirements for all Federal grants and cooperative agreements. The Code of Federal Regulations update of August 13, 2020 supersedes the OMB Circular A21 principles.

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Digital Neuropathology Guidelines

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A Guide to Digital Slide Scanners and Associated Infrastructure, Frequently Asked Questions

On behalf of the Alzheimer's Disease Research Center Digital Pathology Working Group
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Digital Pathology is a field focused in generating data from digitized specimen scanned slides, sometimes referred to as whole slide imaging (WSI), a succession from traditional microscopy. In its full potential, it is anticipated the further use and development of digital pathology equipment and infrastructure will allow:

- Data/information to be transferred across large distances quickly
- Advancements in research and educational fields
- Advancements in computational analyses such as artificial intelligence/machine learning (scalable deeper phenotyping of specimens)

As many institutions/departments/laboratories may be considering purchasing a slide scanner, the Alzheimer's Disease Research Centers (ADRC) digital pathology working group has developed this Frequently Asked Questions (FAQ) Sheet to aid in common inquires investigators may have. In addition, a corresponding excel workbook with worksheets containing comparisons of common slide scanning systems, server/data storage options, and open source image viewing programs is available upon request. By no means are these resources exhaustive or are slighted to endorse certain products or methods.

Limitations and Disclaimer:

This document was developed with the intent to be a transparent, yet limited and non-exhaustive resource for persons interested in setting up a digital slide scanner system, geared towards those within Alzheimer's Disease Research Center community without certifying one vendor, brand, and/or institution above another. The commercial products on this page do not constitute an endorsement by the National Alzheimer's Coordinating Center (NACC), National Institute of Aging (NIA), and/or other persons/affiliated institutions with the ADRC digital pathology working group. Neither NACC, NIA, and/or other affiliated personnel/institutions with the ADRC digital pathology working group, assume any responsibility for errors or omissions found in this document. Similarly, this resource document is provided "as is" without warranty of any kind, either express or implied, including the implied warranties of merchantability, fitness for a purpose or non-infringement. The NIA, NACC, and other persons/affiliated institutions with the ADRC digital pathology working group further disclaim any liability for any information provided on this document or other related materials provided here.

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1. How can I afford a WSI digital slide scanner and what should I include in my budget?

There can be many means for amassing resources to purchase and set-up infrastructure for a digital slide scanner. A recent survey reported in ADRC neuropathology cores, half received institutional support (Table 1). Others reported the use of funding from specific grants (i.e. NIA, NINDS, NCI) or administrative supplements to existing grants, departmental funds for recruitment, and/or philanthropy. It may also be important to identify and reach out to other departments and/or centers at your institution (i.e. cancer, neurology, neuroscience, pathology, dermatology, GI, and/or telehealth) as they could benefit from the resources and could contribute to initial costs and/or service contracts. It can be very advantageous to amass multiple stakeholders within your institution as many small investments will allow purchase of a slide scanner and infrastructure/support needed.

Table 1. Types of funding used to cover the purchase and operational cost of digital slide scanners (results are not mutually exclusive).

ANSWER CHOICES	RESPONSES	
NIA funding (R01, U, P grants, administrative supplements, etc.)	11.54%	3
NINDS funding (R01, U, P grants, administrative supplements, etc.)	0.00%	0
NCI funding (R01, U, P grants, administrative supplements, etc.)	7.69%	2
Philanthropy	15.38%	4
Institutional support	50.00%	13
Unsure	26.92%	7
Other (please describe)	23.08%	6
Total Respondents: 26		

Table 2. Common slide scanner brands used by ADRC neuropathology cores (responses are not mutually exclusive).

ANSWER CHOICES	RESPONSES	
Aperio/Leica	62.96%	17
Olympus	7.41%	2
Zeiss	14.81%	4
Perkin Elmer	14.81%	4
Philips	11.11%	3
Keyence	3.70%	1
Huron	0.00%	0
Don't know	14.81%	4
Other (please specify)	14.81%	4
Total Respondents: 27		

In respect to finances, the purchase of the slide scanner may have a hefty initial price cost-- and there are additional costs to account for such as the purchase, set-up, and maintenance of a file-sharing/file storage system, personnel expenses (i.e. a 20% effort of a staff member to aid in slide scanning and management), an uninterruptable power-supply, and allocation of space to accommodate the equipment. All these are recommended to be worked into the budget/resource list.

2. What personnel and other infrastructure should be considered?

An investment in personnel is important for the efficient use of the slide scanner and for data management. In most cases, the vendor will install the machinery and then train 1-2 personnel on staff for the hardware/software aspects of the slide scanner. These 1-2 personnel are then “primary users” who should commit their efforts into developing standard operating protocols, carrying out operations (i.e. slide loading, slide scanning, and general software set-up) and finally exporting/managing data. There is also the topic of data management, and without dedicated personnel this can cause disarray of what has been scanned in. Institutional personnel (such as those in IT) should also be involved in conversations regarding slide scanner purchases as they may be needed to advise on optimal network connectivity for data input/output from an onsite or approved offsite server.

3. What hardware features should I consider for a WSI digital slide scanner?

When choosing a WSI digital slide scanner, one should list all potential purposes for the machine and understand what features would be needed to support them. Table 2 represents common slide scanner brands used by ADRC neuropathology cores (responses are not mutually exclusive). Each brand may have different models and based on the distribution there is a clear representation that there is no defined choice for the “best” slide scanner. Below are some details on features to consider:

I. Load capacity (i.e. how many slides can be loaded and continuously run at a time). There are many affordable, smaller scale slide scanners (with a load capacity of 5 - 6 slides/run) and although these can be very efficient it can be time

consuming for personnel to operate when working with large quantities of slides. A higher capacity load slide scanner (with load capacities at 100 or more slides) may cost more, however, the ability to load slides less frequently and let the machine continuously run until complete may be more efficient and offset the cost associated with personnel in the long-term.

II. Brightfield/Immunofluorescent capabilities. Brightfield capabilities allow for scanning of H&E, histochemical, and immunohistochemical stains at a reported 1.0 – 4.0 mins/slide (standard size) based on tissue area and objective. Immunofluorescent (IF) capabilities are available, and increase costs considerably, and can be considered an optional feature available in some slide scanners. Furthermore, IF scan speed can be lengthy depended on the number of channels, exposure time, and typically takes much longer and files sizes much larger than traditional brightfield. If IF is important to your research, consider the number of channels your slides will have when choosing a WSI digital slide scanner.

III. Compatible Objectives. Microscope objectives for slide scanners typically range from 5x – 40x, with some commercial models advertising optional objectives up to 63x/100x. Typically, slides scanned at higher magnifications take additional time to scan and can be much larger in their WSI file size. It is important to determine if the needs of your research require a true objective or could be met by a digital zoom (i.e. 20 x objective moved closer to appear at a 40x resolution, sometimes referred to as a pseudo doubler).

IV. Slide Size. The standard slide size supported by all slide scanners is 26 mm × 77 mm, with a glass/glass cover thickness 0.9 mm - 1.2 mm in depth. If your research/institution uses another slide size, ask if the slide scanner offers optional cassette sizes— this will depend on the manufacturer. Some slide scanner manufactures have reported support for the following slide sizes:

52 mm x 75 mm
75 mm x 100 mm
100 mm x 126 mm (thickness from 1.1 mm–1.4 mm)

V. Slide Format. Based on the slide scanners you choose, the slide format may vary (i.e. TIFF, JPEG- see Table 5 for examples). It may be beneficial to work with a slide scanner that exports files in format compatible with current software (comparison of open source image programs are contained within the companion xls file that is available upon request) or contain relevant metadata important to you study.

Table 3. Average slide scan file size across ADRC neuropathology cores.

ANSWER CHOICES	RESPONSES	
100MB or less	3.70%	1
101MB to 500MB	3.70%	1
501MB to 1GB	3.70%	1
Greater than 1GB but less than 4GB	29.63%	8
Greater than 4GB	3.70%	1
Unsure	37.04%	10
N/A: We do not currently use a slide scanner in our ADC	18.52%	5
TOTAL		27

4. Where should I place my slide scanner?

Slide scanners are costly investment, and it is recommended to place the slide scanner in a safe location with low chance of disruption (i.e. personnel traffic or workflow). Additionally, be mindful of room ventilation, airflow, and duct/pipe work as it would be tragic if there was a water leak that could cause physical damage to the machine and associated infrastructure. The lighting of the room may also be important. Some slide scanners advertise a “closed environment” (having all machinery encased on a sturdy covering), however, having a setting with multiple windows may still affect immunofluorescence capabilities or cause overheating due to increased room temperature. Lastly, as many slide scanners are often a shared resource one may consider placing their machine in a centrally located room with controlled access (as a side note, having a slide scanner as a shared resource can aid as leverage when asking permission for additional space from your institution).

With respect to file-sharing and storage, slide scanners create large data amounts of data per slide (see Table 3 and Table 4). If you will be transferring data, it is important to note that many slide scanners have a minimum requirement for connectivity (such as 10 – 100 MB/sec) to assure optimal transfers. Furthermore, it is always advantageous to check

with your institution on what file sharing options are approved, especially if you are within a healthcare setting and your slides may contain person health information (PHI).

5. What viewing/analysis software options (proprietary or open-source) are available-- and are we restricted to certain file formats?

Many slide scanners may have proprietary software (included, or optional during the purchase of the slide scanner) that work well with the scanner's native file format types (for examples see Table 5). Although the native file format allows the image to contain important metadata, it comes at the expense that it restricts which software options may open the file. Furthermore, many software packages may require substantial computational power for analysis, and this can be taxed further with large image files (i.e. software may easily analyze a specific anatomic region of a mouse brain but could stall when doing similar analysis on a larger human specimen). It is important to discuss with the vendor your specific needs to make sure you have a system to work optimally for your needs.

There are open-source software options (i.e. ImageJ) that can open and work with some images in their native file format types but may require some basic programming skills and trainings. In some circumstances where the slide scanners native file format needs to be changed to be viewed on another platform or for analysis, there are often options in the proprietary and open-source software to exported the file format into a more universally used file format (i.e. TIFF) but this can take some computer processing and graphical power depending on image/file size. Lastly, as many investigators may be within an institution or health care center, one should check with appropriate personnel to denote if the software they intend to use/install is approved by their institution/center. One should consider benefits/limitations of available software and file format as well as open-source software options.

Table 4. Current total storage space used across ADRC neuropathology cores.

ANSWER CHOICES	RESPONSES	
Less than 1TB	8.33%	2
Greater than 1TB but less than 10TB	8.33%	2
Greater than 10TB but less than 20TB	4.17%	1
Greater than 20TB but less than 30TB	4.17%	1
Greater than 30TB but less than 40TB	8.33%	2
Unsure	50.00%	12
If greater than 40TB, please state the estimated amount:	16.67%	4
TOTAL		24

Table 5. Types of digital pathology slide formats across ADRC neuropathology cores.

ANSWER CHOICES	RESPONSES	
SVS	52.00%	13
CZI	12.00%	3
TIFF	16.00%	4
QPTIFF	8.00%	2
JPEG	0.00%	0
VSI	4.00%	1
iSyntax Philips proprietary file	4.00%	1
Unsure	28.00%	7
Other (please specify)	16.00%	4
Total Respondents: 25		

6. What file storage or server/file-sharing options are available for digital images?

An average digital slide scan file within the ARDC can range from 1.0 to 4.0 GB in size (depending on percent compression- see Table 3), and if an institution is scanning multiple cases containing multiple slides, this can create TBs of data quickly. Although scanning onto a computer's internal hard drive (HDD) or onto an external HDD may seem appealing and easy, we recommend a long-term storage plan as well as dedicated method for data management (involving your institution's IT department and/or data core personnel are highly recommended). Having files directly scanned onto the internal HDD may cause the computer to crash (overburdening local memory) and may ultimately cause data loss. There are several options to explore for long-term storage, as well as additional options such as server/file-sharing integration which allows you to store data and access it from multiple locations (referred to as "endpoints"). Table 6 is an overview of how digital slide storage has been handled within ADRCs.

Long-term storage can be accomplished by several means. If most of your ADRCs work is internal, one can contact their IT department or other members of institution/center to set-up an approved on-site server (if the institute allows) which can guarantee a secure method to access or archive (back-up) data. The server can be set-up to connect with the slide scanner and an uninterruptable power-supply (UPS) so there is a dedicated method of transfer from the slide scanner to on-site server—this will prevent error or data loss in case of emergency power shut-downs. If your ADRC is expanding its collaborative efforts, then it can be reasonable to move toward a server/file-sharing platform. A cloud-based server (i.e. Globus, OMERO, etc.) and file-sharing platform (Amazon AWS S3, Google Drive, Box, Dropbox, OneDrive, etc.) differ in the method and structure that data is stored and shared. We recommend understanding if servers/platforms are HIPAA compliance, how much storage is allowed and costs, what speed of access is needed (immediate access, or glacial), and any associated fees with large file transfers- uploads may be free but downloading may come at a cost. The services provided by each option are scalable (will work pending on the site and/or reach of your institution), and an annual cost based on your needs. Always check/consult with your institution as certain storage means may not be approved, and a risk assessment may be warranted.

Table 6. Types of digital slide storage (top) and sharing mechanisms (bottom) across ADRCs (categories are not mutually exclusive).

ANSWER CHOICES	RESPONSES	
Onsite storage directly controlled by the ADC (i.e., on-premises network attached storage)	34.78%	8
Onsite storage directly controlled by an entity other than the ADC	30.43%	7
Offsite storage directly controlled by the ADC	4.35%	1
Offsite storage directly controlled by a department (i.e., shared departmental server)	17.39%	4
Offsite centralized storage (i.e., shared server with other departments)	26.09%	6
Offsite Cloud storage provided by a third-party vendor	4.35%	1
Other (please specify)	17.39%	4
Total Respondents: 23		

ANSWER CHOICES	RESPONSES	
Web portal (e.g., eSlide Manager)	28.13%	9
File sharing (e.g., Google Drive, Box)	12.50%	4
External hard drives	12.50%	4
Unsure	3.13%	1
N/A: We have scanned slides but do not share	25.00%	8
N/A: We do not utilize a digital slide scanner	34.38%	11
Total Respondents: 32		

Furthermore, there may be initial set-up required, and the most important may include a reliable network connectivity (i.e. network speed and manageable firewall rules). There are means to test connectivity such as the following website: https://www.speedtest.net/ . There is no firm recommendation for one service or another, however, back-up and reliable archival in addition to data loss prevention features are invaluable and must be considered. Overall, one may want to engage in conversations with their institution IT team to discuss options.

7. How should one approach file organization and transferring/sharing?

Organizing file names and indexing slides is essential once the slide scanner and infrastructure are in place. The following should be considered when creating an index or file naming scheme: Patient/Specimen Identifier, Case #, tissue region, and tissue stain. Additional details relevant to your slides can be added as necessary. With respect to transferring/sharing, as ADRCs are funded by the National Institutes of Health, they are required to report each year on resources they have shared, furthermore there may be specific acknowledgement wording for utilizing the WSIs as well as restrictions on sharing with third parties. Hence, if one is transferring/sharing WSIs, one may want to set up a request system, and establish data use agreement (DUAs) and/or collaborative agreements. For sharing files, we have stated above in section 5 some options, depending on what information is contained within the WSIs, one may want to consider an institutional approved HIPPA compliant means.

8. Should I opt-in for a slide scanner service contract and if so, how do I support the finances when my grant runs out?

There are often service contracts and warranties available at the time of purchase which cover maintenance and other specific instances when things break. Many vendors offer annual service contracts on their slide scanners, which

can be approximately 10 percent of the initial slide scanner cost (in some cases 13,000.00 USD annually) and one can even add additional years to the service at the initial time of purchase. In some cases, vendors have instead moved to a business model that supports repairs free of cost, on a per-case/per-repair bases or includes the costs of repairs with the initial costs. These plans should be discussed with the vendor, as well as if there are applicable discounts for the purchase if a service contract is purchased.

9. Are there any additional resources for digital pathology?

Yes, please follow the link to the following resources:

Digital Pathology Association: https://digitalpathologyassociation.org/
College of American Pathologists Digital Pathology Topic Center: https://www.cap.org/member-resources/councils-committees/digital-pathology-topic-center
National Alzheimer's Coordinating Center (NACC): https://www.alz.washington.edu/BiospecimenTaskForce.html

Contact information:

Please contact Dr. Brittany Dugger (bndugger@ucdavis.edu) with an email titled "A Guide to Digital Slide Scanners comments and contributions" to submit additional resources in a follow-up draft. We thank all our contributors in advance.

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DNA, RNA, and Protein Guidelines

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

DNA /RNA / PROTEIN GUIDELINES

I. General

A. Whether prepared from biofluids or from tissue, must be collected according to local IRB and state legal codes, using appropriate informed consent forms, with adherence to HIPAA regulations[1,2] (see Informed Consent, Confidentiality and Privacy Guideline) and NIH Genomic Data Sharing (GDS) Policy.

B. Bioanalysis for quality control (e.g., standard assays for integrity of RNA) is recommended, if funding permits, using as little of the specimen as possible.[3]

C. Protein is best preserved by rapid postmortem body cooling and freezing of samples up to 50 hr postmortem.[4]

II. Safety Provisions

A. Laboratories must have safety plans.

B. Laboratory personnel

a. Immunization for hepatitis B is recommended.

b. Must be trained in safety procedures related to handling of human tissue

c. Must observe universal precautions; all specimens must be handled as if infectious

C. Biospecimens

a. It is recommended that a disclaimer accompany all biospecimen disbursements, even if tested negative for HIV and hepatitis B and C, which PIs sign and return to Core leaders. The disclaimer would indicate that they understand that absence of infectivity of biospecimens cannot be guaranteed, that laboratory personnel have been trained in procedures related to handling of human tissue, and that universal precautions will be observed.

b. HIV and hepatitis B and C

1. Testing of blood for hepatitis and HIV may be performed, if desired. However, as there can be both false positives and negatives, a negative test for hepatitis or HIV does not guarantee absence of infectivity. **NOTE: Good lab practice for working with any biospecimen sample is to assume that the sample is positive and should be treated accordingly.**

2. Cases with a history of hepatitis B or C or HIV infection may be excluded from brain donation unless a study specifically requires this type of tissue.

3. It is recommended that frozen brain, blood, and DNA not be distributed from cases positive for hepatitis or HIV, unless a study specifically requires this type of tissue. These may be kept and labeled as either hepatitis or HIV positive for such needs. Fixed tissue may be distributed with specific hepatitis and HIV warnings as above.

III. Annotating

It is essential that all biospecimens be de-identified and highly recommended they be given a unique identifier that follows the specimen from acquisition through processing and storage to retrieval and distribution.

IV. Storage and Retrieval

A. Storage

a. It is recommended that a portion of brain tissue be frozen and stored for biochemical and molecular/genetic studies and the remainder of the brain be fixed for preparation of paraffin blocks, etc., which are kept permanently.

b. Stabilization

1. Note: Consideration given to storage bags/containers that protect the integrity of the contents is recommended.

2. Freezers that are monitored by automated security alarm systems that contact laboratory director and personnel by telephone or pager when failure occurs are recommended.

3. Freezers with back-up systems (*e.g.*, CO_2 or LN_2) or spare freezers for emergency situations are recommended.

c. Temperature recommendations

1. Formalin-fixed: room temperature (20-25°C)

2. Paraformaldehyde-fixed, sucrose/sodium azide preserved: refrigerator (2-8°C)

3. Frozen: -70-80°C or liquid nitrogen vapor

B. Retrieval

a. Biospecimen requests must be approved by the appropriate decision-making body (see Dissemination / Discarding Guideline).

b. Effective annotation that results in minimal effort expenditure to retrieve samples is recommended.

c. Tracking and storage methods that minimize disruption of stable state during retrieval to ensure biospecimen quality are recommended.

d. Inventory database is recommended to track specific position of each biospecimen.

e. Investigators receiving biospecimens must be warned to observe universal precautions; all specimens must be handled as if infectious.

References

1. Federal Register Department of Health and Human Services, Title 45, Code of Federal Regulations, Parts 160 and 164

2. Root J. Field guide to HIPAA implementation, rev. ed. American Medical Association Press, 2004.

3. National Biospecimen Network Blueprint, Andrew Friede, Ruth Grossman, Rachel Hunt, Rose Maria Li, and Susan Stern, eds. (Constella Group, Inc., Durham, NC, 2003); Appendix M, Advanced Analysis Techniques

4. Ferrer I, Santpere G, Arzberger T, et al. Brain protein preservation largely depends on the postmortem storage temperature: implications for study of proteins in human neurologic diseases and management of brain banks: a BrainNet Europe study. J Neuropathol Exp Neurol 66:35-46;2007.

5. National Cancer Institute, NCI best practices for biospecimen resources, 2011; NCI Best Practices website: http://biospecimens.cancer.gov/practices/; PDF of the NCI Biospecimens Best Practice: http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf

6. Alzheimer Disease Genomics Sharing Plan: https://www.nia.nih.gov/research/dn/alzheimers-disease-genomics-sharing-plan

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EAC Guidelines

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Alzheimer Disease Centers' Guidelines Committee for External Advisory Committee Visits and Progress Reports

(AKA THE MORRIS METRICS)

THIS AD HOC COMMITTEE was formed on August 30, 2017, by Dr. Nina Silverberg and Dr. Cerise Elliott of the Alzheimer Disease Centers (ADCs) Program of the Division of Neuroscience, National Institute on Aging (NIA). The Committee's charge was to identify the basic organization and conduct of an annual External Advisory Committee (EAC) visit to review a particular ADC's progress and plans. This Committee also is charged with recommending the type of information to be presented at an EAC Meeting. It is anticipated that the Committee's recommendations will be useful regarding the content of each ADC's annual Progress Reports that are submitted to the NIA and for the Progress Report/Preliminary Findings section of the Research Plan for new and competing renewal applications for the ADCs. Of note, the Committee's recommendations are meant to be just that — recommendations that are developed in the spirit of enabling effective communication across the Centers Program but in no way are mandatory. Given the diversity across the Centers Program, each ADC can decide whether to incorporate none, some, or all of the recommendations.

Purpose of an ADC

An ADC should "foster research on the nature of Alzheimer disease and related dementias (ADRD) and serve as major sources of development of more effective approaches to prevention, diagnosis, care, and therapy. ADCs are expected to contribute to the development of shared resources that support ADRD-relevant research, collaborate and coordinate their research efforts with other programs and investigators, and disseminate research findings for the benefit of the community". (NIA's NOT-AG-17-016).

Each ADC is required to have an EAC that meets annually to review the ADC's progress toward its stated goals. The EAC's charge is to "evaluate the ADC's programs, research progress, effectiveness of communications within the ADC, interactions with the National Alzheimer's Coordinating Center (NACC), and any other activities for which outside expertise is required or desirable" (RFA-AG-16-018). A member of the NIA extramural program staff traditionally attends the EAC Meetings, either in person or remotely. The EAC's report of its Meeting is sent to the NIA as well as to the ADC Director. (Note: Discretion is permitted regarding the scheduling of EAC Meetings. For example, if an ADC's new budget period begins in May and its EAC typically meets in June, the ADC Director and EAC Chair, in consultation with the NIA, may forego the EAC Meeting that year due to insufficient progress to evaluate. Although the EAC members typically visit the ADC in person, in some circumstances it may be that alternative formats, such as video conferencing, are appropriate.) Generation of the EAC report can be the responsibility of the EAC Chair with review and input by the EAC members. Another approach is for the ADC, often represented by the ADC Director and/or

Administrator, to incorporate the EAC's feedback into a draft report that then is circulated to the EAC Chair and members for review to ensure that it captures the feedback appropriately.

EAC Membership

The EAC should have members with the requisite expertise to evaluate specific components of a particular ADC. In general, this means that the EAC should have at least one expert in the functions of the mandated Cores of an ADC: Administration, Clinical, Data Management and Statistics, Neuropathology, and Outreach, Recruitment, and Engagement. (Note: this last Core transitioned in 2017 from an Outreach, Recruitment, and Education Core to the Outreach, Recruitment, and Engagement Core to accommodate the new Research Education Component, which addresses professional and research education). ADCs with additional non-mandated Cores (e.g., Imaging) also will require one or more experts in that area. An individual EAC member may have experience relevant to more than one Core (e.g., Administration and Clinical).

The Chair of the EAC should be an established leader in ADRD research. Typically, the Chair is a current Director of another ADC. The EAC Chair and the Director of the ADC being reviewed ideally should interact in formulating the agenda for the EAC Meeting. A sample EAC Meeting agenda is provided in Table 1. Both the Chair and the ADC Director are responsible for maintaining the schedule (so that EAC members can attend the entire Meeting and still make their flight connections or other transportation arrangements).

Suggested Content for an EAC Meeting

Given that the EAC's role is to provide a "friendly" evaluation of an ADC's effectiveness and accomplishments (as opposed to the more formal NIA review panel's evaluation of an ADC's initial or renewal application), it is appropriate for an ADC to invite the EAC's advice concerning three general areas:

1) Progress toward stated goals, both for the ADC as a whole as well as for each of its components
2) Current problems encountered by the ADC
3) Current and future plans for the ADC

It may be helpful for the ADC to provide relevant material to the EAC members in advance of the EAC Meeting. Examples of such material could include: 1) for each Core and Component, the Specific Aims pages from the most recent ADC application; 2) the Summary Statement from the most recent ADC application; 3) the most recent NIA Progress Report (particularly Sections B2. Accomplishments) for the ADC; 4) a copy of the Minutes from the most recent EAC Meeting; and 5) specific questions (if any) that the ADC would like the EAC to address concerning any challenges it is facing. These materials and questions usually are developed by the ADC Director and Administrator with input from the ADC as a whole. The Administrator typically plans the Meeting and arranges travel and reimbursement (including honoraria for EAC member, often $500-

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$1,000 per Meeting). The ADC may find it beneficial to have a practice session to preview the planned presentations prior to the EAC Meeting.

The EAC can advise an ADC in addressing challenges and problems that are encountered by ADCs. For example, if an ADC might benefit from stronger institutional support, the EAC's report can include a recommendation for such support to provide the ADC with increased leverage with the institutional leadership. The EAC also can advise regarding current and future plans for the ADC, including changes in scientific directions. The ultimate measure of any ADC's success lies in its scientific contributions. Hence, for the reporting period being reviewed by the EAC, the ADC should provide an overview of the key research findings emanating from the Center and the projects it supports. Ideally, the EAC Meeting can include at least brief reports of the scientific progress by relevant ADC faculty and their ADC-supported research projects. New scientific initiatives being considered by the ADC also should be presented for the EAC's input.

Progress Toward Stated Goals

There is no single method to ascertain "progress". Items common to all ADCs (e.g., ability to follow the desired number of active participants in the Clinical Core) help an EAC gauge an ADC's effectiveness, but over-reliance on a checklist approach can obscure other relevant information. For example, recruitment goals for a particular ADC as regards individuals with Alzheimer disease (AD) dementia may not have been met in the previous year because the ADC had instead focused on increased recruitment of individuals with frontotemporal dementia to better meet the needs of investigators using ADC resources. Nonetheless, certain metrics can be useful for an EAC to evaluate "progress toward goals".

A. ADMINISTRATION CORE

1. Demonstrate the "centerness" of the ADC that unites its Cores and investigators with a common vision and purpose. This could include an overarching scientific theme around which the ADC's research is organized, although a central theme is not a requirement for an ADC. Also, "centerness" reflects the cohesiveness and integration of all components of the ADC to enable it to achieve its goals. One simple metric might be how frequently the leaders of the ADC's components meet with the ADC Director and Administrator. Another metric is the concordance of the numbers reported by various ADC components, such as whether the number of deaths and subsequent autopsies reported by the Clinical Core are consistent with those reported by the Neuropathology Core.
2. Demonstrate the value of the ADC to its academic institution. Is the ADC recognized as the program that fosters and facilitates ADRD research at the institution, or would ADRD research at that institution continue successfully if the ADC were to disappear? One example of a metric to demonstrate the value of the ADC to its institution is the number of departments utilizing ADC resources or collaborating with ADC investigators.

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3. Describe any changes in the scientific focus of the ADC in comparison with its original stated aims.
4. Discuss leadership changes (if applicable) for any Core or other ADC component and how they were addressed, as well as the addition of any new faculty and their role within the ADC.
5. Review the succession planning for the ADC Director and other key ADC leaders, as applicable.
6. Describe the ADRD research that is supported by the ADC
    a. The number and type of NIH grants, as well as those from other funding agencies, that leverage ADC resources
    b. The number of requests for access to ADC research participants, their data, and their biospecimens for use in investigator-initiated research (see Table 2). Describe the process wherein such requests are evaluated and fulfilled (if approved) and methods for tracking the impact of this resource sharing (e.g., publications, new grants, or assay development).
    c. Scientific productivity as measured by peer-review publications that were directly supported by the ADC; publications that were indirectly supported by the ADC should be listed separately. [Note: "Direct support" typically indicates that ADC resources are integral to the resultant manuscript, whereas "indirect support" applies to the situation where an ADC investigator may be an author on a manuscript but ADC resources were not utilized in the study.] Productivity also includes new grants that are supported by the ADC, research collaborations, and novel assays (see Table 3).
    d. Number of applications for the most recent ADC pilot grant process, including the departments at the ADC's institution represented by the pilot applications. Indicate if additional pilot grants are awarded using funds (e.g., philanthropy) outside of the ADC's NIA funds (see Table 4).
    e. The success of previous pilot grant awardees, as indicated by the ability of the awardee to obtain external funding for the research initiated by the pilot award. Publications that derive from the pilot award also are very useful to cite but the selection by the ADC of applications for pilot grant funding that later secure external funding is the key metric.
7. Describe any operational or financial synergies with other grants, projects, or centers, both inside and outside the institution, and philanthropy directed to the ADC. The NIA award for an ADC may not cover all of the costs necessary to fulfill its full research mission, including the conduct of federally funded clinical trials or other programs that do not fully reimburse the attendant costs, so it is increasingly important to demonstrate institutional support (including philanthropic support) that enables the ADC to optimally function.

8. If the ADC is within a year or so of its deadline for submission of its renewal application, the plans (to the extent that they are developed) for the renewal should be presented to the EAC.
9. The ADC should describe how it has responded to the EAC's recommendations from previous meetings.

B. CLINICAL CORE

1. The Clinical Core and its cohort(s) are the quintessential components of an ADC. The EAC agenda should allot sufficient time (i.e., more than for other ADC components) for the presentation and discussion of the Clinical Core and its "bread and butter" functions.
2. In general, the cohort should reflect the diversity that characterizes the population served by the ADC. The size and characteristics of the cohort(s) should be justified by the science that the cohort supports. For example, should an ADC support studies that examine the interaction of cerebrovascular disease and neurodegeneration, the individuals in the cohort should be enriched with cardiovascular risk factors. Alternatively, if investigators at a particular ADC are examining aspects of preclinical AD (i.e., cognitively normal individuals who are positive for one or more molecular biomarkers of AD), then the cohort may recruit and follow a disproportionately high percentage of cognitively normal older adults compared with persons with symptomatic AD. A focus on preclinical AD also implies that the participants in the cohort are both eligible for and willing to complete lumbar puncture (LP) (to obtain cerebrospinal fluid [CSF]) and/or positron emission tomography (PET) using tracers for amyloid and/or tau so that their biomarker status can be characterized. In this way, the research studies supported by the ADC determine the composition of the Clinical Core cohort(s). It is preferable that the ADC establish its scientific theme(s) prior to recruiting its cohort. Themes may evolve over time and, if so, the cohort will need to evolve as well to address the new directions.

   Regarding cohort size, ideally the number of cognitively normal and symptomatic participants should be sufficient to allow the specific aims of the projects utilizing the cohort to be addressed as determined by power calculations. This stipulation extends to under-represented groups (URGs) included in the cohort. (The specific URGs included in the Core's cohort largely depend on the demographics of the ADC's catchment area; for example, in some regions of California the dominant URG may be Latino but in others it may be Asian or African American. In any event, sufficient numbers of individuals from the URG should be included to permit comparative analyses). Because the Clinical Core budget is finite, enrolling and following an adequate number of participants may mean that the Core can only follow one symptomatic group (e.g., AD dementia) rather than to try to follow participants across a range of dementing disorders. The decisions the Core

makes in regard to the size and composition of the cohort should be made clear to the EAC. Describe the demographic and clinical characteristics of the active cohort (i.e., all participants who are being scheduled for baseline and follow-up assessments) to ensure that those characteristics are "matched" across clinical groups (e.g., show that cognitively normal controls are roughly equivalent in age to affected individuals) (see Tables 5a and 5b).

Finally, differentiate and describe any additional cohort(s) beyond the active Clinical Core cohort. The Clinical Core cohort represents individuals who are followed longitudinally with Uniform Data Set (UDS) protocol and whose data are submitted to NACC, but ADCs may follow select individuals whose data are not assessed with the UDS and/or are not submitted to NACC. Collaborations with other ADCs and with non-ADC programs that address ADRD also should be described.

3. The Core should describe to the EAC the characteristics of the recruitable pool of potential participants and those who already are enrolled (e.g., geographical area; recruitment from the community or from a clinic) as well as the sites where participants are accessioned and followed. Consider possible biases or problems these pools may introduce into the cohort (e.g., may be difficult to recruit cognitively normal participants from a memory disorders clinic). Describe the recruitment strategies, as developed by the Core and other ADC components (e.g., Outreach, Recruitment, and Engagement Core) with special consideration on individuals from URGs. Beyond the UDS, any other assessment instruments should be described as well as the data collection methods. Describe how the data flow into the central database, as well as the efforts made by the Core to ensure the quality and consistency of the data across Core clinicians and staff (e.g., training and certification procedures for new faculty and staff, consensus conferences, clinicopathological case reviews, etc.)
4. Describe the process for seeking autopsy consent, both antemortem and at time of death. Provide the true autopsy rate (number of autopsies divided by number of deaths of all ADC participants, not simply those who preconsented for autopsy) over a relevant timeframe (see Table 6). Ensure that these numbers correspond with what is being reported in the Neuropathology Core.
5. Provide information as to how participant burden is monitored and addressed. One relevant metric may be the "completion rate": the number of active participants who complete specific components of the assessment protocol (e.g., annual UDS clinical and cognitive assessments; structural brain imaging; amyloid PET scan) divided by the number of active participants who are eligible for that component (e.g., the individual is due for his/her annual UDS assessment) (see Table 7). Discuss whether completion rates vary by participant subgroup. For example, do individuals from URGs in the cohort complete biomarker studies, participate

in clinical trials, and have similar autopsy rates as non-Hispanic whites? A related metric is the attrition rate, which is the percentage of individuals in the cohort who had at a minimum a baseline UDS assessment but no longer participate in the ADC assessment protocol (the main reasons for attrition are refusal, relocation, and death). Describe plans to address remediable factors that contribute to less than optimal completion and attrition rates.

6. The productivity noted in Administration Core above for the ADC as a whole can be expressed in Core-specific terms: how many peer-review publications and research projects use Core data and how many investigator requests does the Core support? How many funded research projects developed from studies using Core resources? If the Core is involved in clinical trials, the recruitment, enrollment, and retention information should be provided for the specific trials being supported by the Core.
7. If applicable, describe how consent for LP, neuroimaging, and other biomarker procedures is accomplished and how these procedures accommodate special circumstances, such as may be encountered in URGs.

C. DATA MANAGEMENT AND STATISTICS (DMS) CORE

1. Discuss the database structure, describing the data input and outflow from the Cores and projects. Describe the quality control procedures for the data.
2. Discuss rules for accessibility to the data.
3. Demonstrate that Core members are integrated into study design and data monitoring of projects, not simply given the data for analysis at study conclusion. The involvement of Core members from the outset of a project results in sounder and more statistically appropriate studies and also allows statisticians to become familiar with the scientific rationale and with the methodology of the study. Investigators should seek the statisticians' input and adopt their recommended rigorous statistical approaches to ensure unbiased scientific conclusions. One metric for the degree to which DMS personnel are involved in the design and conduct of studies is their inclusion as authors/co-authors for resulting publications.
4. Is there sufficient time and effort provided to database managers, programmers, Information Technology specialists, and faculty statisticians and their support staff (e.g., masters level statistical data analysts; students) for the work involved?
5. Promote methodological development by the statisticians that results in new or improved analytic approaches and that also advance their academic careers.
6. Describe audit trail procedures to record changes or corrections of data submitted to the DMS Core (and eventually to NACC).
7. Discuss how the DMS Core interacts with other Cores to promote ADC functions,

such as the recruitment and retention of participants and tracking of research visits (see E. below).

D. NEUROPATHOLOGY CORE

1. Report the number of brain or whole body autopsies versus the number of deaths in individuals who have one or more ADC assessments in the Clinical Core.
2. Report the number of brain or whole body autopsies from sources other than the Clinical Core and justify why such autopsies were accepted, including an assessment of the accompanying clinical data.
3. Be prepared to report on the protocol for dissection, tissue blocks obtained, and staining. Describe whether both frozen and fixed tissues, as well as postmortem CSF, are available from these cases.
4. Provide some indicator of the quality of the postmortem brain tissue as regards molecular studies. Although no metric is perfect, commonly used indicators include postmortem interval, the RNA Integrity Number (RIN), and tissue pH.
5. Provide clinicopathological correlations for the brain autopsies using consensus neuropathologic guidelines. For example, for all ADC participants who came to autopsy and were diagnosed with AD dementia during life, how many had intermediate or high neuropathologic AD change? To aid in the clinical diagnostic process, some ADCs conduct a retrospective dementia interview (essentially, the Informant component of the UDS clinical assessment) with a family member shortly after the participant's death to capture any relevant diagnostic information that may have developed in the participant after their final ADC evaluation. (Note: Such information may be presented in the Clinical Core)
6. Describe the specimen inventory process and database that tracks specimen input and output from the Core and to whom specimens are provided. Describe the number of requests for biospecimens and by whom, as well as indicating whether resources are sufficient to meet the needs of investigators. Indicate what cost recovery mechanisms are used when ADC resources are insufficient. Ideally, link the provided specimens to resulting publications, funded research, and collaborations.
7. Describe the process by which the Core (most often in conjunction with the Clinical Core) provides a report of the neuropathologic evaluation to the next-of-kin of the decedent, and include the mean turn-around time for report generation.

E. OUTREACH, RECRUITMENT, AND ENGAGEMENT (ORE) CORE

1. Describe the planning and outreach methods for the successful recruitment of participants into the Clinical Core. Similarly, describe retention efforts for

ADC participants. Describe the coordination of the ORE Core's recruitment activities with other relevant Cores, such as the Clinical Core and the DMS Core. For example, the DMS Core can provide a potential sampling frame and/or statistical sampling plan that can guide recruitment strategies. Finally, detail how recruitment and retention efforts are tailored to engage individuals from URGs.

2. Demonstrate the effectiveness of the ORE Core's outreach and recruitment efforts, and discuss how the Core self-evaluates whether a given approach should be discontinued if it is ineffective. If there are collaborative efforts with other programs at the ADC's institution (e.g., Older Americans Independence Center; Resource Center for Minority Aging Research) or other ADCs regarding outreach, recruitment, and retention of participants, or with educational efforts about ADRD for lay audiences, describe them here.
3. Describe the efforts used to encourage participation and retention in biomarker studies (e.g. PET imaging; LP) and autopsy programs.
4. Describe the programming and educational activities for lay audiences, including caregivers. Include the Core's interactions with the local chapter of the Alzheimer Association and other relevant organizations.
5. Describe special programs and efforts to engage participants, including those from URGs, in biomarker and brain autopsy protocols.

F. RESEARCH EDUCATION COMPONENT

1. Describe professional education and training activities that are aimed at developing the future research workforce that will address ADRD, and indicate the professional backgrounds of the trainees to include MDs (e.g., neurologists, neuropathologists, psychiatrists, geriatricians), PhDs (e.g., neuropsychologists, neuroscientists), nurses, and social workers. Review the mentoring program that will support the professional development and advancement of postdoctoral fellows and early-stage faculty.
2. Summarize any multi-disciplinary curricula with structural didactic training to support the career development of early-stage faculty who focus on ADRD.
3. Describe efforts to engage in ADRD research those trainees who are women and/or are from URGs and to develop and promote these individuals into academic leadership positions, including in ADRD research.
4. Outline evaluation programs to assess the effectiveness of the training and mentoring initiatives, including benchmarks for trainee competency, skills acquisition, research collaborations, presentations, publications, and successful grant applications.

G. IMAGING CORE *(optional; the metrics below are provided as an example that may be appropriately modified to address other optional Cores, such as Genetics or Biomarkers)*

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1. Describe which imaging modalities are obtained and detail how well the ADC meets its Imaging Core recruitment goals.
2. Describe how the Core and its Aims integrate with the goals of the ADC as a whole and discuss the Core's interactions with the other ADC Cores and its supported research programs. Similarly, describe the correlative studies of the Core with biofluid, genetic, neuropathological, and other initiatives.
3. Indicate whether Core data are integrated into Clinical Core assessments and also discuss whether and how feedback about individual imaging results are provided to participants.
4. Detail the collaborations of the Core with other projects at the ADC's institution and beyond to indicate whether non-ADC protocols use Core data. Describe how investigators external to the ADC request and obtain Core data.
5. Describe whether Core images are shared with NACC and, if not, whether there are plans for future sharing.
6. Describe policies and methods for access to raw images and processing pipelines and how processed imaging data are integrated into the ADC database.

RESPECTFULLY SUBMITTED on November 30, 2017

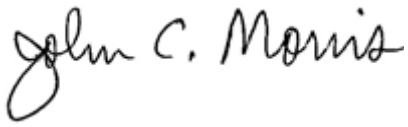

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Table 1. Sample Agenda for Alzheimer Disease Research Center (ADC)
External Advisory Committee (EAC) Meeting
Month/Date/Year

EAC members in attendance: Name/institution; Chair; names/institutions of remaining members. Indicate if any member participates remotely (e.g., by telephone)

National Institute on Aging (NIA) representatives: Names/positions; indicate if these representatives participate remotely (e.g., by telephone). If a NIA representative participates remotely, often it is for the Executive and Feedback sessions (see below).

AGENDA

		ADC Core Leader (name)	**Presenter** (name)
7:30 am	Breakfast		
8:00 am	Welcome and Introductions[1]	ADC Director	
8:05 am	Overview of ADC; Administration Core	ADC Director	
8:25 am	Clinical Core[2]		
9:00 am	Neuropathology Core[3]		
9:20 am	Data Management and Statistics Core		
9:40 am	Outreach, Recruitment, Education Core		
10:00 am	Break		
10:20 am	Research Education Component		
10:40am	Any optional Core(s) (e.g., Imaging)		
11:00am	Research progress supported by the ADC		
11:30am	General Discussion (e.g.,specific issues that the ADC wishes the EAC to address; new Aims; renewal preparation)		
12:00 pm	Executive Session/working lunch (for EAC members only); NIA may join by telephone		
1:00 pm	Feedback of EAC to ADC Leadership[4]		
2:00 pm	Departures		

Caveat: Each ADC is unique. This Sample Agenda and the subsequent Tables are provided only as guides; each ADC should tailor the EAC Agenda and Tables to meet their needs.

1. Institutional support can be demonstrated when institutional leaders (e.g., Dean of the School of Medicine; Chair of the Department where the ADC is administered) attend at least the Welcome remarks.
2. The Clinical Core should be allotted more time than the other ADC components.
3. In general, each Core presentation (other than Clinical Core) should be for 10 minutes (with 10 or fewer slides), leaving 10 minutes for questions and discussion. If the ADC provides its EAC members with a copy of its most recent Progress Report prior to the Meeting, there is no need to reproduce these Specific Aims with a slide.
4. At a minimum, the ADC Director and Administrator should receive the EAC's verbal feedback. Other ADC leaders may also attend at the discretion of the EAC Chair and the ADC Director.

Final Note: It may be helpful for an ADC to designate one or more scribes who attend and record the entire EAC Meeting (including the Feedback Session). The notes of the scribes may be helpful to the ADC leadership in appreciating the EAC's comments during the Feedback Session. For example, a particular EAC recommendation may have its origin in the questions and discussion that occurred during that component's presentation. In the instance that an ADC prepares the draft of the EAC report, the scribe's notes can be invaluable.

Table 2. Data Sharing for (Reporting Period)

Request Type \ Funding source	Federal	Non-federal	Industry	Total
Data Only (including APOE and Imaging)				
Tissue (including DNA, CSF, fibroblasts, and brain)				
Participant Requests				
Total				

Table 3. ADC Productivity During (Reporting Period)

- XX center-supported publications
- YY studies supported with data, tissue or participants
- ZZ trainees on K awards or other training grants
- XYZ continuing multi-site collaborations (NACC, NCRAD, ADCS, ATRI, ADNI, LOAD, ADGC, GAP, IDEAS)
- Other collaborations
- Externally funded grant awards

Table 4. ADC Pilot Grant Program for (Reporting Period)

- XX applications from YY departments: Genetics, Neurology, Psychiatry, Biomedical Engineering, etc
- List each Pilot Grant #, name/degree/department of awardee, and Pilot Grant title for each application selected for funding by the ADC's Executive Committee
  - Indicate if any Pilots are being funded with resources other than the ADC budget

Table 5a. ADC Active Cohort (N = XXX)

	CDR 0 N=	**CDR 0.5** N=	**CDR 1** N=
Age (y)			
Education (y)			
Male (%)			
African American (%)			
MMSE			
% with *APOE4* allele			

Note: Other variables may be incorporated; for example, some ADCs may wish to replace the MMSE with the MoCA. Also, the summary statistics may include the clinical diagnoses of individuals who are cognitively impaired (see Table 5b).

Table 5b. ADC Active Cohort (N = XXX)

Disorder/Syndrome (D1)	N=
MCI	
Amnestic dementia	
PCA	
PPA	
bvFTD	
DLB	
Nonamnestic multidomain	
Other	

Etiology (D1)	N=
AD	
LBD	
MSA	
PSP	
CBD	
FTLD-MND	
FTLD-NOS	
Vascular	

Note: Data can be pulled from NACC Form D1

Table 6. Autopsy Rate (Reporting Period)

- ADC Participants (everyone with one or more ADC clinical assessment)
  - XX autopsies in YY deaths; XX/YY = ZZ%

Table 7. ADC Participation in Study Procedures

(ever in active participants)

	2015	2016	2017
Amyloid PET imaging			
CSF			
MRI			
Blood for Genetics			

Note: If other biomarkers variables are obtained by the ADC, they also should be included (eg, tau PET imaging; fibroblast collection for generation of induced pluripotent stem cells, etc).

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Informatics Guidelines

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

INFORMATICS GUIDELINES

The future of Alzheimer's disease research relies heavily upon research in the basic sciences, and flexible and robust informatics systems for biospecimen resources are vital to collaborative research efforts and progress. Best practices for biospecimen resource data system structure, function, and operational procedures are outlined below.

I. Database Structure

A. ADRC local databases or biospecimen informatics systems should track, or have linkage capabilities to systems that track, a single biospecimen through all aspects of collection, processing, storage, dissemination, return, depletion, and disposal.

B. Biospecimen informatics systems should track associated clinical data and/or link to external sources of clinical data, where applicable.

C. At a minimum, it is recommended that biospecimen acquisition date and current availability status be tracked and linked to the Neuropathology Data Set, the Uniform Data Set, and the Biomarker and Imaging Database, where applicable.

a. Informatics systems should have linkage capabilities such that the physical tube or label of specimen containers or slides is linked to additional data on that specimen in the system.

b. It is recommended that each biospecimen be assigned a unique identifier in the form of a barcode and/or other identifying number.

c. Specimen ID format and database structure should be capable of tracking derivatives, aliquots, and mother/daughter sample relationships.

II. Data Procedures

A. Informatics systems should be capable of generating a spreadsheet or CSV file representing current biospecimen availability that could be uploaded to NACC to keep the data current.

B. Informatics systems should be flexible and adaptable to add new biospecimen collection or processing protocols and data upload specifications as new specimen types are collected.

C. Informatics systems should be capable of performing the following functions: tracking, processing, data entry, data verification, querying, label printing/scanning, and audit trails.

III. Sharing and dissemination of data

A. Center-specific guidelines that incorporate best practices for the dissemination of identifiable, de-identified and anonymous data, including genetic and biomarker data, are recommended to be established and adhered to for all data requests from academic and non-academic collaborators.

B. Policies and procedures for requesting ADRC resources should be published on each Center's website.

C. ADRCs should document and archive researcher requests for biospecimens and clinical data as well as the review outcome, and if possible, resulting publications with attribution to their grant. If possible, data should include characteristics of the individual researcher.

IV. Quality Control, Security and Regulations

A. It is recommended that informatics systems document and monitor measures of biospecimen quality.

B. Database repositories are recommended to be installed on secured servers/network systems and should be backed up at least daily. For safety, additional copies of the data should be stored in a separate geographic location. The use of encrypted, cloud-based, multi-region, tiered storage is encouraged for long-term archival and disaster recovery as large providers offer automated backup, encryption, data redundancy, and data recovery for a fraction of what it would cost to implement these standards on the local level.

C. Network security may be established through consideration of (a) an institutional network firewall; (b) database password, user, group and role-based security; (c) application-level security with passwords and login required to access an application; (d) server-level access passwords. Multi-factor authentication is recommended for all administrator accounts.

D. Passwords should be required to contain, at a minimum, 8 characters including at least one number, capital letter, and special character. Users should be encouraged to use a secure and trusted password manager. This allows a user to auto-generate a unique, long, and complex password for each account while needing to remember only a single strong password. Additionally, two-factor authorization should be required wherever feasible, most notably on high-impact credentials such as root and administrator accounts.

E. Database write access is recommended to be limited to key authorized users and only from trusted Internet addresses, including trusted VPN address ranges.

F. Tiered-access should be specified to allow definition of “authority levels” for accessing and updating of data, particularly identifiable and genetic information These access definitions including user, database, and service account permissions should follow the Principle of Least Privilege.

G. Range checks and logical error checks are recommended for data, and as a quality control measure, errors should be flagged back to a user and disallowed entry into the database until repaired. All data entered into the database should be traceable back to a user through an automatic audit trail system. User metadata should be recorded entirely by the system, asking users to record their own name or identifier at the time of data entry is not a valid alternative.

H. Authorized data transfer is recommended to be protected via strong encryption capabilities through a secure Web or FTP site; data transfer via email is unacceptable. A minimum of a 128-bit encryption suite is recommended for web sites.

I. All databases must comply with HIPAA (Health Insurance Portability and Accountability Act of 1996) regulations to appropriately protect access to individually identifiable protected health information. All databases must comply with the Federal Information Processing Standards, if applicable.

J. All information on a participant should be linked within an ADRC by a common ID. This should be accomplished through an overall database design that allows creation of this ID at participant entry into the ADRC. Where possible, an NIA GUID should be generated and used as the participant ID or stored alongside the participant ID. See Best Practices GUID document.

V. System Support and design

A. A designated team of institutional Information Systems personnel and system administrators are recommended to be in place for routine technical maintenance and trouble- shooting issues. Current CV and training records for Information Systems personnel should be kept on file.

B. Software development and data mining capabilities are recommended to evolve locally under the direction of a committee that may include database users and investigators, bioinformaticians, statisticians and software engineers.

C. The use of open-source platforms and software is heavily encouraged as it promotes sharing and collaboration, not only among ADRCs but with the larger research community.

D. When possible, systems should be designed with future integration and interoperability in mind. This includes designing modular and scalable architecture, considering secure ways to connect with new data sources, and planning for the potential for secure authorization of users and applications outside of the ADRC.

References:

1. National Cancer Institute, NCI best practices for biospecimen resources, 2011 (NCI Best Practices website: http://biospecimens.cancer.gov/practices/; PDF of the NCI Biospecimens Best Practice: http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf

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Intellectual Property Guidelines

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

INTELLECTUAL PROPERTY GUIDELINES

Note: This guideline refers to inventions, as a form of intellectual property, and is not meant to address authorship issues. The need for intellectual property protections is likely low for biospecimen transfers from Alzheimer's Disease Centers where tissue collection has been standardized. Such tissue itself does not represent a unique resource that was created, engineered or invented (e.g. an investigator would be unlikely to 'patent' blood samples). The NIA endorses the least restrictive policies when it comes to sharing biospecimens.[1]

A. Recognize that as custodians of biospecimens, biorepository faculty and staff members are not *a priori* considered inventors under patent law for inventions made using materials distributed by the biorepository. In general, the staff should be informed that one whose sole contribution to an invention consists of the routine collection, handling, storage, and disbursement of biospecimens might not rise to the level of ''inventor'' of an invention. Inventorship is determined by patent law taking into account the role and contributions of individuals involved in the development of the invention and must be considered on a case-by-case basis by trained legal personnel.

B. If true research collaboration is contemplated with the involved biorepository faculty and staff, the nature of that collaboration may qualify for intellectual property rights and can be detailed in intellectual property contractual arrangements or by a material transfer agreement ("MTA").

C. Recognize that biorepositories may not have inherent rights to future intellectual property, but can protect existing rights by contracting with recipient to refrain from filing for intellectual property protection incorporating the biospecimens without express written permission of biorepository. Recipient scientists can protect future intellectual property should they develop inventions from use of banked tissue and data and should notify the biorepository of any intellectual property filings claiming modifications or methods of manufacture or uses of the biospecimens. MTAs can define and secure these rights for both the biorepository and recipient.

D. Ensure through data use agreements and/or MTAs, when applicable, that research data developed using biospecimens are made available to the research community.

References:

1. National Cancer Institute, NCI best practices for biospecimen resources:
    a. 2011 NCI Best Practices website: http://biospecimens.cancer.gov/practices/
    b. PDF of the NCI Biospecimens Best Practice: http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf

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Material Transfer Guidelines

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BEST PRACTICES FOR THE ALZHEIMER'S DISEASE RESEARCH CENTERS

MATERIAL TRANSFER GUIDELINES

The NIH has established principles and policies for the sharing of biospecimens in "Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice"[1] in order to achieve the widest possible dissemination of "unique research resources" to promote research progress. The tissues obtained from carefully-characterized clinical populations, such as from ADCs, represent important resources to be considered in the same way. It is the obligation of the Principal Investigators to act as good stewards of these resources to ensure that they are used for the greatest good. NIH has also formally endorsed the use of material transfer documents known either as "material transfer agreements" (MTA) or "simple letters of agreement" (SLA).[2, 3] These documents, executed usually between institutions not individual scientists, define the terms and protections of the exchange. The SLA is a simpler, less detailed version of the MTA.

Why MTA/SLA? In the past, tissue samples were often exchanged without MTAs because they did not represent a unique resource that had been created, engineered or invented. The need for intellectual property and financial protections did not apply (e.g. an investigator would be unlikely to 'patent' blood samples). However, MTAs offer other protections and restrictions that make them useful. Most academic and government research institutions have technology management offices that govern/negotiate the material transfer agreements of their faculty and staff scientists. Such offices often have institutional templates, which usually can be customized for the individual material transfer (see Item L. below).

In addition to individual institutional documents, the NIH published the final version of the Uniform Biological Material Transfer Agreement (UBMTA) [4] and a Simple Letter Agreement for the Transfer of Non-Proprietary Biological Material in 1995. Institutions can sign the UBMTA Master Agreement and transfer materials under the terms of the UBMTA upon execution of an Implementing Letter for the particular transfer. The Association of University Technology Managers (AUTM) serves as the repository for the signed UBMTA Master Agreements from those institutions wishing to use the UBMTA for some or all of their exchanges of biological materials.

Regulatory Issues Related to Material Transfer: Compliance with federal, state and local laws regarding confidentiality of research participants can also be assured in MTAs. Some institutions routinely review the Institutional Review Board approvals under which tissue was collected to determine if the sharing is permitted. Other institutions require that the recipients' institution certify, in the MTA, that the study is compliant with all national and local regulations. Either approach is acceptable.

When providing data protected under the Health Insurance Portability and Accountability Act (HIPAA) and/or omic or other data which can be potentially used to identify individuals, a data use agreement should be put in place, i.e., these should not be considered de-identified datasets.

Recommendations: The following outline contains items/issues that are typically addressed in MTAs:

A. Identify the parties and specific material to be transferred – Formally identify the provider and recipient to ensure that there can be no accusations of misappropriation or misdirection of materials at a later date. Formally confirm provider has the authority to transfer material based on consent and authorization and how provider will notify the recipient of consent is withdrawn.

B. Protect intellectual property – Refer to Intellectual property section of the Best Practices for guidance.

C. Issues of academic freedom and integrity –

Few limitations should be placed on publication rights and conditions. Confidential review by the biospecimen provider of publications prior to submission (usually 30 days) can afford the opportunity to ensure that nothing confidential or proprietary is disclosed and that relevant grant support to generate the biospecimens are acknowledged. Scientific collaborations are encouraged when appropriate but should not be mandated as part of the agreement.

D. Protect against improper or unsafe use of the material – An MTA informs the recipient of their institution's responsibility if their handling of the material results in injury or damages. Indemnification may also be part of the MTA. It is recommended that both institutions be fully informed and aware of the assignment of responsibility and liability.

E. Provide and document explicit warnings – If the material requires special warnings they can be part of the MTA language (e.g., a warning should be included for tissue that has not been tested for infectious agents). However, the MTA need not be the only place such warnings are provided.

F. Restrict any further dissemination without permission – A recipient scientist cannot provide materials received under the MTA to a third party without written approval. The ADCs and NIH wish to account for the use and productivity of biospecimens they share. Unacknowledged third-party sharing of material thwarts such accountability and should be prohibited without explicit permission of the provider.

G. Restrict and define the scope of how the material may be used – An MTA can contain language that limits the use of the material. For example, the use and development of the material may be restricted to non-profit research or teaching uses. Material may also be restricted from use in research involving human subjects. However, it is recommended that the least restrictive language allowed by the consent be used in sharing tissue.

I. Agree to protect the confidentiality of research participants by not attempting to identify them.

J. Agree to follow cybersecurity best practices.

K. Agree to provide new data generated from the material to the Center and/or the NIA repository as agreed upon to be shared with the wider ADRD research community.

L. MTAs/SLAs can be modified for unique situations and requirements. If your Center has special requirements, they can be added. For example, the following items can be part of the MTA language:

a. Provide a copy of any publication that contains experimental results obtained from the use of the Material. Any publication using this Material must follow NIH Public Access Policies (e.g. a PubMed Central ID)

c. Provide a brief progress report XX months from the receipt of the requested tissue.

d. Acknowledge your Center grant in any presentation or publication that may result from this research:

1. Acknowledge the Center grant number (P30AGXXXXX) in all publications using the Material. Often the material is accompanied by other data generated from the material that require acknowledgements of additional grants

2. Adhere to NIH Public Access Policies and provide PubMed Central ID numbers for all publications.

3. Should funding result from this research now or in the future, please notify the Alzheimer's Disease Center with details so we may report productivity derived from our resources to NIA.

References

1. Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice http://www.gpo.gov/fdsys/pkg/FR-1999-12-23/pdf/99-33292.pdf

2. The NIH Office of Technology Transfer (OTT): http://ott.od.nih.gov/

2a. Simple Letter of Agreement: https://www.ott.nih.gov/sites/default/files/documents/pdfs/slaform.pdf

3. The NINDS Technology Transfer Office: http://tto.ninds.nih.gov/Mta.asp

4. Association of University Technology Managers: http://www.autm.net/Technology_Transfer_Resources/8395.htm

5. National Cancer Institute, NCI best practices for biospecimen resources:

5a. 2011 NCI Best Practices website: http://biospecimens.cancer.gov/practices/;

5b. PDF of the NCI Biospecimens Best Practice: http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf