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.

References

1. Wendler, D. One-time general consent for research on biological samples. British Medical Journal 332:544-547;2006.

2. Electronic Code of Federal Regulations, Part 45 – Protection of Human Research Subjects, https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML

3. OHRP, Guidance on research involving coded private information or biological specimens. August 10, 2004.

4. Attachment: Recommendations Regarding Research Involving Individuals with Impaired Decision-making. March 4, 2009. Recommendations from HHS Secretary's Advisory Committee on Human Research Protections (SACHRP). https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2009-july-15-letter-attachment/index.html

4. National Institutes of Health, "Research Involving Individuals with Questionable Capacity to Consent: Points to Consider," November 2009. https://grants.nih.gov/grants/policy/questionablecapacity.htm

5. Appelbaum PS; Grisso T. Comparison of Standards for assessing patients' capacities to make treatment decisions. 1995. https://www.ncbi.nlm.nih.gov/pubmed/7793439

6. National Cancer Institute, NCI best practices for biospecimen resources, 2011 (NCI Best Practices website: http://biospecimens.cancer.gov/practices/index.asp ; PDF of the NCI Biospecimens Best Practice: https://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf.

7. NIH Genetics Home Reference's "What are the risks and limitations of genetic testing?" https://ghr.nlm.nih.gov/primer/testing/riskslimitations?_ga=2.117768329.1842763676.1574463576-1334347967.1574463576

8. Hamilton RKB, Phelan CH, Chin NA, Wyman MF, Lambrou N, Cobb N, Kind AJH, Blazel H, Asthana S, Gleason CE. The U-ARE Protocol: A Pragmatic Approach to Decisional Capacity Assessment for Clinical Research. Journal of Alzheimer's disease : JAD. 2020;73(2):431-442. PubMed PMID: 31868663; DOI: 10.3233/JAD-190457.

Resources

1. https://www.apa.org/pi/aging/programs/assessment/capacity-psychologist-handbook.pdf
2. Appropriate Use Criteria for Amyloid PET: A Report of the Amyloid Imaging Task Force (AIT), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer Association (AA): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3733252/
3. MacArthur Competence Assessment Tool
   Grisso, T. & Applebaum, P.S. (1998). Assessing Competence to Consent to Treatment. New York: Oxford University Press
4. NCRAD's recommended consent language for sharing samples with NCRAD: https://ncrad.iu.edu/recommended_consent_language.html
5. National Human Genome Research Institute's Informed Consent Resource for Genomic Research: https://www.genome.gov/about-genomics/policy-issues/Informed-Consent
6. NIH's Example Informed Consent Language for Certificates of Confidentiality: https://grants.nih.gov/policy/humansubjects/coc/helpful-resources/suggested-consent.htm
7. NIH Guidance on Consent for Future Research Use and Broad Sharing of Human Genomic and Phenotypic Data Subject to the NIH Genomic Data Sharing Policy: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidance_on_Elements_of_Consent_under_the_GDS_Policy_07-13-2015.pdf
8. NIA's Tips on Communicating About Brain Donation: https://www.nia.nih.gov/health/brain-donation-resources-adrcs#tips
9. NIA's Fact Sheet "Biomarkers for Dementia Detection and Research" https://order.nia.nih.gov/sites/default/files/2018-05/biomarkers-for-dementia-detection-and-research.pdf
10. NIA's "Understanding Alzheimer's Genes" booklet: https://order.nia.nih.gov/sites/default/files/2017-07/Understanding_Alz_GENES_508.pdf
11. NIA's Glossary from their Alzheimer's Disease Genetics Fact Sheet: https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet#glossary
12. NIH Genetics Home Reference's "APOE gene," specifically "Health Conditions Related to Genetic Changes: Alzheimer disease" [sic] https://ghr.nlm.nih.gov/gene/APOE
13. Office for Human Research Protection (OHRP)'s Guidance on the Genetic Information Nondiscrimination Act (Specifically, see section B: "GINA and the Requirements for Informed Consent," which includes sample consent language) https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-genetic-information-nondiscrimination-act/index.html