

Alzheimer's Disease Neuroimaging Initiative - Neuropathology Core (ADNI-NPC)

Brain Donation and Neuropathology Manual

Protocols for ADNI/ADNI-GO/ADNI2/ADNI3

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Introduction and ADNI-NPC Specific Aims

The aims of the ADNI-NPC are:

- (a) To provide and implement training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants.
- (b) To maintain a central laboratory to provide uniform neuropathological assessments in all autopsied ADNI participants in accordance with standard criteria and to promote clinical-neuroimaging-neuropathological correlations.
- (c) To determine the relationship between the molecular neuropathology, structural, and functional changes, including Pittsburgh Compound-B (PiB), Florbetaben and Florbetapir, in early Alzheimer's disease.
- (d) To maintain a state-of-the-art resource for fixed and frozen brain tissue obtained from autopsied ADNI participants to support ADNI's biomarker studies (John Q. Trojanowski, Biomarker Core Leader) and to provide investigators with access to the tissue and data for research purposes.
- (e) To Interact with ADNI's Data Coordinating Center to ensure appropriate entry of the Core's data into LONI's (Laboratory of Neuroimaging) database, promote data sharing and collaborative research, and maintain the established integration of ADNI-NPC with all ADNI components to support its administration, operations, and progress toward goals.

To accomplish these aims, the ADNI-NPC capitalizes on the existing infrastructure of the Washington University Alzheimer Disease Research Center (WU ADRC; P50AG05681, JC Morris, PI), funded continuously by the National Institute on Aging since 1985. The ADRC's Administrative (Dr. Morris), Neuropathology (Dr. Perrin), and Data Management and Statistics Cores provide the framework and support for the ADNI-NPC. Moreover, the Form developed by the National Alzheimer Coordinating Center (NACC; U01AG016976, W. Kukull, PI) for all Alzheimer Disease Centers (ADCs) to report neuropathological findings from autopsied cases will be the primary data collection instrument. In this way, the ADNI-NPC uses standard criteria for neuropathological diagnoses of dementing illness and existing protocols and procedures to achieve these diagnoses.

The ADNI-NPC does not interfere with or supercede neuropathological activities at any ADNI site. It uses brain tissue obtained at the sites to provide a uniform neuropathological assessment to support the clinical classifications and research aims of ADNI.

Prior to Obtaining Autopsy Consent

Prior to obtaining autopsy consent, each ADNI site is required to have an IRB approved ADNI brain donation consent form for utilization in the consent process. Each site is required to send their informed consent form (ICF) to ATRI Regulatory Affairs (RA) atri-ra@usc.com for review. ATRI RA will provide the ICF to the ADNI-NPC coordinator for review of accuracy related to brain donation requirements and provision of tissue to the

NPC. The ADNI-NPC will provide their comments or approval to ATRI RA for review/approval. ATRI RA will send the ICF back to the site for submission to their local IRB. Note: Sites may use a non ADNI centric local consent form (e.g., a brain bank, hospital pathology department, or Alzheimer Disease Research Center [ADRC] consent) as long as it allows for the provision of tissue to the ADNI-NPC and is approved by ATRI RA, ADNI-NPC and the site's local IRB.

Guidelines for Obtaining Autopsy Consent

An ADNI clinician will lead a discussion about autopsy with all ADNI participants (demented and cognitively normal) at their initial assessment (study partners and families are welcomed in the discussion and required for demented participants).

There are 3 objectives of the discussion:

- 1) To convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding dementing illnesses.
- 2) To initiate consideration of the individual's wishes concerning an autopsy.
- 3) To answer questions, misconceptions, or concerns about autopsy.

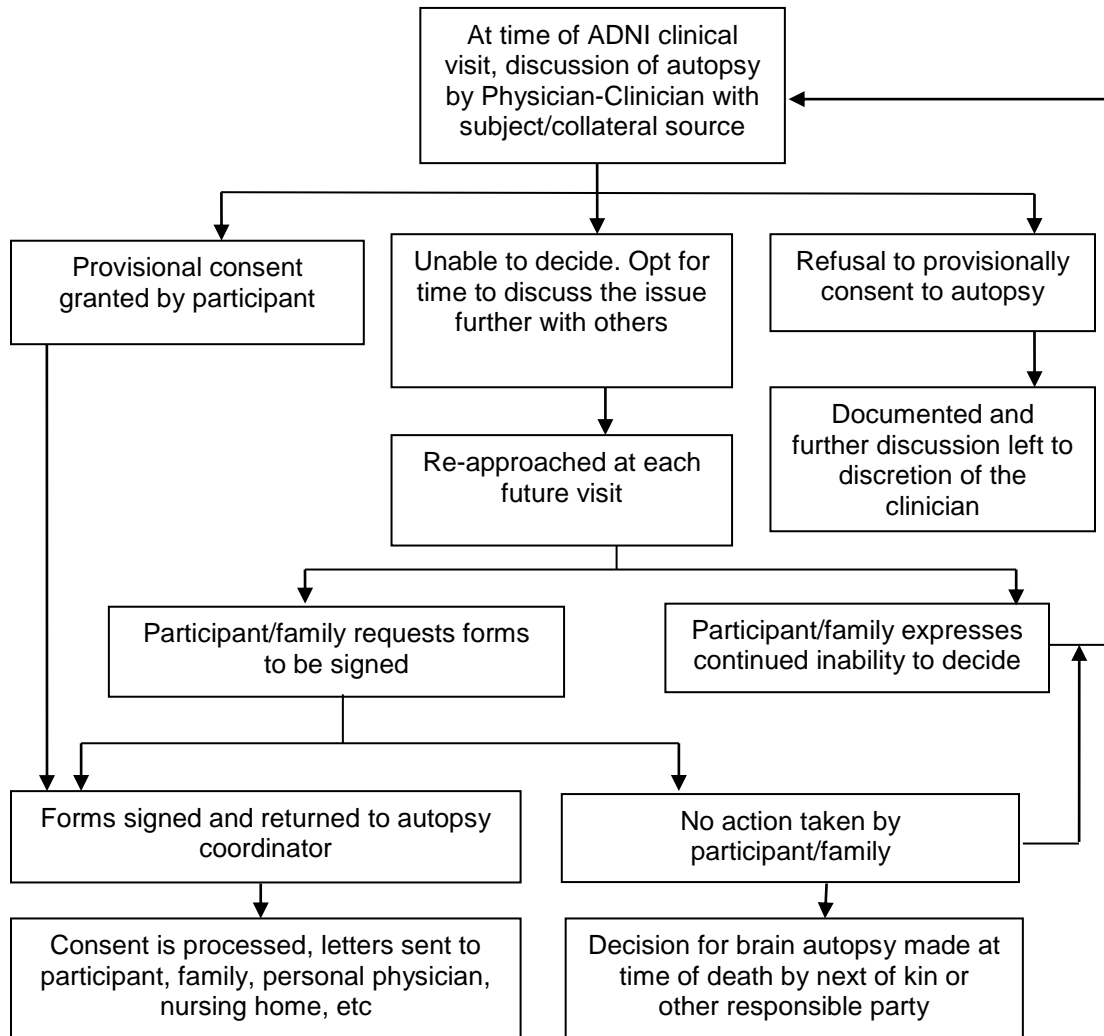
The involvement of the physician in these discussions emphasizes the importance of autopsy.

- If the participant wishes to postpone their decision about autopsy, the discussions are repeated at each of the participant's annual visits until a decision is made (consent or refusal).
- If provisional consent is provided, the ADNI site team works to ensure the participant's wishes regarding brain donation are carried out and that family members and/or other responsible party are aware of the participant's wishes.
- An individual may decide not to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that a decision not to have autopsy in no way jeopardizes their research participation or any other participant rights.

When voluntary consent is granted, more detailed information is provided about procedures to follow at time of death, including telephone numbers to call and other guidelines (sample forms available in manual appendix and online). Participants are strongly encouraged to share this information with next-of-kin, other responsible parties, and private physicians. In many states, final legal authorization by the next-of-kin must be obtained at the time of death. As ADNI is a multi-center study involving sites in the US and Canada, please be sure to follow state and local laws regarding autopsy consent procedures.

The research clinic staff will make regular contact (e.g., at each in-clinic visit, phone checks) with individuals who have provisionally consented to help ensure that autopsy arrangements are made in advance, which aids successful brain donation. This includes in person visits and, to the extent possible, phone checks every 6 months after

completion of the ADNI study, until the death of the participant. Periodically reiterating the participant's wish for donation and reviewing with family members the procedure that should be followed at the time of death will increase the likelihood of a completed brain donation.



Each ADNI site is encouraged to establish an autopsy coordinator (typically a research nurse or coordinator) who processes the autopsy consent, provides information as needed, and monitors the need to update any information (e.g., change in residence) at the ADNI participant's longitudinal assessments. The coordinator also will develop procedures for that site to facilitate autopsies outside of usual hours (e.g., evenings and weekends). The actual procedures are expected to vary in accordance with local needs and resources (one model used by many Alzheimer Disease Centers is to provide 24-hour telephone access).

At the time of death, the autopsy coordinator (or a suitable representative) facilitates arrangements to ensure the completion of the autopsy. The coordinator also notifies the

ADNI-NPC of the death and verifies that the site neuropathologist or autopsy technician has the dissection protocol and necessary materials to send the required tissue to the ADNI-NPC.

The ADNI-NPC, in addition to instructing site personnel in these procedures via regular webinars and site calls (as needed), will be available at any time to answer questions. Contact information, including a 24-hour pager, for ADNI-NPC personnel is listed on page 3. ADNI sites that already have ADRC/ADC Neuropathology Services will continue to follow their own existing protocols. For ADNI sites that do not have established neuropathology services, reasonable costs related to brain donation such as transportation costs from point of death to the autopsy site costs of the autopsy procedure, and shipment of materials are covered by the ADNI-NPC so that the decedent's family and the individual ADNI site do not incur extra expense. The potential costs associated with ADNI autopsies ideally will be discussed with and approved by the ADNI-NPC **PRIOR** to the autopsy.

Acknowledgement of Autopsy Authorization

Once the Participant has given consent (provisional or otherwise) the Acknowledgement of Autopsy Authorization letter and wallet cards (see appendix) should be sent to the following:

1. Participant and/or family and/or applicable other (e.g., Durable Power of Attorney)
2. Nursing home (include chart cover sheet)
3. Funeral home/transport service (as requested)
4. Private Physician (as requested)

Autopsy Costs to Family

The ADNI-Neuropathology Core (ADNI-NPC) will cover brain autopsy costs, with the following limitations. **Please consult the NPC regarding additional financial support if needed to secure a brain donation.**

1. ADNI sites **with** existing ADRC/ADC neuropathology arrangements in place for handling ADNI participant brain donations will continue to make their own arrangements for brain autopsies.
2. ADNI sites **without** an established autopsy system (making autopsy arrangements on a case by case basis): Any costs for transportation above \$200 will be incurred by the ADNI site or the deceased's estate. The additional costs are to be communicated to the participant's next-of-kin prior to transport.
 - i) Local transportation costs will be paid by ADNI-NPC if arrangements are approved by the ADNI-NPC (see the Out-of-Town Arrangements below). If not, ADNI-NPC will pay up to \$200. Brain removal performed out-of-state or out of local area: Brain removal costs will be paid by ADNI-NPC if

arrangements are approved by the ADNI-NPC in advance. Brain removal costs should be limited to \$500 whenever possible.

Death certificates and related paperwork and transport to funeral home or body donor programs post-autopsy are not covered by ADNI-NPC.

Exceptions: The ADNI-NPC Coordinator must approve any exceptions to the above costs via communication with the Leader or Co-Leader of the ADNI-NPC. However, if a death occurs after regular business hours or if the Leader or Co-Leader of the ADNI-NPC are unreachable, the Coordinator is empowered to allow charges of up to \$1000 (for transportation and brain removal) if the expenses seem justified. As a rule, this amount should be for the extreme exception. Please inform the transporter/ pathologist that ADNI-NPC is a research study with limited funds and suggest a cost reduction.

ADNI-NPC Neuropathology Protocols

Where possible, each center will undertake its own brain assessment and forward a standard set of fixed tissue blocks or sections and frozen tissue to the ADNI-NPC (see below). For sites that do not routinely undertake neuropathologic studies, a separate brain removal protocol is listed on page 15.

Financial Assistance with Block Sampling, Preservation, and Shipping Costs

The ADNI-NPC will fund all costs in shipping frozen and fixed tissue samples to St. Louis. To assist participating centers and neuropathologists with the costs of providing frozen tissue slices and/or formalin-fixed paraffin wax-embedded tissue, the following costs will be reimbursed, if requested. Please address an invoice for these costs to the ADNI-NPC Coordinator at Washington University School of Medicine. **The ADNI-NPC is unable to provide funds without an invoice. Please consult the NPC regarding additional financial support if needed to reimburse for materials, time, and effort in provision of tissue samples.**

1. Recovery of coronal frozen tissue slices and formalin-fixed paraffin wax-embedded tissue blocks (*see list of brain regions below) \$300.
2. Recovery of formalin-fixed paraffin wax-embedded tissue sections (*see list of brain regions below) \$100.

ADNI-NPC Block Sampling

Resources to defray the costs of sampling, tissue processing, administration, and transport will be made available to each center already undertaking neuropathology. These resources are to facilitate the provision of the standard set of blocks to the ADNI-NPC. To minimize the burden on participating centers, formalin-fixed, paraffin wax-embedded tissue blocks from the following 17 areas from the left cerebrum will be forwarded to the ADNI-NPC. Whenever possible, blocks should be labeled with the

number below in parenthesis. If this is cannot be accommodated, a key to the block numbers should be included with block shipment. Please provide a **macroscopic or gross description of the brain**. This description should include any observations of the brain made prior to sampling including the fresh brain weight and date and time of autopsy. Please see *Example Macroscopic Description* on page 18.

1. Middle frontal gyrus (Block 1)
2. Superior and middle temporal gyri (Block 2)
3. Inferior parietal lobe (angular gyrus) (Block 3)
4. Occipital lobe to include the calcarine sulcus and parastriate cortex (Block 4)
5. Anterior cingulate gyrus at the level of the genu of the corpus callosum (Block 19)
6. Precentral gyrus (Block 21)
7. Posterior cingulate gyrus and precuneus at the level of the splenium (Block 30)
8. Amygdala and entorhinal cortex (Block 23)
9. Hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus (Block 5)
10. Striatum (caudate nucleus and putamen) with olfactory cortex at the level of the nucleus accumbens (Block 6)
11. Striatum and pallidum at the level of the anterior commissure to include nucleus basalis of Meynert, basal forebrain, and septum (Block 17)
12. Thalamus and subthalamic nucleus (Block 8)
13. Midbrain with red nucleus (Block 9)
14. Pons with locus coeruleus (Block 11)
15. Medulla oblongata (Block 12)
16. Cerebellum with dentate nucleus (Block 14)
17. Spinal cord (Block 13)

In the unusual situation where it is impractical to forward a tissue block (e.g., if the block is used for stereology or a particular brain area cannot accommodate an additional tissue block for the ADNI-NPC), 10 paraffin wax sections (4-8 μm) from each block will be provided to ADNI-NPC for systematic neuropathology and research diagnosis.

Frozen Tissue

To provide tissue for biochemical studies and to advance the aims of the Biomarkers Study, snap frozen tissue will be dissected, frozen, and sent to ADNI-NPC. The following coronal right hemibrain slices (0.5 to 1cm thick), where possible, will be taken:

1. Frontal lobe to include striatum;
2. Frontal and temporal lobe at the level of the mamillary body;
3. Temporal and parietal lobes at the level of the lateral geniculate nucleus;
4. Occipital lobe to include the calcarine sulcus.
5. Cerebellar hemisphere to include the dentate nucleus (parasagittal/radial slice)

Note: It is the responsibility of the shipping institution to initiate a material transfer agreement (MTA) for the provision of tissue to the ADNI-NPC if required.

Histology

In all cases, from the blocks indicated above, the ADNI-NPC lab will prepare slides stained with hematoxylin and eosin and by immunohistochemistry using the following antibodies: phosphorylated tau (PHF1), beta-amyloid (10D5), phosphorylated-alpha-synuclein, and phosphorylated TDP-43 (pTDP-43).

Histology Review

The ADNI-NPC neuropathologist reviews the histological slides in a systematic manner. The data are entered into the National Alzheimer's Coordinating Center (NACC) Neuropathology Data Form and transmitted by the Knight ADRC Biostatistics Core to LONI (Laboratory of Neuroimaging). The final neuropathologic research diagnoses and neuropathologic research report (provided under coded ADNI study ID only) will be forwarded to the center that made available the tissue. A site clinician can then share the report with the participant's family if the family wishes to receive the report. If the family has already received a report from the ADNI site by the time the report from the ADNI-NPC is received, the report from the ADNI-NPC can be reviewed and filed in the participant record. Of note: the report generated by the site and by the ADNI NPC may vary due to differences in brain tissue sampling, staining protocols, and microscopic review of the histologic slides.

Neuropathologic Assessment and Diagnostic Criteria

The operational criteria for the classification of AD and other pathologies defined by NACC will be applied to all ADNI-NPC cases (and are currently applied to all WU ADRC cases). The neuropathologic diagnoses will be determined by Dr. Richard Perrin (Division of Neuropathology, WUSTL) using consensus neuropathologic criteria for AD, and for non-AD disorders. Four sets of neuropathologic criteria for AD will be used: NIA-AA, CERAD, NIA-Reagan, and Khachaturian. ADNI-NPC cases thus will be diagnosed in accordance with each of these sets of criteria, as no consensus currently exists in favor of one set in relation to the others (particularly for the incipient stages of AD addressed by the ADNI study). This approach will allow investigators maximal utility in applying the neuropathological diagnoses most appropriate to their research aims.

Providing Participant Data to ADNI-NPC at Time of Death

At the time of death, the ADNI-NPC will ask for information regarding the participant's cause of death and the individual's cognitive status since the time of the last ADNI assessment. An ADNI site clinician will review possible changes that occurred with the participant from time of last assessment including a medical record review to capture the circumstances leading to death and interviews with next of kin to capture cognitive and health changes. The clinician will provide this review to the Neuropathology Core along with the brain tissue. Please see Appendix doc. "Preparing Brief Expiration Summary for Deceased ADNI Participants with Postmortem Examination" on page 16 for details. This

information is required to safeguard ADNI-NPC personnel from potentially infectious (prionopathy) tissue and to update the research record with information relevant to the neuropathological examination. The ADNI3 site will be reimbursed \$50 for providing this information to the ADNI-NPC at the time of death. **Please consult the NPC regarding additional financial support required for providing this “Expiration Summary”. All requests for reimbursements must be submitted in the form of an invoice addressed to the ADNI-NPC Coordinator at Washington University School of Medicine.**

Accessing Autopsy Data and Tissue from the ADNI Neuropathology Core

Data Data generated by the ADNI-NPC will be transmitted securely to LONI for storage, management and distribution according to ADNI procedures. These de-identified data will be available with the relevant clinical, biological and imaging data on LONI’s public access web site.

Tissue Applications for Biospecimens, including brain tissue, will follow the format of NIH RO1 grants limited to 5 pages. Only manuscripts accepted for publication, published manuscripts, and submitted grants will be considered as appendix material. Applications will be sent to the Chairman of the Resource Allocation Review Committee (RARC; Thomas J. Montine, MD, PhD, Chairman, Department of Pathology, University of Washington, Seattle, WA). The criteria used by RARC will be: scientific merit, feasibility, appropriateness of principal investigator qualifications, burden on ADNI samples, and appropriateness to ADNI goals/themes. Case selection for approved tissue requests will be achieved through discussion with the requesting investigator, the ADNI-NPC staff, and the ADNI Coordinating Center. A Data Use Agreement and Material Transfer Agreement must be executed prior to the shipment of tissue. Upon shipment, a final list of samples shipped is shared with the ADNI Coordinating Center for purposes of reporting and tracking the transfer.

In return for the use of ADNI autopsy tissue, we ask the following of investigators: acknowledgment of the ADNI grant number in publications and presentations, productivity reports on publications or funding that were derived from the project, and no third-party sharing without notification. We do not charge for sharing materials/data unless the request requires effort beyond what can be subsumed under normal ADNI-NPC budgeted effort (as recommended by NIA). If the request justifies a charge, the cost is kept to a minimum and based on actual expenses (effort and materials).

Frequently Asked Questions

1. Who is eligible for brain donation as part of the ADNI study?

Individuals who have participated in the any of the ADNI studies are eligible to donate their brain to ADNI provided that the appropriate consents are in place. Individuals may remain in the ADNI study for ‘brain

donation only' and re-enroll in each new ADNI study as such. Periodically reviewing the procedure that should be followed at the time of death and reiterating the participant's wish for donation to family members will increase the likelihood of a completed brain donation at time of death.

2. Who may give consent?

Laws governing consent for autopsy and brain donation vary by jurisdiction. It is incumbent upon each ADNI site to seek consent from participants, next-of-kin, Durable Power of Attorney and/or Legal Authorized Representative in accordance with local laws. One potential resource for reliable information on this topic for sites in the United States is the local Medical Examiner's Office.

3. Who will cover the transportation and brain removal costs?

For ADNI sites that do not have established neuropathology services, transportation costs from point of death to the autopsy suite, costs of the autopsy procedure, and shipment of materials are covered by the ADNI-NPC so that the decedent's family and the individual ADNI site do not incur extra expense. If the ADNI site or other tissue procurement mechanism do not have funds to pay for the transportation of the body from the place of autopsy to the funeral home the family of the decedent may be asked to cover this cost. Please inquire with the ADNI-NPC prior to charging the family for these expenses.

4. Who will cover the extra expenses incurred in my lab from the additional work required to fulfill the ADNI-NPC protocols?

Resources to defray the costs of sampling, tissue processing, administration, and transport will be made available to each center already undertaking neuropathology. These resources are to facilitate the provision of the standard set of blocks for ADNI-NPC. (See page 8)

5. What if a participant expires in the middle of the night? When should the autopsy be performed?

While it is important that the brain be removed as soon as possible after death, when a participant expires outside of normal business hours the brain removal can be performed the following morning. For sites that currently undertake neuropathology, please follow the established after hours procedures.

6. Whom should I contact if I need assistance at night or on the weekend?

The ADNI-NPC Coordinator is available by pager at **+1-314-841-4738** should you need emergency assistance.

Arranging Autopsy Service for Sites without Neuropathology Resources

These procedures should be used to identify a person and location where a brain removal can be performed at an ADNI site that does not currently undertake neuropathology. These arrangements should be made in advance with the assistance of the ADNI-NPC Coordinator.

1. Contact the participant, informant or collateral source to clarify the autopsy procedure. Obtain information about the closest hospital and the funeral home that will be used at the time of death.

2. Contact the closest hospital and request to speak to the Department of Pathology (Autopsy Service). Inquire with the Pathology Department staff, regarding the availability of a pathologist / autopsy technician to perform brain removal. If they do not have a pathologist / autopsy technician who is available to assist, inquire about the protocol they follow (whom they might contact) when an autopsy is needed.
 - If there is a local ADC/ADRC, contact the autopsy coordinator to make arrangements for autopsy.
 - If you are unable to find someone, contact the local funeral home for any suggestions they may have.
 - Look up neurologists in the area in the membership directories of the American Academy of Neurology www.aan.com/ or the American Association of Neuropathologists www.neuropath.org/ and ask them for suggestions.
 - Contact the local Alzheimer's Association for any recommendations they may have regarding local autopsy services.
 - Consider other hospitals, medical schools, and the local coroner or medical examiner.
3. Once a named pathologist is identified, contact the participant's funeral home and make preliminary arrangements for transportation to the autopsy location at time of death. Obtain a preliminary cost estimate for these services. Discuss any atypical cost with the ADNI-NPC Coordinator.
4. Fax, mail, and/or email a copy of the Autopsy Brain Protocol to the out-of-town pathologist. Answer any questions they may have or refer them to Dr. Perrin at ADNI-NPC.
5. Inquire as to the cost for the pathologist's services. Remind them we are a research study and have limited funds.

Please contact the ADNI-NPC Coordinator should you need assistance in arranging for autopsy/brain removal for ADNI participants.

Autopsy Procedures

To be carried out by the site ADNI coordinator at the time of death.

1. Notify the ADNI-NPC of the death of the ADNI participant. If the participant passes away overnight and assistance with handling the death is not required, this can be done via e-mail or by phone the following business day.
2. Contact family or informant/collateral source to clarify autopsy procedure. Obtain information about the funeral home they plan to use.
3. Contact the pathologist or technician who has agreed to perform the brain removal. These arrangements should be made in advance with the assistance of the ADNI-NPC Coordinator. If arrangements have not been made in advance or you are unaware of the arrangements, contact the ADNI-NPC Coordinator.
4. Ensure that the pathologist or person performing the brain removal has a copy of the ADNI-NPC Brain Removal Protocol. This should also be supplied

in advance; however, copies are available in the document repository at the ADNI website or download. If there are any questions, the person recovering the brain should contact Haley Bernhardt at 1-314-273-1269 or by pager at 1-314-841-4738 **before** they begin the procedure.

5. Schedule the brain removal in accordance with the pathologist's schedule. While it is important that the brain removal take place as soon as possible after death, participants who die outside of normal business hours (i.e. overnight) can have the brain removed the following morning.
6. Once the pathologist and brain removal location have been identified, contact the participant's funeral home and make arrangements for transportation to and from the autopsy location. Obtain a preliminary cost for these procedures. Discuss any atypical costs with the ADNI-NPC Coordinator.
7. After brain removal, the pathologist should ship the fixed (two weeks following the removal) and frozen brain tissue in separate containers to the ADNI-NPC following the Brain Removal Protocol (see below).
8. The ADNI-NPC Coordinator will follow up with the pathologist to ensure that the tissue is shipped and received at the ADNI-NPC lab. The ADNI-NPC will provide approved shipping containers to the pathologist for the shipment of tissue.
9. The neuropathological examination of the brain is completed and usually takes 6-12 months after the brain tissue is received at the ADNI-NPC to generate a final neuropathologic report. It is left to the ADNI Clinician's discretion to obtain the neuropathology autopsy reports and share the findings with the participant's family or other responsible party.

ADNI Neuropathology Core Brain Removal and Shipping Protocol

Thank you for helping with the donation of this brain. Your contribution will help us to find the causes and more effective treatment of neurodegenerative diseases.

1. Weigh the brain fresh with the dura removed. Record the weight and the time interval between death and removal of the brain and fixing/freezing of brain specimens.
2. Separate the two cerebral hemispheres and brainstem by a midline/sagittal cut. Separate the right brainstem and right cerebellum from the right cerebral hemisphere by a cut across the midbrain (third cranial nerve to superior colliculus). Place the **RIGHT** half brain (medial surface face down) on smooth aluminum foil flattened over a pre-cooled metal plate/tray (e.g. brass, aluminum), on dry ice, if available. If no dry ice is available, freeze hemisphere by placing on foil on a tray or plate in freezer (at below -20°C, -70°C is better). The right half brainstem and cerebellum should be frozen with the medial (cut) surface flat to the plate. Once frozen, remove aluminum foil and place: (1) the right half brain and (2) the right brainstem and cerebellum in labeled zip-lock plastic bags. Ship frozen tissue in container with dry ice.
3. Place the **LEFT** half-brain, brainstem and -cerebellum in 10% neutral buffered formalin **at room temperature** for at least two weeks prior to shipping to St. Louis. For shipping, wrap brain in tissues/cloth soaked in formalin to provide physical support in transit (**DO NOT SHIP FORMALIN FIXED TISSUE IN DRY ICE**). Place in sealed plastic bag. Place in rigid watertight container and in a rigid outer container for transport. Use separate containers for frozen and fixed material. **IT IS CRITICAL THAT YOU DO NOT TRANSPORT FROZEN AND FIXED BRAIN IN THE SAME CONTAINER. THIS WILL PRODUCE ARTIFACTS ON THE SLIDES USED FOR DIAGNOSTIC PURPOSES.** The ADNI-NPC will send to you two shipping boxes that are approved for this type of shipment, if you have not discussed this shipment with the ADNI-NPC or requested boxes, please contact Haley Bernhardt (information below).

If you have any queries regarding this protocol please contact:

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Appendix

Preparing Brief Expiration Summary for Deceased ADNI Participants with Postmortem Examination:

Purpose:

1. Capture any information about changes in health or cognition since the final in-person ADNI assessment.
2. Identify any safety concerns for personnel involved in conducting the post mortem examination, with specific notes about rapidly progressive dementia * and/or prion disease and other potentially transmissible diseases.

Information to be recorded:

1. ADNI ID#, date of birth, date of expiration, age of onset of symptomatic Alzheimer disease (if applicable).
2. Place of death and cause(s) of death (even if presumptive), dates of first and last ADNI in-person assessment, with clinical diagnosis and CDR score at each of those assessments.
3. State other relevant information (e.g., history of Alzheimer dementia in a first degree relative).
4. In the interval from last ADNI in-person assessment to death, describe cause of cognitive impairment/dementia (if present) using information gleaned from medical records/nursing home records and from a postmortem interview with the decedent's family and/or caregiver. Estimate an "expiration CDR" just prior to the terminal illness. Provide the expiration diagnosis (include relevant comorbidities) and predict the neuropathological diagnosis.

***Rapidly progressive dementia can be operationalized as a dementia course of 5 years' duration or less from symptomatic onset (encompassing MCI due to Alzheimer disease) to death, OR by a change in more than two global Clinical Dementia Rating stages in two years or less (e.g., from CDR 0.5 to CDR3 in two years). In all cases, fulfilling these criteria for rapidly progressive dementia and/or a clinical diagnosis of Creutzfeldt-Jakob disease or other prion disorder, appropriate precautions should be taken by the local autopsy service with tissue being sent to the National Prion Disease Pathology Surveillance Center (NPDPS; <http://case.edu/med/pathology/centers/npdpssc/>) and cleared prior to tissue being sent to the ADNI NPC. The ADNI NPC coordinator can facilitate this process. The ADNI NPC will pay for shipment of tissue to the NPDPS.**

Example Expiration Summary

ADNI ID#: XXX_S_XXXX

DOD: 03/31/2019

Time of Death: 17:25

Age of Onset of Symptomatic Alzheimer Disease: subjective memory complaints began in 2003; diagnosed with MCI on 6/13/2012, which remained stable.

Family History: Her mother died of severe Alzheimer type dementia which had an onset when she was 75 years old. The participant's sister died of severe Alzheimer type dementia and stroke. The sister's age of onset of dementia was 58 years old.

Place of Death: Mercy Hospital

Cause of Death: Acute respiratory failure, resulting from pneumonia.

Dates of first and last ADNI in-person assessment, with clinical diagnosis and CDR score at each of those assessments:

This individual started in ADNI as a control in 2006, however, I do not have access to visit information that took place prior to ADNI2. Her first ADNI2 visit was 2/2/2012; her global CDR score was 0.5 and she was diagnosed MCI (amnesic).

Her most recent in-person visit for ADNI3 was on 3/26/19. Her global CDR was 0.5 and her diagnosis was MCI.

In the interval from last ADNI in-person assessment to death, describe cause of cognitive impairment/dementia (if present) using information gleaned from medical records/nursing home records and from a postmortem interview with the decedent's family and/or caregiver. Estimate an "expiration CDR" just prior to the terminal illness. Provide the expiration diagnosis (include relevant comorbidities) and predict the neuropathological diagnosis.

Her most recent in-person ADNI3 assessment was only 5 days prior to her death, so all information from that visit (CDR 0.5, diagnosis of MCI) is accurate.

She seemed to be doing well at her ADNI3 visit on 3/26/19, and her death came as a shock to her family as well as site staff. She was found unresponsive in her home on 3/29/19 and was taken to Mercy Hospital where she was diagnosed with pneumonia. She refused all intervention (including antibiotics) and died on 3/31/19 at 17:25 hours.

Medications included atorvastatin (10 mg QD), amlodipine (5 mg QD), aspirin (81 mg QD), vitamin D3 (1000 IU QD), galantamine (24 mg QD), melatonin (3 mg QD), naproxen (200 mg PRN) and Tylenol (1000 mg PRN). She also received one dose of morphine before she died. Comorbidities included hypertension, hyperlipidemia, chronic low back pain, tendonitis in hip, and knee pain resulting from a fall in December of 2018. No concerns for rapidly progressive dementia or Creutzfeldt-Jakob disease (CJD) given the clinical course and rate of change of CDR scores.

Example Macroscopic Description

The unfixed, fresh brain weighed 1060 grams. The pituitary gland weighed 0.8 grams. The leptomeninges at the base of the brain were translucent. The cranial nerves appeared normal. Examination of the Circle of Willis revealed no significant atherosclerosis. The convexities showed severe atrophy of the frontal and anterior temporal lobes and moderate atrophy of the parietal lobes; the occipital lobes were relatively spared. The brain was sagittally bisected. After a cut through the right midbrain at the level of the superior colliculus, the right hemibrain was sliced (coronally/axially/parasagittally), photographed, and frozen between Teflon-coated aluminum plates cooled with liquid nitrogen vapor. The left hemibrain was fixed in formalin. Coronal slicing of the supratentorial components of the formalin-fixed left hemibrain confirmed the regional observations of cortical atrophy and also revealed moderate dilatation of the lateral ventricle with rounding of the angle and moderately increased space in the temporal horn. The hippocampus showed moderate atrophy. Axial sections of the brainstem showed moderate depigmentation of the locus coeruleus but were otherwise unremarkable, without significant depigmentation of the substantia nigra. Parasagittal sections of the cerebellum showed no pathologic features. No hemorrhages or infarcts were observed.

Sample Forms and Letters

****Please check with your site's IRB to determine if the following letters require IRB approval **prior** to sending them.****

****PLEASE UPDATE THESE ITEMS WITH YOUR SITE-SPECIFIC INFORMATION AND PUT ON SITE LETTERHEAD BEFORE SENDING TO PARTICIPANT OR OUT UPON HIS/HER BEHALF****

Acknowledgement of Autopsy Authorization Letter-Participant Copy

Date:

Name and Address

Re: Research participant's name

Dear:

Thank you for your continued support of the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3). We very much appreciate your cooperation regarding our brain donation program because it is an extremely important component of our research.

Please share your wishes about brain donation and the details with your family and/or persons who will be taking care of those arrangements. Enclosed are several copies of this letter as well as wallet-sized cards with instructions about how to contact us at the time of death for your/their convenience.

At the time of death our office should be called at **XXX-XXX-XXXX**. If the office is closed, a recorded message instructs the caller to ***(Please fill in your site-specific after hours autopsy procedures here)***.

The Alzheimer's Disease Neuroimaging Initiative2 (ADNI2) Coordinator will arrange for the autopsy and transportation of your body to ***(insert autopsy location)*** where the autopsy takes place. A complete report of the brain autopsy findings will be sent to your Power of Attorney, next of kin, or person you have designated.

Thank you again for participating in our project. If you have additional questions, please feel free to contact the autopsy coordinator at the ADNI3 office. Please notify us of any changes in your address, telephone number or other contact information.

Sincerely,

(Include signature for Site ADNI3 Director and/or Autopsy Coordinator with contact information)

Acknowledgement of Autopsy Authorization- Nursing Home Copy

Date:

Attn: Administration
(address)

RE: Participant Name

Dear Administrator:

One of your residents, **Subject Name**, is a participant in the research study program of the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3) at ***(insert site location)***. He/She has given consent for a brain autopsy at the time of death.

We greatly appreciate your assistance in the collection of this valuable human tissue to be utilized in advancing our knowledge about Alzheimer's disease. We have enclosed instructions for this. Please place these instructions in the resident's chart. We are also enclosing a sticker to be placed on the face sheet in order to alert the staff to the family's wishes.

At the time of death, we ask that you fax a copy of the following medical record to our office at ***(insert site fax number)***: most recent physician progress note, last two weeks of nursing notes, and the current medication record.

Thank you for your cooperation and interest. Should you have any questions concerning this protocol, please do not hesitate to contact us at ***(insert ADNI3 site coordinator contact number)***.

Sincerely,

(Insert ADNI3 coordinator signature)

(Place Participant's Name Here)

PROTOCOL FOR PREPARATION FOR BRAIN DONATION

At the time of death, the following steps should be taken after notifying the family members and personal physician of the deceased patient:

1. Contact the Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Coordinator's office during working hours (**XXX-XXX-XXXX**). If after 5:00 PM or on weekends, (***insert site specific after hours autopsy protocol here***)
2. The Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Coordinator will arrange for transportation of the body to (***insert autopsy location***) where autopsy will be performed.
3. **IMPORTANT:** If at all possible, the body should reach the morgue within six hours of death, sooner if possible.

Acknowledgement of Autopsy Authorization Letter- Funeral Home Copy

Date

Funeral home

(Address)

Ladies and Gentlemen:

(insert participant's name), a resident at ***(insert location)***, is a participant in the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3) at ***(insert site name/location)***. Consent for a brain autopsy at the time of his/her death has been granted by ***(insert person granting consent)***. Plans have been made to have the autopsy performed by ***(insert pathologist)*** at ***(insert location)***

(Insert participant's name) family has made the decision to use your funeral home when his/her mother's death occurs. Should you have any questions, do not hesitate to contact me at the ADNI3 Coordinator's office at ***(XXX-XXX-XXXX)***.

Thank you for your time and consideration of this matter.

Sincerely,

(Insert ADNI3 Coordinator's signature)

***Acknowledgment of Autopsy Authorization Letter - Personal Physician
Copy***

Date:

Physician Address

RE: Participant Name

Dear Dr.:

We have been informed by ***(insert participant's name)*** that he/she is under your medical care. ***(Insert participant's name)*** is a participant in Alzheimer's Disease Neuroimaging Initiative3 (ADNI3) and consent for a brain autopsy at the time of his/her death has been granted by ***(insert person granting consent)***. Plans have been made to have the autopsy performed by ***(insert pathologist)*** at ***(insert location)***.

We realize that your awareness of this information will aid in the success of this endeavor. Should you have any questions, please do not hesitate to call. Our number is ***(XXX-XXX-XXXX)***.

Sincerely,

(Insert ADNI3 Coordinator signature)



Wallet-sized cards, front and back, given to participant when consent signed:

<p>The undersigned has registered intent for BRAIN DONATION upon death, for purpose of research, with the Alzheimer's Disease Neuroimaging Initiative3 (ADNI3), <i>(Insert ADNI3 site location)</i></p> <p>Name _____ Date _____</p> <p>Signature _____</p>	<p>AT TIME OF DEATH: Contact the Alzheimer's Disease Neuroimaging Initiative3</p> <p>(XXX-XXX-XXXX): Monday-Friday, 8 a.m - 5 p.m. (XXX-XXX-XXXX): Weekends or evenings</p> <p>As soon as practicable after death, the body of the deceased should be moved to a place of cold storage.</p>
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