1. General Instructions

This checklist provides a step-by-step guide to assist all investigators applying to the NNTC. The intent is to help ensure that each investigator submits a complete application with all relevant detail for their first submission. The NNTC requires that **all investigators submitting an application MUST submit a completed, signed copy of this checklist as part of their application to the NNTC**.

1. Abbreviations

|  |  |
| --- | --- |
| **Abbreviation** | **Description** |
| ADL | Activities of Daily Living |
| ANI | Asymptomatic Neurocognitive Impairment |
| ARV | Antiretroviral |
| BDI | Beck Depression Inventory |
| CBC | Complete Blood Count |
| CHARTER | CNS HIV Antiretroviral Therapy Effects Research Study |
| CIDI | Composite International Diagnostic Interview |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| CTRL | Control |
| CV | Curriculum Vitae |
| DCC | Data Coordinating Center |
| DNA | Deoxyribonucleic acid |
| FFPE | Formalin-fixed paraffin-embedded tissue sections |
| HAD | PWH-Associated Dementia |
| HCV | Hepatitis C virus |
| HIV | Human Immunodeficiency Virus |
| MCMD | Minor Cognitive Motor Disorder |
| MND | Mild Neurocognitive Disorder |
| MRI | Magnetic Resonance Imaging |
| NIH | National Institutes of Health |
| NNTC | National NeuroHIV Tissue Consortium |
| NP | Neuropsychological |
| NPI-O | Neurocognitive Impairment Other: Probable neuropsychological impairment or dementia due to other cause |
| PAOFI | Patients Assessment of Own Functioning Inventory |
| PBMC | Peripheral Blood Mononuclear Cells |
| PI | Principal Investigator |
| PML | Progressive Multifocal Leukoencephalopathy |
| PRISM | Psychiatric Research Interview for Substance and Mental Disorders |
| PWH | People with HIV |
| PWoH | People without HIV |
| RNA | Ribonucleic Acid |

1. Definitions

|  |  |
| --- | --- |
| **Term** | **Description** |
| DCC | The Data Coordinating Center (DCC) is responsible for management of the review and approval process for applications. Should you have any questions regarding your request, please contact [nntc@emmes.com](mailto:nntc@emmes.com). |
| Specimen | A quantity of tissue, blood, or other biologically derived material. |
| Donor | An individual person who has donated tissue to the NNTC. |

1. Request Processing Checklist

| **Application Component** | | **Done?** |
| --- | --- | --- |
| **Defining Requested Resources** | | |
| Define cohort resource(s) for your application | * **NNTC Resources**: Tissue and fluid specimens from PWH and PWoH * **CHARTER Resources**: Pre-mortem fluid specimens from PWH only   + **Note:** For CHARTER, only **pre-mortem fluid** **specimens** from PWH are available * **Either**: Requesting from either NNTC or CHARTER |  |
| Define application type | * **Specimen Application:** For specimen requests * **Data Application:** For data-only requests   + *\*Data can be provided to characterize specimens requested as part of a Specimen Application – a separate Data Application is not needed.* * **Analysis Application:** Requests for analysis(es), to be performed by the NNTC DCC. |  |
| **Investigator Information** | | |
| Provide basic investigator contact and related information | * For this you will need to provide:   + First Name:   + Last Name:   + Title:   + Institution:   + Department:   + Phone:   + Fax:   + Email:   + Biosketch or CV   + Is there a supervising PI on this project?     - If Yes, provide (1) the name of supervising PI, and (2) a copy of the supervising PI biosketch or CV. |  |
| **Shipment information for specimens and data** | | |
| Provide the requested shipping information | * Indicate whether you are the person who will receive specimen shipment and, if not, who will receive the specimen shipment. You will need to provide an accurate shipping address and contact information for shipment recipient, \*\*\*Please note that shipping addresses are frequently different than mailing addresses. We will not ship specimens unless you verify that shipping information is correct. * You will need to provide the following information:   + Contact phone number   + Street Address (city, state, zip, country)   + Courier information     - Courier name     - Courier account number |  |
| **Project Summary** | | |
| Project Title | * Provide the title of your proposed project.   + ***Note****: This is the project title that will be reflected on any communication from NNTC (e.g., Letter of Support). Ensure that the project title is entered exactly as you would like it to appear in any such documentation.* |  |
| Is your proposed research primarily CNS-focused? | * Indicate whether your proposed research is primarily CNS-focused. |  |
| Project Outline | * You will need to complete the NNTC project outline template. [Click here](https://nntc.org/system/files/yyyymmdd_NNTC_Concept_Outline.docx) to download a blank copy. * As you will see in the template, the following elements are required for all concept outlines:   + **Background Research:** *Briefly describe prior research that highlights the importance of the proposed research topic.*   + **Major Goals of the Research:** *Describe the major goals of the research. List specific aims and hypotheses and how these relate to the research questions.*   + **Experimental Methodology**: *For all specimen types/preparations requested in your application, outline your experimental design and methods for the research. Include sufficient information and detail to enable reviewers to evaluate the specific parameters associated with your request (e.g., brain region, specific techniques to be used, specimen weight/size, number of sections, section thickness).* *This portion of your concept outline should not exceed one page.*   + **Justification:** *Justify the specific specimen types and amounts you are requesting. If this is a data only request, justify the types of data you are requesting.* * Files must be less than **10 MB** * Allowed file types: **pdf doc docx**. |  |
| **Resource Utilization**   * This section is required for all investigators who have either (a) **current funding** to support the work proposed in their NNTC application, or (b) are actively seeking funding via a specific funding mechanism to support their work. * Investigators without current funding may leave this section blank. | | |
| Total anticipated duration for this project: | * Enter the total number of months your project is expected to take, overall. |  |
| Funding for this project is: | * Indicate whether funding is:   + Currently being sought,   + Pending award decision, or   + Currently available. |  |
| Letter of Support Requested | * *This is applicable* ***only*** *if you are actively seeking funding and would like to request a provisional Letter of Support from the NNTC to support the funding application.* * Indicate if a provisional letter of support is required from the NNTC.   + If you require a provisional letter of support from the NNTC, it is **imperative** for you to provide any **submission deadline** you have for your funding application. |  |
| Funding Support | * If you have a grant/contract supporting your proposed research, you will need to provide the following information:   + Funding Source     - If you do not find your funding source in the dropdown list, please specify in the “If Other, Specify” field.   + Grant/Contract Number   + Funding start date   + Funding end date * *Indicate if funding is supported by NIH or other (e.g., other government sources besides NIH). If funding is supported by NIH, indicate the specific grant or contract number.* |  |
| **Participant Group Selection**   * For each of the study groups in your application, you must specify all of the following. * It is critical that your group definitions be mutually exclusive. | | |
| Number of cases | * Specify the number of individual cases (donors) that are required for the study group. |  |
| HIV status | * Choose the appropriate HIV status for the study group:   + PWH   + PWoH   + Seroconverted |  |
| Include Pathology | * Choose any pathology(ies) that apply to the study group as an **inclusion** criterion. All [pathologies available for selection](#pathologies) are available for reference below in this document. * *This only pertains to requests for specimens from decedents.* |  |
| Exclude Pathology | * Choose any pathology(ies) that apply to the study group as an **exclusion** criterion. All [pathologies available for selection](#pathologies) are available for reference below in this document. * *This only pertains to requests for specimens from decedents.* |  |
| Neurocognitive Strata | * Select the neurocognitive strata appropriate for cases that should be included in the study group. [See below](#neurocogdx) for further guidance for the diagnoses listed below. Select from the following options:   + **N/A**: *Any of the below classifications would be appropriate for the study group you are defining.*   + **Normal**: *Participant had no significant cognitive complaints, no evidence of impairment on neuropsychological testing, and/or no loss of functional capacity. Normal should not be considered analogous to ANI/Subsyndromic.*   + **ANI/Subsyndromic**: *Participant had no significant cognitive complaints, but neuropsychological testing revealed evidence of mild NP abnormalities that do not impair activities associated with daily living or manifest themselves with clinical symptoms. ANI/Subsyndromic should not be considered analogous to Normal.*   + **MND/MCMD**: *Participant or others report symptoms of cognitive decline; evidence of mild NP impairment; decline in functional capacity that does not reach severity required to diagnose dementia. Subject may or may not have had a diagnostic evaluation to rule out other causes of cognitive impairment.*   + **HAD**: *Participant or others report symptoms of cognitive decline; evidence of moderate or severe NP impairment on neuropsychological testing; decline in functional capacity that reaches the level of a dementia; subject may or may not have had a diagnostic evaluation to rule out other causes of neuropsychological impairment.*   + **NPI-O**: *Participant has impairment of some degree but there is history, physical finding, or laboratory evidence of one or more opportunistic infections (such as Toxoplasmosis encephalitis, Cryptococcal meningitis, etc.), tumors (such as Primary CNS Lymphoma), other acquired neurological diseases (such as stroke), metabolic disease (such as hepatic encephalopathy) or any other condition that would cause the impairment. A specific diagnosis is given for common AIDS-related CNS diseases.* |  |
| Age | * Define any age range requirements for the study group * *Note: If you require that cases come from a range of ages, you can specify that here (i.e., “18 – 45”).* |  |
| Gender | * If cases to be included should be of a particular biological sex or gender, you must indicate the appropriate sex or gender here. Select from the following:   + Male   + Female |  |
| Inclusion Criteria | * Define any other inclusion criteria |  |
| Exclusion Criteria | * Define any other exclusion criteria |  |
| Comments | * Use this field to specify any other clarifying or helpful information, not otherwise covered in one of the other fields on this part of your application. |  |
| Add/Remove a Row | * Each group defined in your application must have its own dedicated row in this table. Add rows as appropriate, using the “Add a Row” button.   + *Note: If you need to modify your request to remove an entire row, there is a “Remove a Row” button as well. This will delete the entire row for the last group in the grid.* |  |
| **Sample Selection**  *This section is only applicable for specimen requests. If you are submitting a data request, you may proceed to the* [*Data Request Elements*](#datarequestelements) *portion of this checklist.*  *Please note that NNTC “standard” specimen types, preparations are defined throughout this portion of the checklist. Please be reminded that selecting options beyond NNTC standards may impact your Request Complexity Level. Non-standard selections are likely to lead to longer review and fulfillment timeframes.* | | |
| Samples requested | * Select the type(s) of specimens you are requesting:   + CNS   + Systemic   + Fluids * *If you would like to request more than one of the above specimen types, you can select multiple options by clicking on your first choice, then hold CTRL while you select any additional types.* |  |
| **For CNS and/or Systemic Specimens, you will need to provide the following details**  *For each CNS, Systemic Specimen requested, you will complete all of the following.* | | |
| CNS Type | * Select a specific specimen type you are requesting   + For **CNS specimens**, see the [Appendix C](#cnsspecimens) for a listing of the options you can select.   + For **Systemic Specimens**, see the [Appendix D](#systemicspecimens) for a listing of the options you can select.   + If your specimen type of interest is not among the available options, use the “Other” selection. |  |
| If other, specify | * If you select “Other” as your specimen type, you will need to specify your own detail in this free-text field. |  |
| Preparation | * Specify the specimen preparation you require for your specimen type. * Options for **CNS tissues** include:   + Snap frozen block -70oC (not treated with cryopreservatives) (standard)   + Fixed in 10% buffered formalin (standard)   + Formalin-fixed paraffin-embedded tissue sections (FFPE) (standard)   + Fresh (not standard for NNTC, will require special arrangement) * Options for **Systemic tissues** include:   + Snap frozen block -70oC (not treated with cryopreservatives) (standard)   + Fixed in 10% buffered formalin (standard)   + Paraffin sections (standard) |  |
| Weight/dimensions | * *Weight/Dimensions and # of Blocks are to be completed only for Frozen preparations.* * Specify the weight or dimensions for any tissue blocks you are requesting. * *Standard block size is ~500 mg (1 cm x 1 cm x 0.5 cm). If you are requesting a different thickness, please ensure that you include justification for non-standard thickness in your concept outline.* |  |
| Number of blocks per case | * *Weight/Dimensions and # of Blocks are to be completed only for Frozen preparations.* * Specify the number of blocks per individual you are requesting. |  |
| Thickness | * ***Level 1 requests cannot include a request for microtomy.*** * *Thickness and # of Sections are to be completed only for Paraffin preparations.* * If you are requesting sections, specify the desired thickness here. * *Standard section thickness is 4-6µm. If you are requesting a different thickness, please ensure that you include justification for non-standard thickness in your concept outline.* |  |
| Number of sections per case | * ***Level 1 requests cannot include a request for microtomy.*** * *Thickness and # of Sections are to be completed only for Paraffin preparations.* * Specify the number of sections per individual you are requesting from the NNTC. * *Standard number of sections per case is < 6. If you are requesting a different number of sections per case, please ensure that you include justification for non-standard amounts in your concept outline.* |  |
| Specimens critical for protocol | * Indicate whether these specimens are critical for the completion of your proposed research. |  |
| Add/Remove a Row | * Each specific specimen type being requested must have its own dedicated row in this table. Add rows as appropriate, using the “Add a Row” button.   + *Note: If you need to modify your request to remove an entire row, there is a “Remove a Row” button as well. This will delete the entire last row in the grid.* |  |
| **For Fluid Specimens, you will need to provide the following details** | | |
| Fluid sample | * *Please note that selection of non-standard preparations may impact your Request Complexity Level.* * Select a specific fluid specimen type you are requesting. Available options are as follows:   + Any blood (not standard)   + CSF (standard)   + PBMC (standard – *non-cryopreserved*)   + Plasma (standard)   + Serum (standard)   + Urine (standard)   + Cardiac aspirate (not standard) |  |
| Aliquots | * Enter the number of aliquots per case that you are requesting for any fluid specimens that are part of your application. |  |
| Non-standard volume | * Indicate whether you require a non-standard volume for your aliquots. * *The standard NNTC aliquot volume is 0.5 mL for plasma, CSF, serum, and urine and 5x106 for PBMCs (non-viable). If a non-standard aliquot volume is required, you may indicate this in the table; however, please include justification in your Concept Outline section.* * *For CHARTER, the standard aliquot volume is 0.5 mL for CSF and CSF pellets, 1 mL for plasma, 1.8 mL for PBMCs, 2.5 mL for PaxRNA, 4 mL for whole blood, 8 mL for PaxDNA, and 100 µL at 10ng/µL for DNA. For any non-standard CHARTER volumes requested, please include justification in your Concept Outline section.* |  |
| Volume required | * *This is only required if you indicated that you need a non-standard aliquot volume.* * Enter the volume per aliquot being requested. Be sure that sufficient justification is included in your Concept Outline to justify the specific volume being requested. |  |
| Specimens critical for protocol | * Indicate whether these specimens are critical for the completion of your proposed research. |  |
| Add/Remove a Row | * Each specific specimen type being requested must have its own dedicated row in this table. Add rows as appropriate, using the “Add a Row” button.   + *Note: If you need to modify your request to remove an entire row, there is a “Remove a Row” button as well. This will delete the entire last row in the grid.* |  |
| **General info for any/all specimens included in your application** | | |
| Specimen Data | * If you are requesting data in association with your specimens, indicate what data points you would like to receive. For each, you will need to provide the following:   + Data Fields: Select the data field(s) you are requesting from the dropdown. Each selection requires its own row. Options available for selection are as follows:     - Plasma HIV RNA     - CSF HIV RNA     - Other       * If you select “Other”, please use the Rationale field to specify what is being requested. |  |
| Are post-mortem fluid specimens acceptable? | * Indicate whether you would be able to conduct your research with post-mortem fluid specimens. |  |
| Comments on requested specimens: | * Use this free-text field to specify any additional details/notes not otherwise covered in the other fields pertaining to specimen parameters. * *Note: If you have a desired postmortem interval for specimens requested, please include the appropriate details here.* |  |
| **User Agreements** | | |
| Reading, Understanding, and signing the User Agreement | * Download the User Agreements for Specimen Applications [***here***](https://nntc.org/system/files/yyyymmdd_NNTC_Specimen_User_Agreements.docx). Reviewing the agreements in their entirety and complete all necessary entries/signatures. * Once fully signed, upload the completed agreement to your application. |  |
| **Data Request Elements**  Select the data required for your study and provide rationale for requiring those data for your analysis. Hold CTRL to select multiple types of data for each domain.  See [Appendix E](#datadomains) for a listing of the data domains available for selection by NNTC requestors.  For additional detail on the types of data available, please refer to the [NNTC Annotated Data Dictionary](https://web.emmes.com/study/hbb/DataDict/NNTC_annotated_DD.xlsx) . This data dictionary is available to download and review to help you select specific data points required for analysis.  **If you are requesting resources from both NNTC and CHARTER, and you made data selections on the previous page, you do not need to re-select those same data here (i.e. data collected in both NNTC and CHARTER). Only CHARTER-specific data (i.e. collected in CHARTER but not in NNTC) need to be selected on this page and rationalized.** | | |
| Data Field(s) | * Specify all fields you are requesting from each data domain. |  |
| Rationale | * Include rationale for all data fields being requested |  |
| Data format required | * Specify whether you would like to receive data in either Excel, or CSV format. |  |
| **User Agreements** | | |
| Data User Agreement Upload | * Download the Data User Agreements [here](https://nntc.org/system/files/yyyymmdd_NNTC_Data_User_Agreements.docx). Reviewing the agreements in their entirety and complete all necessary entries/signatures. * It is critical to be sure you have signed every page before uploading. |  |

1. Pathologies (Group Selection)
   * Any/All
   * Normal
   * Aseptic leptomeningitis
   * HIV encephalitis
   * CMV encephalitis
   * Microglial nodule encephalitis
   * Toxoplasmosis, active
   * Toxoplasmosis, healed
   * Cryptococcus
   * PML
   * Lymphoma
   * Bacterial leptomeningitis
   * Bacterial parenchymal infection
   * Tuberculosis
   * Other infections
   * Anoxic-ischemic encephalopathy (focal or global)
   * Alzheimer type 2 astrocytosis
   * Focal (territorial) infarct
   * Hemorrhage, dura or leptomeninges
   * Hemorrhage, parenchymal
   * Other, non-infectious pathology
   * Minimal, non-diagnostic abnormalities
   * Atherosclerosis of brain
   * Severe Atherosclerosis
   * Chronic hypertension
   * CNS Neoplasm other than lymphoreticular
   * Contusion
   * Leukoencephalopathy
   * Neurofibrillary pathology
   * Optic nerve atrophy/degeneration
   * Other infections
   * Senile plaque
   * Synucleinopathy/Lewy body
   * Thrombus/Thromboembolus
   * Vascular siderocalcinosis
   * Spinal Cord: Normal
   * Spinal Cord: HIV myelitis
   * Spinal Cord: CMV myelitis (includes myeloradiculopathy)
   * Spinal Cord: Vacuolar myelopathy
   * Spinal Cord: Microglial nodule myelitis, not otherwise specified
   * Spinal Cord: Toxoplasmosis, active
   * Spinal Cord: Toxoplasmosis, healed
   * Spinal Cord: Cryptococcus
   * Spinal Cord: Aseptic leptomeningitis
   * Spinal Cord: Lymphoma
   * Spinal Cord: Bacterial leptomeningitis
   * Spinal Cord: Bacterial parenchymal infection
   * Spinal Cord: Tuberculosis
   * Spinal Cord: Other infections
   * Spinal Cord: Anoxic-ischemic damage
   * Spinal Cord: Hemorrhage, dura or leptomeninges
   * Spinal Cord: Hemorrhage, parenchymal
   * Spinal Cord: Neuropathy
   * Spinal Cord: Other, non-infectious pathology
   * Spinal Cord: Minimal, non-diagnostic abnormalities
   * Spinal Cord: Descending fiber tract degeneration
   * Spinal Cord: Gracile tract atrophy (ascending tract degeneration)
   * Spinal Cord: Motor neuron disease
   * Spinal Cord: Myelitis

1. Neurocognitive Diagnoses (Group Selection)

| **Neurocognitive Diagnoses** | |
| --- | --- |
| **Diagnosis** | **Description** |
| Neurocognitively Normal | Participant had no significant cognitive complaints, no evidence of impairment on neuropsychological testing, and/or no loss of functional capacity. |
| Asymptomatic Neurocognitive Impairment (ANI) | Participant had no significant cognitive complaints, but neuropsychological testing revealed evidence of mild NP abnormalities that do not impair activities associated with daily living or manifest themselves with clinical symptoms. |
| Mild Neurocognitive Disorder (MND) | Participant or others report symptoms of cognitive decline; evidence of mild NP impairment; decline in functional capacity that does not reach severity required to diagnose dementia.  Subject may or may not have had a diagnostic evaluation to rule out other causes of cognitive impairment. |
| HIV-Associated Dementia (HAD) | Participant or others report symptoms of cognitive decline; evidence of moderate or severe NP impairment on neuropsychological testing; decline in functional capacity that reaches the level of a dementia; subject may or may not have had a diagnostic evaluation to rule out other causes of neuropsychological impairment. |
| Neurocognitive Impairment Other: Probable neuropsychological impairment or dementia due to other cause (NPI-O) | Participant has impairment of some degree but there is history, physical finding, or laboratory evidence of one or more opportunistic infections (such as Toxoplasmosis encephalitis, Cryptococcal meningitis, etc.), tumors (such as Primary CNS Lymphoma), other acquired neurological diseases (such as stroke), metabolic disease (such as hepatic encephalopathy) or any other condition that would cause the impairment.  A specific diagnosis is given for common HIV-related CNS diseases. |

1. CNS Specimen Types
   * Cerebellum
   * Cingulum
   * Corpus callosum
   * Frontal lobe
   * Medulla
   * Meninges
   * Midbrain
   * Occipital lobe
   * Other brain tissue
   * Parietal lobe
   * Pons
   * Spinal cord
   * Temporal lobe
   * Thalamus

1. Systemic Specimen Types
   * Adipose
   * Adrenal gland
   * Bone marrow
   * Colon
   * Esophagus
   * Ganglion
   * Gut
   * Heart
   * Kidney
   * Lesion
   * Liver
   * Lung
   * Lymph node
   * Muscle
   * Other systemic tissue
   * Ovaries
   * Pancreas
   * Peripheral nerve
   * Skin
   * Spleen
   * Testes
   * Thyroid gland
   * Uterus
2. Data Domains available for selection

| **For NNTC** | **For CHARTER** |
| --- | --- |
| * Neuromedical data:   + Neurological Diagnoses   + ARV Medication History   + Cerebrovascular Disease   + Anthropometric Data   + Comorbidities   + Fried Frailty   + HIV Motor Scale * Neuropsychological data:   + Neuropsych Testing   + Medication Management Task   + PAOFI   + ADL   + Pittsburgh Sleep Quality * Psychiatric data:   + PRISM/CIDI   + BDI * Laboratory data:   + CBC   + Chemistry   + T-Cell   + Plasma Viral Load   + CSF Viral Load   + Other CSF   + Concomitant Medications   + Urine   + Other * Participant Characterization data:   + Demographics   + Pathology | * Neuromedical data:   + Neurocognitive Diagnoses   + Neurological Diagnoses/History   + ARV Medication History   + Abbreviated Physical Examination   + Medical History/Comorbidities   + Anthropometric Data   + Cranial Nerve Examination   + Other Diagnoses   + Gait Response   + HIV Disease Progression   + Health Outcomes   + Lipoatrophy Questionnaire   + Concomitant Medication Summary   + Neuropsychological Impairment   + Reflexes/Sensation   + Vital Signs   + Self-Reported Substance Use   + Neuropathy   + Psychotropic Drug Use * Neuropsychological data:   + Neuropsych Testing   + Dementia   + Employment Functioning   + VALPAR   + Medication Management Task   + BDI   + ADL   + PAOFI   + CIDI * Laboratory data:   + Biomarker   + CBC   + Chemistry   + Lymphocyte   + Plasma Viral Load   + CSF Viral Load   + Other CSF   + HCV Testing   + Urine   + Other Lab * Neuroimaging data:   + MRI   + Participant Characterization data:   + Demographics |

**All requestors must sign and date this checklist document below. The *signed version* MUST be included as part of your NNTC application:**

**Requestor Name:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Requestor Signature:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Signature Date:** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (ddMMMyyyy)