Neurodegenerative disease may present with cognitive impairments that leave the participant with diminished capacity for consent or inability to consent. As these impairments are part of the diseases being studied, it is necessary and reasonable to include these subjects in our research program. Additionally, it is important to include as diverse a population as possible in the study and not exclude eligible participants based on language. For this reason, it is necessary to open the study to non-English speakers.

Participants are required to have a Study Partner/Caregiver present for the study visits, and surrogate consent will be sought if any participant is deemed of diminished capacity to consent, as described in the consent section of this application.

At the initial consent visit, the investigator will assess the participant's capacity to consent, and a worksheet (attached as “Capacity Assessment Checklist”) that is currently in use at the UCSF Memory & Aging Center to access the decision making capacity of the participant will be completed.

Subjects’ capacity to consent will be evaluated using the standards and procedures adapted from the standardized and validated instrument that can be tailored to the specific study protocol, such as the MacArthur Competence Assessment Tool – Clinical Research (MacCAT-CR) developed by Appelbaum and Grisso (1995) as described below and the results will be recorded on a Capacity Assessment Record (CAR). Even when there is an indication of diminished capacity, the presumption of capacity remains. There are four different standards that we use to assess capacity. They are listed below in rough order of ascendancy. It is the policy of the UCSF Memory and Aging Center to accept a subject as competent to consent to research only when the person is judged capable with regard to all 4 standards.

Standard 1. Did the research candidate "make a choice"? "This standard focuses on the presence or absence of a decision and not on the quality of the decision" This is simply a question as to whether the subject can evidence a choice. If the subject offers a consistent choice about participating in the study this standard is met. If the subject’s choice is ambiguous, either because it is inconsistent or unclearly demonstrated, then the standard is failed.

Standard 2. Did the research candidate show "understanding"? "This standard requires memory for words, phrases, ideas, and sequences of information, and also comprehension of the fundamental meaning of information about treatment." A subject need not demonstrate complete or comprehensive understanding of the study in order to meet this standard. However, verbatim recitation of fact without evidence of comprehension is not sufficient either. Consider whether or not the potential subject grasps sufficient information to form the basis for a reasoned decision. If the subject comprehends and remembers (even with assistance) a) that participation is voluntary, b) the major procedures c) main risks and d) benefits, then this standard is met. Failure on any element (a-d) means this standard is failed.

Standard 3. Did the research candidate show "reasoning/rational reasons"? "This standard tests the capacity to use logical processes to compare the benefits and risks of various treatment options and weigh this information to reach a decision." The core of this standard is the ability to logically compare risks and benefits in order to reach a rational decision regarding participation. To meet this standard the subject needs to demonstrate the ability to consider both risk and benefit in relation to each other and use the information in a logical manner to come to a decision.

Standard 4. Did the research candidate show an "appreciation" of the personal risks/benefits of the study? "This standard emphasizes the patients' awareness of the consequences of a treatment decision: its emotional impact, rational requirements and future consequences." Appreciation seems to imply something more than an intellectual understanding, and incorporates an affective judgment of the impact of study participation in the context of the particular individual in his or her particular situation. Meeting standard 3 would seem to generally suffice for meeting this standard as long as the subject has a realistic understanding of his or her circumstances.

Assent: If the investigator determines that the subject lacks decision-making capacity, the investigator shall inform the subject of the investigator's intent to seek surrogate consent and shall document this discussion in the research file/chart. If the subject expresses resistance or dissent to participation or to the use of surrogate consent, the subject shall be excluded from the research study. The MAC follows the guidelines for surrogate consent established by the University of California-Office of the President. Subjects who are not capable of consent to research still must assent to research in order to take part. Assent implies willingness or, minimally, lack of objection to taking part. It does not imply understanding. An interpretable statement from the subject regarding assent must be taken as valid regardless of the subject's level of confusion or dementia. Thus, a statement such as "whatever my daughter says is OK with me" is fine. The demonstration of assent need not be verbal. Passive lack of objection is acceptable in an alert patient. Indications of distress such as crying or attempts to escape the situation should be taken as refusals to assent to the study.

If it is determined that the participant lacks decision-making capacity, the participant will be informed of the investigator's intent to seek surrogate consent, and this will be documented in the participant's research file. Should the participant express resistance or dissent to participation or use of surrogate consent, s/he will be excluded from the study. Surrogate consent will be obtained from potential surrogates as outlined in the "Investigators' Responsibilities Regarding Surrogate Decision-makers" section of the UCOP Guidance on Surrogate Consent for Research guidelines (1-Jan-2003). All participants who agree to participate in the study (including those deemed incapable of giving consent) will be given an opportunity to sign the consent form if they wish. Surrogates will be required to fill out the "Self-Certification of Surrogate Decision Making" form (attached). All participants will be required to be accompanied by a Study Partner who will answer questions about the participant's cognitive and functional capacity, and in the cases of participants with dementia, will be responsible for transporting and accompanying the participant to study visits. The potential Study Partner will be informed about these requirements. If the Study Partner agrees to perform these duties, then s/he will be asked to sign a section of the Informed Consent Form reserved for the Study Partner. If the Caregiver or Study Partner is not willing to cooperate with the Study Partner requirements, then the participant will be excluded from the study.

For non-English-speaking participants, they will be consented in their language with approved translated versions of the English consent and will follow the process outlined above. If a translated version of the consent is unavailable in their primary language, a qualified interpreter will orally present the Informed Consent Form information and facilitate the consent discussion. By answering and asking questions, the study team will determine whether the participant comprehends the consent information to ensure the informed consent is valid. If it is determined that the participant lacks decision-making capacity, then the surrogate consent procedure described above will be conducted using the interpreter. If it is determined that the participant has decision-making capacity, but does not comprehend the

information presented, then the participant will be excluded from the study. The interpreter will sign the Informed Consent Form on the designated "Person Obtaining Consent" line. The study team will write a statement on the "Experimental Subject's Bill of Rights" that the elements of consent from the Informed Consent Form were presented orally. The participant or legal surrogate, as well as the interpreter, will sign a Bill of Rights written in a language in which the participant is fluent after the interpreter has explained it.