**I. Explanation of Clinical Programs**

**A. Memory and Aging Project (MAP): clinical research office**

1. Site of annual clinical and psychometric assessments
2. Serves longitudinal studies of aging and dementia
   a. Alzheimer Disease Research Center (ADRC; P50AG05681)
   b. Healthy Aging and Senile Dementia (HASD; P01AG03991)
   c. Alzheimer Disease Cooperative Study (ADCS; U01AG10483)
3. Does not provide fee-for-service activities (e.g., diagnosis or treatment)

**B. Clinical practice**

1. Memory Diagnostic Center (MDC) is a fee-for-service faculty practice for physician-referred patients
2. Some “data” collected; supports funded projects (RO1 MH 60833) and - industry-sponsored clinical drug trials

**II. MAP Subject Sample: volunteer convenience sample**

**A. Recruitment process**

1. Participant/family initiates contact—some referrals from physicians but 80% of participants are recruited from the greater Sr. Louis area through media appeals and word of mouth.
2. MAP Telephone Inquiry and Screener—From 7/30/99-9/26/02, there were 1370 inquiries to MAP about participation. After speaking to the recruitment coordinator, 665 declined further involvement (generally because they sought dementia care). The remaining 705 were screened for eligibility.
3. Eligibility criteria.
   a. Age (≥50y, unless a member of a kindred with inherited dementia.
   b. Absence of exclusionary factors. Of the 705, 174 (25%) were ineligible. Some exclusionary factors are:
      1) Dementia severity greater than “mild” (MAP recruits ONLY subjects who are CDR 0, 0.5, or 1).
      2) Medical conditions that confound evaluation/follow-up (e.g., dialysis; insulin-dependent diabetes). We employ a 5-year Rule: potentially dementing disorders (e.g., hypothyroidism) are permitted when stable (e.g., on replacement) for at least 5 years before enrollment or dementia onset.
   c. Availability of collateral source-- The absence of a collateral source was reported for 1% (9) of the ineligible inquirers.
4. Current recruitment pool totals about 400 individuals.
5. MAP Satellite (MAPS) - African-American Outreach refers eligible cases (identified by health care workers) to MAP

**B. Current recruitment goals (annual)**
1. ADRC: 15 controls, 15 subjects with dementia of Alzheimer type (DAT)
2. HASD: 25 subjects age 65-84 (5 controls; 20 DAT)
5. Additional case material as appropriate (e.g. familial dementia; atypical dementia)

C. MAP Sample Characteristics
1. Demographics
   a. 58% women
   b. 85% white, 13% African American
   c. Mean age for controls is 77.6 y and for DAT subjects is 78.5 y

2. Since the original participant was enrolled in 1979, there have been 2864 individual subjects evaluated at MAP and a total of 9703 assessments (3.4 assessments per subject). There have been 1177 deaths and 665 autopsies (56%).

D. As of 8/1/04, all newly enrolled participants agree in principle (and are eligible) to complete all MAP procedures: clinical assessment psychometrics, blood for genetic analysis, MRI, and lumbar puncture for CSF.

III. Dementia Diagnoses
A. Alzheimer Disease and Dementia of the Alzheimer Type (DAT)
   2. DAT: the disease when diagnosed by clinical criteria.

B. Dementia Categories. All participants currently are classified by clinical means into one of three categories:
   1. Dementia is defined as the sustained loss of multiple intellectual abilities in an alert patient. We use standard DSM-IV criteria for dementia diagnosis: “the development of multiple cognitive deficits that may include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. [These disturbances are sufficiently severe] to cause significant impairment in social or occupational functioning and represent a decline from a previous level of functions.”
   2. Uncertain dementia is diagnosed when the cognitive impairment is so questionable that it is not possible to know whether it represents true impairment, or there is another condition (e.g., depression) that may be responsible. The clinician is not confident that a dementing process is present.
   3. No dementia is defined as the absence of cognitive impairment.

C. Clinical Diagnostic Criteria.
   1. Diagnostic criteria prior to 2002. The original criteria were comparable to but more stringent than those published later for “probable AD” and required the presence of the sustained deterioration of memory in an alert subject, plus impaired cognitive ability in at least 3 of these 5 categories: 1) orientation, 2) judgment and problem solving, 3) community affairs, 4) home and hobbies, and 5) personal care. We also required the gradual onset and progression of cognitive impairment for at least 6 months.
   2. Modified (2002) clinical diagnostic criteria for DAT. We now require impairment in only one domain in addition to memory for a diagnosis of DAT. Our recent
studies have shown that even individuals with impairment in fewer than 3 additional categories beyond memory, when judged by our research clinicians to be demented, progress predictably in dementia severity and have neuropathologic evidence of dementing illness, (almost always AD). We also have relaxed our exclusionary criteria to permit comorbid disorders, including depression and stroke, that are judged clinically not to be primarily responsible for dementia. We continue to exclude severe disorders (e.g., active major affective disorder; insulin-requiring diabetes) that not only could confound cognitive assessment but also interfere with participation in our longitudinal studies.

3. **Controls** do not have cognitive impairment but otherwise are similar to the demented subjects.

4. Our criteria for DAT and nondemented aging have been validated: of 207 subjects age 43-106 considered to have DAT by our clinical criteria, AD was the primary neuropathological diagnosis in 193 (93%), and of 15 subjects considered to be nondemented at death, AD was absent in 13 (87%). We also have clinicopathological data on 6 cases identified as uncertain dementia at entry: 5 had neuropathologic AD (one with associated cortical Lewy bodies) and one was a control brain.

5. **NonDAT Disorders.** We employ standardized criteria for NonDAT disorders to screen individuals with vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and other nonDAT disorders. If such disorders are identified, we refer subjects to ADRC studies for which they may be appropriate. All diagnostic criteria and all assessment procedures are standardized in the *Manual of Operations* for the Memory and Aging Project or MAP, our clinical research office.

D. **Depression**—To allow the opportunity to evaluate whether depression influences onset or course of dementia, since 1996 depressive features or frank depression are not considered to be exclusionary disorders unless urgent medical attention (e.g., major affective disorder) is needed.

E. **Contribution of other disorders to dementia.**

1. Other disorders (e.g., depression; stroke) are classified on clinical grounds in one of two categories:
   a. Believed not to contribute importantly to DAT
   b. Believed to contribute importantly to DAT

2. Classification is determined by the clinician at each time of assessment and is based on clinical evidence that the other disorder did or did not affect the mode of onset or the course of dementia. Such evidence must be present to determine that the other disorder does contribute importantly to dementia ("burden of proof").

F. All relevant diagnoses are recorded on the Diagnostic Impression page of the ISP (Attachment A).

**IV. Controls**
1. Longitudinal sample
   a. Pure controls: no dementia, no potentially dementing disorders
   b. Other “controls” include nondemented subjects with:
      1) Prior suspicion of dementia
      2) Other potentially dementing conditions (e.g., Parkinson’s disease)
2. Short Assessment Controls (SAC)
   a. Spouse controls are spouses of MAP subjects who agree to brief evaluation and are interested in participating in selected research protocols
      1) Collateral Sources (CS) for subjects are ineligible to be MAP participants
      2) Spouse controls are spouses of MAP subjects who agree to brief evaluation and are interested in participating in selected research protocols
   b. Non-spouse, Non-collateral sources
   c. Assessment (annual)
      1) Health history (including medications)
      2) Family history
      3) Mini-Mental State\textsuperscript{12}, Short Blessed
      4) Global nurse clinician evaluation of cognitive status
   d. Blood for genotyping, banking drawn every three years; MRI; LP
   d. No Clinical Dementia Rating, no psychometric evaluation. Hence, SAC are not equivalent to longitudinal controls who receive full clinical and psychometric assessments of control groups

V. Dementia Staging
A. Clinical Dementia Rating (CDR)\textsuperscript{13,14} \textbf{(see Attachment B)}
   1. Clinical instruments to stage presence of absence of dementia and, when present, its severity
   2. Cognitive domains assessed are linked directly to the original MAP research diagnostic criteria for DAT: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care
   3. Derived without reference to psychometric performance
   4. Five original global CDR stages: CDR 0=no dementia, and CDR 0.5, 1, 2, and 3 = questionable, mild, moderate, and severe dementia
   5. A more quantitative representation of the CDR is the Sum Boxes, derived simply by totaling the numeric level of impairment for each of the 6 CDR domains.
B. The Initial Subject Protocol (ISP). The instrument used to obtain the information necessary to stage the CDR (and determine the diagnosis) is the Initial Subject Protocol (ISP) and contains semistructured interviews with the Collateral Source (CS) and Subject (S). The ISP includes a health history, drug inventory, Depression (including the GDS) and Aphasia Batteries, and several brief cognitive scales (Mini-Mental State; Short Blessed Test 15, Blessed Dementia Scale 16, including its Activities of Daily Living scale).

C. Quality Assurance
1. All MAP clinicians are extensively trained in the CDR; level of agreement is ≥ 80% 17 18.
2. At entry and every 2 years thereafter (unless subject has a CDR 0.5 or greater and the diagnosis of DAT at 2 successive assessments) assessments are videotaped.
   a. Both the examining clinician and the tape reviewer independently generate a CDR score and diagnosis without reviewing previous assessments and ratings.
   b. Disagreements in CDR or diagnosis are brought to the Thursday MAP Clinical Conference for resolution. Cases for whom resolution is not possible are considered as “agree to disagree”; the examiner’s CDR and diagnosis are entered into the database in this situation.

E. Evolution of CDR 0.5
1. CDR 0.5/DAT  -- fulfill diagnostic criteria for DAT (see II.C.2.) and now includes individuals previously designated as "CDR 0.5 incipient". Experience shows such subjects progress predictably to more severe stages of DAT and have AD at autopsy19 20. We now consider the CDR 0.5 stage in such subjects to designate very mild (not “questionable”) dementia. Other centers retain the original “questionable” designation.
2. CDR 0.5/Uncertain Dementia These CDR 0.5 subjects either have impairment so questionable that it is not possible to know whether it represents true impairment or they have another condition (e.g., depression) that may be responsible for the questionable impairment. It cannot be stated by the clinician that a progressive neurodegenerative process is present. The subject’s questionable cognitive impairment thus is not expected to progress to definite dementia (i.e., CDR 1 or greater) with time. These subjects are diagnosed as Uncertain Dementia.
3. These subcategories of CDR 0.5 reflect, at least in part, the range of impairment that can be included under the global CDR 0.5 designation.

VI. Expiration Summary
A. Voluntary permission for autopsy (rates approximate 56%)
B. Expiration evaluation
   1. A nurse clinician interviews a CS shortly after death using an ISP-based telephone interview to obtain information regarding the subject’s cognitive and health status from time of the last MAP assessment to death.
2. A MAP clinician reviews the nurse’s postmortem interview, all ISPs, and any medical records. Based on all information, the clinician provides a final (Expiration Summary) CDR and diagnosis \^{6,20}.

VII. Important Considerations for Investigators Using Clinical Core Subjects/Data

A. For most clinical projects requesting MAP subjects for study participation, the following categories of subjects are referred from the MAP sample, unless investigators specifically request otherwise (CDR and diagnostic status based on last MAP assessment):

1. Controls: CDR 0, no other potentially dementing disorder
   *Note: Subjects may have had a previous CDR 0.5 designation

2. DAT
   a. CDR \( \geq 0.5 \)
   b. DAT alone or with other disorders, believed not included to contribute importantly to dementia
   *Note: Unresolved CDR or diagnostic disagreements will not be reflected

B. CDR and diagnostic status may change

1. With Thursday Noon Conference discussion (e.g., it may take weeks or even months before CDR or diagnostic agreements between examiners and tape reviewers are resolved; the original ratings of the examiner may change as part of this resolution).
2. With followup (e.g., subsequent annual assessments may yield different CDR scores or diagnoses)
3. With Expiration Summary

C. CDR 0.5/DAT generally is considered by non-Washington University investigators to be too mild to meet criteria for dementia diagnosis (e.g., terms such as “mild cognitive impairment” may be used to designate equivalent cases)

D. We are not perfect (but nonetheless pretty good)

1. Clinical diagnostic accuracy = 93% (AD confirmed in 192 of 207 DAT subjects, including 17 of 18 CDR 0.5 subjects)\(^6\)
2. 13 of 17 controls had no pathological AD\(^6\)
   *Note: Preclinical AD is found in \(~30\%\) of CDR 0 controls who die after age 75\(^{21}\)
3. Longitudinal follow-up in nondemented controls shows surprisingly stable cognitive performance\(^{22}\)

E. We work very hard to protect our subjects and ensure their continued cooperation.

1. Minimize burden
2. Safeguard cognitively impaired subjects
3. Confidentiality is preserved
4. Orientation required for all investigators/staff using Clinical Core resources

VIII MAP Manual of Operations (MOO): Protocols, procedures, policies, publications, diagnostic criteria, and instruments relevant to the Clinical Core are
contained in the MOO (available to all investigators in the MAP office), which is revised and updated as appropriate.

**VIV Important Tips from Clinical Core and Biostatistics to maintain confidentiality**

1. Subject names and ID numbers should not be included together in the same e-mail unless the e-mail is encrypted.
2. Data/samples should be assigned "false IDs" when information is being sent to investigators outside of our center. The biostat core is happy to provide these IDs and to them for the occasion when we might need to go back to the original ID.
3. IDs, initials, etc. should not be used in presentations or in publications. When investigators publish tables with individual subject data, they should number the cases and provide a key to Biostat so we can go back to the original subject data if necessary.
Reference List


