
UNIVERSITY OF NORTH TEXAS
HEALTH SCIENCE CENTER AT FORT WORTH
1970

USING A DATABASE TO FACILITATE THE ACCRUAL OF GERIATRIC SUBJECTS WITH DEMENTIA FOR CLINICAL RESEARCH STUDIES

Jessica Alexander, BAAS

APPROVED:

Major Professor- Patricia Gwirtz, PhD

Committee Member- Janice Kriebl, D.O., MBA

Committee Member- Barbara Harty, RN, GNP

Committee Member- Dan Dimitrijevich, PhD

University Member- John Aschenbrenner, PhD

Chair, Dept. of Biomedical Sciences

Dean, Graduate School of Biomedical Sciences- Thomas Yorio, PhD

USING A DATABASE TO FACILITATE THE ACCRUAL OF GERIATRIC SUBJECTS WITH DEMENTIA FOR CLINICAL RESEARCH STUDIES

An Internship and Practicum Project Report

Submitted to the Graduate Council of the Graduate School of Biomedical Science at The University of North Texas Health Science Center at Fort Worth

in Partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE

in Clinical Research Management

by

Jessica Alexander

Fort Worth, Texas

April 23, 2007

Acknowledgements

I would like to thank the all of the members of my advisory committee for their commitment to this project and their guidance throughout the process. I especially appreciate Dr. Janice Knebl for giving me the opportunity to work with her and her staff during my internship. Despite the fact that she leads an extremely busy medical practice, teaches students, visits nursing facilities weekly to care for the residents, actively participates in research endeavors, and chairs more committees than there is time to mention, she always made time to review my work and provide direction.

I would like to thank Dr. Annita Bens for her advice and expertise in the area of clinical research and project development and management, as it was very valuable in keeping me focused and prepared. Her involvement is especially appreciated, given the fact that she attended all of my committee meetings and defense without being a formal member of my advisory committee.

I want to acknowledge Dr. John Aschenbrenner for going above and beyond to support me in my academic and career choices, as well as committing time in the past and pledging his continued support to my future academic endeavors.

I would like to thank Dr. Dan Dimitrijevich, in particular, for sharing his expertise in projects on aging and for his guidance in the area of scientific project development and research proposals.

I need to thank Wendy Hammons from the Office of Clinical Trials for taking me under her wing and spending a tremendous amount of her time to teach me the details of clinical trial contracts management. This was not her obligation. However, she was a fantastic teacher, and her attitude and sense of humor made the time I spent in contracts management one of the most enjoyable experiences of the internship.

I want to express much gratitude to Dr. Patricia Gwirtz for her loyal support and encouragement over the past year. As my major professor, she met with me weekly to keep me grounded and focused on the tasks that were ahead. She offered more than editorial and technical advice—she offered her friendship and future support for my academic and career goals. I appreciate the opportunity that I have had to get to know her, for she is a woman of high standards and good character.

I really want to thank my on-site mentor Barbara Harty for her daily involvement in every aspect of my internship and practicum project, despite the fact that she is over-extended in patient care, clinical coordination, teaching, IRB, volunteer work, and speaking engagements. Over the course of the time I spent with her, and as a direct result of her confidence and trust in me, I stepped out of her shadow and became capable of performing the requirements of a clinical coordinator independently. I enjoyed our time together, and I look forward to being friends for many years to come.

Finally, thank you to my husband for being the primary caregiver to our children and a coach to them and their friends in every sport and every season, while I am rapt in my academic pursuits. Thank you for serving the community in the job that you do with the sincerity that is in your heart. Most of all, thank you for being my best friend. Without you to share them with, my achievements would seem hollow.

TABLE OF CONTENTS

CHAPTERS

LIST OF TABLES

CHAPTER I

Is the number of geriatric subjects with dementia who participate in biomedical research sufficient to adequately represent the actual population? The perception of many scientists is that the sample population is neither representative of the actual geriatric population nor sufficient in size. The same obstacles that would result in a general under-representation of all geriatric subjects in research would also be applicable to the subset of geriatric subjects with dementia. Therefore, substantiating the assertion that the whole geriatric population is inadequately represented in clinical research is the foundation from which this specific argument is expanded.

Evidence of a disparity in the representation of the geriatric population in biomedical research emerged in 1987 after the National Institutes of Health issued the Older Americans Act Amendments, Title III-- Alzheimer's Disease Research, which included guidelines that required the inclusion of minority groups in government-funded clinical trials (19). That mandate led to an inventory of research populations, revealing the need to categorize the elderly as a minority group in this context. Ten years later, a failure to adapt to the mandate to include a proportionate representation of elderly subjects in studies was exposed by an examination of the technical literature in the industry. All research articles in the *British Medical Journal, Gut, the Lancet,* and *Thorax* from June 1996 to June 1997 were reviewed by Bugeja, et al, and of the 490 appropriately included articles, 18 were specifically about elderly people, 265 did not address age limit, 37 excluded the elderly for justifiable reasons, and 170 articles excluded them for reasons that were not justifiable (4). This review demonstrated a

continued problem in terms of under-representation of the geriatric population in research.

Recently, a remarkable number of retrospective studies conducted by the National Cancer Institute and various other cancer investigators have shown that there is a disconcerting disparity in the trial subject populations that comprise oncology studies as well. An examination of the registries in 55 clinical trials including almost 29,000 patients found that only 36% of them were over age 65, while 70% of all cancer deaths were patients within that same age group (6). A number of other studies yielded the same results and concluded that there was a "statistically significant under-representation of the elderly ($P < .001$) noted in trials for all cancer treatments except for breast cancer hormonal therapies" (22).

A breakdown of the age groups within the general research population indicates that elderly subjects used in clinical trials are most frequently in their mid-sixties and in excellent health without any cognitive impairment (1), while participation in research seems to be significantly more limited for the subset of elderly subjects with diseases that causes dementia, such as Alzheimer's and Parkinson's. In a systematic search of randomized controlled trials conducted over 30 years investigating drugs used to treat Parkinson's disease, only 5.5% of the subjects that participated in 112 clinical trials were over 75 years of age (18) and less than 2% of persons suffering from dementia were recruited into clinical trials (5). How is it, then, that the elderly are being adequately represented in clinical research for medications used to treat diseases that cause dementia? The evidence indicates that:

(1) There is not a population-proportionate sampling of the elderly as a whole, much less an over-sampling to adjust for the disproportionate drug use and morbidity in seniors; and

(2) Geriatric subjects who suffer from diseases causing dementia are at a greater disadvantage in terms of population representation, which brings into question the validity of therapies aimed at treating those diseases.

If studies exclude such a large portion of their target users from research, how can resultant data be applied with any measure of reliability or confidence? It cannot, and this leaves physicians with two choices when prescribing medications for older patients. Some physicians may prescribe medications off-label due to lack of age-relevant data, even though it is well known that absorption, metabolism, and excretion of medicines change as patients age. Otherwise, physicians may opt not to prescribe some medicines to geriatric patients, despite the apparent efficacy of the medication in treatment of the disease, because efficacy has been based upon incomplete and inadequate testing within the relevant target group. Considering that approximately 14% of the current U.S. population is over 65 years of age, yet account for almost one third of all drug consumption (1), both are sub-standard and unacceptable options. Furthermore, the problem is compounded by the fact that the ratio of women to men increases with age, but women consume more pharmaceuticals than men do (10).

Under-representation of geriatric subjects in biomedical research creates a bias in effect estimates, bringing safe and adequate treatment into question. Securing a proportional and heterogeneous representation of subjects will serve to strengthen the

validity of biomedical research as it applies to therapeutic treatments for the elderly. Developing disease-specific or target population-specific databases, creating a "registry of databases," and conducting a multi-disciplinary assessment of the stringency of exclusionary criteria will, in part, correct the current disparity (2).

CHAPTER II

Part 1: Project Design

Specific Aims of the Internship Practicum Project

Every clinical trial or research study has its own unique challenges; however, it seems that there are additional complicating factors to consider when conducting research that includes geriatric subjects, especially those who suffer from dementia. The goal of the practicum project is to address this burden by evaluating a target population-specific database as a possible tool to be used for increasing the accrual of elderly research subjects with dementia. To accomplish this goal, the following specific aims were addressed:

(1) Identify the major contributory factors that complicate the process of recruiting geriatric research subjects with dementia.

(2) Identify the possible applications of a database as a tool in the accrual of geriatric subjects with dementia for clinical research

(3) Identify the limitations of a target population-specific database in adequately improving accrual of the intended research population.

(4) Assess the practicality and effectiveness of using a target population-specific database of potential subjects to facilitate accrual of geriatric research subjects with dementia.

Project Site and Database

Prior to the commencement of this internship, the site had already established a database of patients with dementia and non-demented controls for research purposes. Consequently, this site was an excellent forum for investigating the effectiveness of the use of target a population-specific database as a tool to facilitate the accrual of geriatric subjects with dementia for research.

Methods

Specific Aim 1. The following methods were used to identifying the major contributory factors related to the challenges of recruiting elderly subjects with dementia for clinical research:

(1) Review of literature. Relevant current literature and research reports were compiled and reviewed. Ovid Medline was used as the main search engine to locate peer-reviewed articles and papers that included recruitment-specific data about this population within the research reports. Many of the authors of the references that were used to prepare the literature review provided recommendations for other databases and sources of statistical data that were thoroughly investigated as well. Among these resources were the American Association of Retired Persons (AARP) AgeLine database, the Center for Information & Study of Clinical Research Participation (CISCRP), Harris Interactive, National Institutes of Health (NIH), ClinTrial.gov, Center Watch, Pharmaceutical Research and Manufacturers of America (PhRMA), and the Agency for Healthcare Research and Quality (AHRQ).

(2) Review of previous studies conducted on site. Clinical trial materials, such as subject folders, IRB review sheets, coordinator notes, etc. from studies that were conducted over the past 7 years at the clinic were located in archived records storage and reviewed. All studies that used strictly a population of subjects older than 55, studies that researched a condition primarily found in older subjects, and studies that tested a medication used almost exclusively by older subjects were included in the review. All materials were examined for documentation of the following data:

- Type of advertising used to market the research
- Number of subjects pre-screened
- Reasons for refusal to participate
- Number of subjects screened
- Number of screen failures
- Reasons for screen failures
- Number of subjects randomized into study
- Number of withdrawals
- Reasons for withdrawal

(3) Tracking of trends. In an effort to identify the most common obstacles to the accrual of geriatric research subjects for previous studies conducted at the internship site, each of the preceding categories of data were compiled from the archived studies and numerically analyzed by simply totaling each category. Furthermore, for subjects who were contacted during recruitment, the overall percentages were calculated for the number of subjects screened, reasons for screen failures, number of those enrolled or randomized, and withdrawn from each study.

Specific Aim 2. The following methods were used to identify the possible applications of a database as a tool for the accrual of geriatric subjects with dementia for clinical research:

(1) Familiarization with the database. The database's construction and procedures were reviewed.

(2) Inventory of content. An inventory of the database fields was recorded.

(3) Field characterization. The characteristics of the database fields and how those fields are defined were examined.

Specific Aim 3. The following methods were used to identify the limitations of the database for its ability to improve accrual of the intended research population:

(1) Recording limitations identified during the process. During the process of assessing the database for possible uses and taking inventory of its fields and characteristics, problematic issues related to the construction, procedures, or application were documented.

(2) Review of regulations. Possible uses of the database were compared to the regulations and laws of the bodies governing research at the site to verify that no rule or law would be broken if the database were to be used as proposed.

Specific Aim 4. The following methods were used to assess how effective using the database as a source of potential subjects and a recruitment tool could facilitate accrual of geriatric research subjects with dementia:

(1) Comparison of obstacles to potential uses. The obstacles identified in the review of previous studies at the site and current literature were compared to the potential uses and limitations of the database.

(2) Technical collaboration. To insure that the evaluation was comprehensive, it was necessary to collaborate with a database specialist to review the project proposal, findings, and suggestions in terms of plausibility and validity for the uses and limitations of the proposed applications of the database.

Limitations to project implementation

Ideally, the results of this analysis would be used to design a two-arm comparison study in which the recruitments strategies— one of which would include the use of a target population-specific database and the other would not— could be compared to one another after recruiting for the same study at two different sites. Time constraints were the main barrier to seeking the participation of either a sponsor company or two sites to conduct such a study.

This research did not include a financial analysis of the costs associated with the personnel and equipment required to develop a database to be used for this purpose as opposed to the cost of successfully recruiting the same population using other methods. Obviously the cost of development would be substantial initially, but once a target population-specific database was built it would benefit all subsequent study efforts without the same costs. This was an investigation of the plausibility and the effectiveness of using a database for recruitment of geriatric subjects with dementia, and therefore, a financial analysis of the associated costs was not within the scope of the project.

Part 2: Results

Literature Review: A search for answers as to why elderly subjects, particularly those with dementia, are under-represented in research.

Many of the studies from which this information was derived cited objectives other than specifically illuminating the disparity between the involvement of younger and older human subjects, with or without dementia, that participate in biomedical research. Nonetheless, these studies inadvertently uncovered a component of the discrepancy between representative populations and cited them within the conclusions of their research reports. In fact, some of the most compelling evidence has come from cancer research trial retrospective analyses that were conducted for the purposes of boosting trial enrollment among minority groups. Once the elderly were identified as the most disparate proportion of enrollees, a survey was sent to 156 oncologists asking what they perceived to be the barriers to accrual of older subjects for their trials (16). The most common responses given by physicians were as follows:

- 16% felt that elderly patients have significant co-morbid conditions that may not be excluded by a protocol, but could still affect how subjects would respond to treatment.
- 16% felt that elderly patients have difficulty understanding what is required in a complicated treatment trial, which would be likely to result in poor compliance.
- 15% said that elderly patients often do not meet the strict eligibility criteria for studies.

- 14% reported they believed treatment toxicity was a too much of a concern to include them in a study.

Concerns about toxicity may be less universal in application, but the likelihood of poor compliance, strict exclusion criteria, and concerns related to co-morbidities all have broad relevance to any research that includes elderly subjects, especially those with dementia. Reviewing the feedback given by professionals who are experienced in dealing with the challenge of recruiting this population for research is the most reasonable place to start a search for answers about why accrual is so low. Therefore, the factors outlined in the fore-mentioned survey will be a main focus for further investigation in this review. However, there are a number of other factors that could contribute to the challenges affecting accrual of the sub-population of older patients with dementia, and those factors will also be addressed in order to ensure a comprehensive examination of this disparity.

As evidenced by the survey results, concern that there may be poor compliance with study protocols is one of the most frequent issues that physicians have to deal with when screening the elderly for their studies. *Compliance* is usually thought to be synonymous with *willingness*, but in the elderly poor compliance may be due to anything from loss of ability to maintain an accurate study diary because of arthritis in the hands to a lack of transportation or altered mental status.

Deficits in hearing, speech, and sight—which are more prevalent among those of advanced age— are also likely to promote deviation from study protocols. In order to adhere to many protocols, elderly subjects must often secure and guarantee the consistent help of a caregiver to evaluate, medicate, and/or keep study diaries for them. Although

this assistance may increase compliance, it has been found that caregivers are more hesitant to report complaints and frequently understate symptoms (3), which compromises the validity of reported data and increases the likelihood of a more serious adverse event when one does occur.

Another barrier to recruitment related to compliance is the possibility that a subject could be institutionalized throughout the course of a study. Institutionalization excludes many elderly subjects from participation in clinical trials because routine care is unlikely to be provided by a consistent caregiver, thus the likelihood of deviation from the study protocol and inconsistent reporting is increased. Considering that more than half of the population that has dementia is institutionalized (12), this is a substantial impediment to accrual of subjects with dementia.

Decreased cognitive capacity is a very reliable indicator of poor compliance. A recent study of subjects with mild-to-moderate Alzheimer's disease concluded that 84% of the Alzheimer's patients showed significant deficits in decision-making ability (15). This indicates that it is not likely for them to have the capacity to understand what would be expected of them in a clinical trial, nor would they be able to provide a truly "informed consent" to investigational treatment without clearly understanding their obligations.

Strict exclusion criteria was another one of the factors that was perceived to be a key causative factor to low accrual according to the physicians participating in the study questionnaire (16). In addition to increasing recruiting complexity, strict exclusion criteria significantly decreases the possibility of examining realistic treatment responses for heterogeneity and brings into question how broadly the results may be applied (14).

A review of a multi-site, randomized trial using nursing home patients to test the efficacy of vitamin E in the prevention of respiratory infections effectively illustrates this point. The study protocol did not exclude subjects on the basis of institutionalization in this case. Instead, researchers used the availability of this large population pool to its advantage by designating institutionalization as an inclusion criterion and then maximizing the enrollment rates by using an individualized approach to recruitment (9). This study should have also presented less of a challenge in terms of recruitment of elderly subjects because it did not require significant scrutiny over a subject's ability to comply with the protocol or a caregiver's willingness to participate, given that it was specifically a nursing home-based study. Furthermore, the study did not represent a high level of risk to the subjects. Nonetheless, after meeting the initial screening criteria and agreeing to participate, the remaining subjects were further screened and 67% of them could not meet all of the eligibility criteria (9). As many study physician have asserted, strict exclusion criteria is obviously a fundamental barrier to the accrual of all elderly subjects for clinical research.

Exclusion criteria will always be particularly pertinent to a population laden with co-morbidities, which is one of the other factors identified by study physicians as a cause for the low accrual of geriatric subjects (16). Issues related to co-morbidities are also of utmost concern to those who wish to safeguard the integrity of their research results by minimizing the occurrence of adverse events. Limiting selection of subjects to those with few or no co-morbidities surely simplifies data interpretation because adverse events that occur in healthy human subjects less frequently require differentiation between adverse events that resulted due to co-morbidities and those that are secondary to the use

of an investigational treatment. Exclusions of this nature are a type of sample enrichment that may lead to limited external validity of the test results. However, testing a therapy by this standard is commonly accepted as a valid source of evidence for the effectiveness of a treatment (17). It is likely that assuming the validity of this method reinforces a barrier to senior enrollment in clinical trials and that the barrier will not be removed until it becomes acceptable to assess the absolute effectiveness and safety of a therapeutic treatment for older patients by using a more representative and heterogeneous sampling of the population.

A collateral effect of having a high incidence of co-morbidities is that the elderly are reluctant to enroll in placebo-control trials. In fact, a questionnaire given to potential subjects that declined participation in a Ginko Biloba study revealed that 9% of them refused because they were unwilling to be assigned to the placebo group (8). Undoubtedly this number is significantly higher in studies that test the efficacy of more essential medicines and treatments, such as dementia medications. The debate over necessity, ethics, and alternatives to placebo-control studies is far too broad for the scope of this discussion. Suffice it to say that the possibility of randomization into a placebo group is a noteworthy reason for declining to enroll in clinical trials. This is particularly true when a subject's participation in research could include being in a placebo-control group instead of the treatment arm of a study when the medication being tested affects cognitive function or behavior as it does for those with dementia.

The influence that family members or caregivers may have on an elderly person's decisions to participate in research should also be considered as a component of recruitment. More than 50% of seniors report having at least one disability that limits

daily activities and requires the assistance of others (3), which can hinder meeting recruitment goals. It is reasonable to assume that the percentage of elderly with dementia requiring a caretaker is higher than that of the general geriatric population because their disabilities are not limited to the dementia, and so caregiver influence may have a more profound effect on accrual within that population.

Family resistance to enrolling loved ones in clinical research is not limited to financial reasons and a matter of convenience, but ethical and moral issues as well. Families often feel conflicted about allowing experimental treatment for their loved ones, which is reasonable if they have accepted any decision-making responsibility for a physically disabled or cognitively impaired person. What is interesting is that a recent survey on the subject concluded that,

> "Survey respondents were most enthusiastic about offering themselves as research subjects with family consent. The clear message is that patients who understand the risks are willing to commit to potentially life-saving research, and they want those who mean the most to them to carry those wishes out as a gesture of love and understanding and perhaps with the hope of changing their own destiny in the process" (21).

This report certainly indicates that willingness to enroll is not the reason for under-representation in this population, which is substantiated by a survey conducted to assess the willingness of the elderly to consider participation in cardiac clinical trials. Six hundred and sixty patients responded concerning their feelings about being a part of randomized clinical trials to assess safety and efficacy of cardiac medications or invasive procedures. As compared to the younger population, patients over 70 years of age were

more willing to participate in both, which demonstrated that reluctance is not the reason for under-enrollment of elderly subjects in trials, even trials with a high risk profile (20).

If none of the previous barriers to recruitment existed and an adequate number of subjects would agree to participate in studies, there may still be significant difficulty in reaching this particular population pool with recruitment propaganda due to cognitive impairment and/or institutionalization. However, it is important to recognize that the average age of onset of dementia is 76 years old (7), which means that legal caregivers—whether they be spouses, siblings, or even children—are more likely to be advanced in age as well. With that in mind, strategies aimed at reaching the elderly population in general should be most effective in accessing those with dementia because recruitment of these subjects is likely to be through caregivers.

Provided that the population can be reached through a caregiver, likelihood of poor compliance, strict exclusionary criteria, issues related to co-morbidities, decreased cognitive capacity, institutionalization, reluctance to enroll in placebo-control trials, and reluctance of family members or caregivers to enroll subjects with dementia are all clearly the major obstacles to overcome when recruiting geriatric subject for participation in research. These issues are applicable to the geriatric population as a whole, but by nature they all have a more profound impact on the subset of potential subjects with dementia.

Review of Previous Studies Conducted at the Site

The following tables were constructed from documentation of recruitment efforts, screening, and enrollment from studies conducted at the site over the past seven years.

TABLE 1

Type of Advertising Used to Market the Research	Study 1	Study 2	Study 3	Study 4
Newspapers and magazines	X°	X		X°
Mailings				
Physician referrals	X	X°	X	X
Public flyers	X			
Reviewing patient charts followed by direct contact (Only a small percentage of all charts were reviewed according to the study coordinators)	X	X	X°	X

**X° means primary mode of recruitment/marketing*

TABLE 2

Recruitment Data	Study 1		Study 2		Study 3		Study 4	
Number of subjects pre-screened	148+		111		50		244	
Number/percent of subjects formally screened with tests	12	<8%	10	9%	6	12%	3	1%
Number/percent of subjects randomized into study	12	<8%	10	9%	6	12%	3	1%
Number of screen failures/% of those formally screened	6	<50%	3	30%	0	0	0	0
Number/percent of withdrawals for reasons other than screen failure	2	<1%	7	6.3%	0	0	0	0
Number/percent of those enrolled to complete the study	4	33%	0	0%	6	100%	1	33%

TABLE 3

Reasons for Non-participation	Study 1		Study 2		Study 3		Study 4	
Number/percent with inclusion/exclusion criteria not met	109	74%	60	54%	23	46%	71	29%
Placebo-control arm	Documented as "numerous"		0	0	0	0	0	0
Number/percent with communication deficits (blind, deaf, unable to write, or non-English Speaking	0	0	2	0.02%	4	8%	2	0.8%
Number/percent with transportation issues	0	0	5	0.05%	0	0	0	0
Number/percent with family concerns or family refusal to participate	0	0	0	0	2	4%	1	0.4%
Refusal without reason	0	0	27	24%	4	8%	17	7%
Study medicine not a new medication	Documented as "numerous"		0	0	0	0	0	0
Number/percent unwilling to commit to long study	23	16%	1	0.09%	0	0	3	1%
Number/percent that refused to change medication routine	3	2%	1	0.09%	9	18%	0	0
Number/percent refused for reasons unknown	0	0	11	1%	0	0	0	0

TABLE 4

Reasons for Withdrawal	Study 1		Study 2		Study 3		Study 4	
Number/percent unable to continue meeting medical criteria	8	67%	3	30%	0	0	2	67%
Number/percent of self withdrawals	1	8.3%	4	40%	0	0	0	0
Number/percent that physician withdrew subjects for medical reasons	1	8.3%	3	30%	0	0	0	0

Inventory of Database Fields and Characteristics

Field	Definition and/or Characteristics of Field
Patient identifier/ID number	No name or private information. Number matching subject name in separate database.
Date of entry	Direct entry
Date of Birth	Direct entry
Sex	Male, Female
Race/ethnicity	White, Black, American Indian or Alaskan Native, Asian or Pacific Islander, Other, Missing
Hispanic origin	Is subject Spanish/Hispanic/Latino- Yes/No
Marital Status	Married, Widowed, Divorced, Separated, Never married, Other, Missing
Primary Language	English, Spanish, Other, Missing/unknown
Education	Elementary=8, Less than high school=8, High school=12, Greater than high school=14, College=16, Masters=18, Doctorate=20, Missing
Residence	Private residence, Retirement community, Assisted living/boarding home/adult family home, Skilled nursing facility/nursing home, Other, Missing
Date of Initial Evaluation	Direct entry
Initial MMSE score	Direct entry
Date of last evaluation	Direct entry
Most recent MMSE	Direct entry
Meets Clinical Dementia Criteria	Yes, No (includes questionable or no diagnosis)
Most recent evaluation diagnosis if not dementia	Not demented/control, not demented with neurological disorder, Questionable dementia, Down's syndrome but not demented, Other, No diagnosis made, Missing/unknown
Primary clinical diagnosis of Alzheimer's Disease	Alzheimer's disease, Alzheimer's disease with other conditions, Non-Alzheimer's dementia, Missing/unknown
Non-Alzheimer's dementia diagnosis	Frontal lobe dementia, Parkinson's disease dementia, Huntington, Progressive supranuclear palsy, Alcohol related, Corticobasal degeneration, Hydrocephalus, Vascular dementia, Dementia with Lewy bodies, Prion-associated, HIV, Primary progressive aphasia, Posterior cortical dysfunction, Down's syndrome, Dementia due to multiple non-Alzheimer's etiologies, Dementia due to other general conditions, Other, Missing

Field	Definition and/or Characteristics of Field
Parkinson's disease	Yes, No, Missing
Lewy Body	Yes, No, Missing
Stroke	Yes, No, Missing
Age at onset of dementia	Direct entry
Delirium at last visit	Yes, No
Depression (yes/no)	Yes, No, Missing
Family history (direct relative)	Yes, No, Missing
How many relatives	Direct entry
Multiple birth	Yes, No, Missing
Vital statistics	Alive, Dead
Date of death	Direct entry
Autopsy	Yes, No
Biopsy	Yes, No
Primary neuropathological diagnostic classification	Normal brain, Alzheimer's disease- definite, Alzheimer's disease- probable, Alzheimer's disease- possible, Idiopathic Parkinson's with cortical and/or subcortical Lewy bodies, Dementia with Lewy bodies and AD, Dementia with Lewy bodies without significant AD changes, Vascular dementia, Pick's disease, Lobar atrophy without Pick's bodies, Hippocampal sclerosis, Progressive supranuclear palsy, Corticobasal degeneration, Prion-associated disease, Down's Syndrome, Other, Autopsy report pending, Missing/unknown
Secondary neuropathological diagnostic classification	No secondary neuropath diagnosis, AD pathology present but insufficient for AD diagnosis, Idiopathic Parkinson's with cortical and/or subcortical Lewy bodies, Dementia with Lewy bodies and AD, Dementia with Lewy bodies without significant AD changes, Vascular dementia, Pick's disease, Lobar atrophy without Pick's bodies, Hippocampal sclerosis, Progressive supranuclear palsy, Corticobasal degeneration, Prion-associated disease, Down's Syndrome, Other, Stroke or cerebrovascular disease but not vascular dementia, Autopsy report pending, Missing/unknown
Frozen brain sample accessible	Yes, No
Formalin brain tissue accessible	Yes, No
Parafin brain sample accessible	Yes, No
Post-mortem CSF accessible	Yes, No

Field	Definition and/or Characteristics of Field
Ante-mortem CSF accessible	Yes, No
DNA accessible	Yes, No
Serum accessible	Yes, No
APOE genotyping performed	Yes, No
Results from neuropsychological testing available	Yes, No
CT data available	Yes, No
PET data available	Yes, No
SPECT data available	Yes, No
Source of data	Clinical core, satellite, Center Affiliated study, Other, Missing/unknown
Date of last MMSE	Direct entry
Date of last contact	Direct entry
Active/Inactive status of ID	Active: further in-person visits expected; Active: further visits expected (phone or other); Active: no further visits expected but autopsy expected or have autopsy consent; Deceased: autopsy pending; Deceased: autopsy complete, neuropathology data available; Deceased: autopsy complete, neuropathology data not available; Inactive: deceased, no autopsy; Inactive: no further data expected (alive at last contact)

Limitations to Effectiveness

As noted during the process of taking inventory of the database fields and characteristics, lack of the following fields could possibly present limitations to its use as a recruitment tool:

- Concurrent medications
- Medical history or significant medical diagnoses
- Neuropsychological test result values

Regulatory Limitations

The Federal Drug Administration, University of North Texas Health Science Center, and the Department of Health and Human Services have rules and regulations that govern the use of private health information, safety, and confidentiality. The explicit purpose of the restrictions placed on research activities by these regulatory entities is to ensure that all research is conducted safely and with respect to the rights and privacy of all subjects, especially those who are particularly vulnerable. Therefore, it was important to verify that the proposed uses of the database would be in compliance with all regulations issued by the fore-mentioned agencies.

Department of Health and Human Services Regulations

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) required the Department of Health and Human Services to establish guidelines for the use of private health information (13). The legislation was intended to facilitate the transition of medical record storage and transmission from paper to electronic format, while maintaining privacy and security of the data. In 2002, HHS issued the "Privacy Rule" to

clearly define the term *private health information* and how it may be used. Private health information is any information that is related to the physical or mental health of a person and identifies that individual or can be used to identify that individual, such as:

- Name
- Social security number
- Medical records identification number
- Address, including zip code or geographical location smaller than state
- Telephone number
- E-mail address

Furthermore, the Privacy Rule states that there must be signed authorization that specifically details any use or transmission of private health information before it may be used. However, health information may be used or disclosed for research purposes without prior authorization or conforming to HIPAA regulations if it is "de-identified" and proof of that process has been reviewed and approved by an institutional review board (13).

The "Final Rule," which was released in 2003, specifically addresses administrative procedures, physical safeguards, and technical security mechanisms and services for electronic protected health information. The following sections of that rule would be directly applicable to the creation, maintenance, and access of a database of patients from a medical clinic (13).

164.310 *Physical Safegaurds*—Policies and procedures must limit physical access to electronic information systems and the facility in which it is housed, while allowing authorized access.

164.312 *Technical Safegaurds*— Users must have a unique ID and audit controls must be in place. There must also be an automatic logoff after a predetermined period of time.

Food and Drug Administration Regulations

In compliance with the Privacy Rule and the Final Rule, the FDA issued guidelines for research. The following FDA regulations are related to the use of electronic medical records systems, and may therefore relate to or restrict the creation and maintenance of any database of potential subjects that includes health information (11).

21 CFR 11.10 Subpart B--Electronic records, controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation

shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform assigned tasks.

21 CFR 21.72: Subpart G--Disclosure of records in Privacy Act record systems to persons other than the subject individual

(a) Individuals may consent to disclosure of records about themselves to other persons in several ways, for example:

(1) An individual may give consent at the time that the information is collected for disclosure for specific purposes or to specific persons.

(2) An individual may give consent for disclosure of his records to a specific person.

(b) In each case the consent shall be in writing and shall specify the individual, organizational unit, or class of individuals or organizational units to whom the record may be disclosed, which record may be

disclosed, and, if applicable, for what time period. A general consent to release all of an individual's records to unspecified individuals or organizational unit are not honored.

The University of North Texas Health Science Center Policies

The university requires all research to be pre-approved by the IRB. This includes creation and maintenance of a database that may be used for retrospective studies, such as the database being evaluated. There were two essential institutional considerations related to the proposed use of the database:

(1) Creation of a database of patients with dementia and entry of health information into that database without specific permission of the patients to approve that use.

(2) Unauthorized recruitment marketing based upon a database-generated list of potential subjects.

The UNTHSC IRB honors FDA guidelines for research approval. According to the federal code of regulations Title 21 CFR 56.111, in order to approve the use of a database of potential subjects with dementia for the purposes of research and recruitment the IRB would have to be certain that the project met the following criteria (11):

- Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, mentally disabled persons, or economically or educationally disadvantaged persons.

- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.
- Informed consent will be appropriately documented, in accordance with and to the extent required by 50.27.
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- When some or all of the subjects, such as mentally disabled persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of those subjects.

Regarding the matter of marketing, UNTHSC is in compliance with the FDA and HHS guidelines for marketing, mandating that written authorization must be obtained prior to any marketing communication, including the use of patient listings for special mailings generated from a database. However, if the communication is a face-to-face encounter with the individual or it concerns health-related products or services provided by the Health Science Center, such mailings would be permitted and not require prior written authorization (23).

Part 4:

A Discussion of the Findings

Obstacles to the accrual of a representative population of elderly subjects with dementia for clinical research.

According to the information presented in the literature review, the major obstacles to recruiting the participation of elderly research subjects, particularly those with dementia, are:

1. Likelihood of poor compliance with protocols, most often due to decreased cognitive capacity, but also due to subject institutionalization or the imminent possibility thereof;
2. Family influence and subject dependence upon relatives for transportation, care, etc;
3. Copious and strict exclusionary criteria applied to a population with an especially high rate of co-morbidity;
4. Lack of willingness to participate in placebo-control trials due to the possibility of hastened cognitive decline and disruptive behaviors with non-treatment; and
5. Limited media access to the population pool.

A review of reasons documented for non-participation from previous trials that were conducted at the internship practicum site indicated that strict exclusion criteria was by far the most common reason for non-participation in patients who met the preliminary

criteria. In fact, data presented in Table 2 demonstrates that in every study reviewed the exclusionary criteria accounted for significantly more loss of potential subjects than all other reasons combined. This reason is followed distantly by unwillingness to change medication routines.

Analysis of the characteristics of the site's database and its ability to address obstacles to recruitment

To assess the possible effectiveness of the database in facilitating accrual of subjects with dementia for clinical research it is essential to compare restrictive factors identified in the *Literature Review* and *Review of Previous Studies* to the characteristics of the database identified in Tables 1 through 4 and the *Inventory of Database Fields and Characteristics* to determine whether or not the features of the database could effectively address any of the obstacles to accrual.

Findings presented in Tables 1 and 2 can be combined to identify trends in effectiveness of the methods of recruitment for previous studies at the site that were specific to this target population. For instance, when public advertisement was used as the primary method of recruitment the number of contacts made was high, while the percentage of enrollees was low. On the other hand, when the primary method of recruitment was clinic chart review for pre-qualification followed by direct contact, the number of contacts was low, the percentage of enrollees was the highest, and retention was 100%. In contrast, retention ranged from 0-33% in all other studies. This trend indicates that the most successful strategy to employ when recruiting subjects for studies

conducted in medical clinics may be to pre-screen the existing patient base by reviewing their charts for inclusion and exclusion criteria followed by direct contact.

Because there are more than 2000 patients at the practicum project site, it would take an immeasurable amount of time to review all of the patient charts for each study conducted at the clinic. For this reason alone, a database of clinic patients could serve as a tool to increase focus and decrease the time required for recruitment efforts. By nature, a database contains data that may be sorted in a query to produce a specified data set. Given the current fields in the database, which are reflected in the *Inventory of Database Fields and Characteristics,* potential subjects can only be sorted by criteria related to basic demographics, type of dementia, and limited medical conditions, such as history of stroke, delirium, or depression. However, the most restricting factor in recruitment of this target population appears to be exclusionary criteria, such as co-morbid conditions and concomitant use of specific medications. The current data points captured in the database are not likely to culminate in an adequate data set to significantly hasten the pre-screening process; nor is it likely to decrease the percentage of potential subjects lost to exclusionary criteria that should have been identified in a initial query used to produce a list of potential subjects. This specific population is most likely to be included in clinical research for dementia medications or research studies of the disease processes that cause dementia, and therefore, the addition of fields to capture the following data points could enrich the ability of the database to quickly pre-qualify a large number of subjects for these kinds of studies.

Concomitant use of specific medication classes, such as:

- Antidepressants
- Acetylcholinesterase inhibitors
- Anti-Parkinsonian agents
- Antihypertensives
- Lipid lowering agents
- Antipsychotics

Co-morbidities, such as:

- Hyperlipidemia
- Diabetes mellitus
- Hypertension
- Obesity
- Cardiovascular history, including Hachinski score
- Inflammatory disorders
- Cancer
- Dementia diagnosis date and level of severity
- Smoking
- Alcoholism
- Drug abuse

Neuropsychological test scores that are used to evaluate and diagnose subjects, such as:

- Geriatric Depression Scale (GDS)
- Clinical Dementia Rating (CDR)
- WMS Logical Memory 1 and 2

While taking inventory of the fields in the current version of the database it became evident that there were other characteristics that were not conducive to use of the database for recruitment of subjects. In particular, 22 of the 48 fields are dedicated to information about banking of post-mortem biological samples or accessibility of neuro-imaging. This may facilitate the identification of subjects to use in retrospective research studies, but would not be relevant to the recruitment of subjects for prospective clinical research. Also, the diagnostic fields may yield more clear usable data if there were to be only two comprehensive pick lists for types of dementia that are labeled, "Primary dementia diagnosis" and "Secondary dementia diagnosis" because oftentimes subjects have mixed forms of dementia and this could be used to capture both.

In terms of the database addressing other obstacles to subject accrual, there are few other applications. In reference to the likelihood of poor compliance, the database would be able to identify some of the contributing factors, such as institutionalization, which is found within the *Residence* field, and level of cognitive capacity, which is reflected in the *Mini Mental State Exam (MMSE) scores*. However, family influence and willingness to participate in placebo-control trials are subjective and cannot be identified in a query.

Regulatory limitations on effectiveness of the database as a recruitment tool

The university's IRB would closely scrutinize the creation and maintenance of any database of clinic patients for the purpose of clinical research recruitment due to HIPAA regulations and informed consent issues related to the use of private health information. However, the site's database contains information that is de-identified, and

therefore, not required to conform to all of the HIPAA regulations for the use of private health information or 21 CFR 21.72, which states that consent is needed prior to the addition of health information into a database. The HHS "Final Rule" sections regarding physical and technical safeguards also regulate accessibility and maintenance of the database by dictating that policies and procedures be put in place for restricted access. This is achieved at the site by storing the database on a network drive that only allows access by personnel approved by the IRB. A master list of corresponding patient names with the designated numerical identifier of subjects who are in the database is kept in a locked office in a locked file, which satisfies the requirements of de-identification procedures and was found to be acceptable by the IRB.

The IRB must approve all aspects of any research study that includes human subjects according to the code of federal regulations 21 CFR 56.111, which means that each study that intends to make use of the database must provide assurances of good practices and lawful use of the database for recruitment prior to its use. Institutional policy does not prohibit use of the database to generate and list of potential subjects for study marketing purposes because that marketing would be for services provided by the Health Science Center and would be at no charge to subjects who choose to participate. Therefore, each of the elements required by the HHS, FDA, and IRB to use the existing database as a recruitment tool is satisfied.

Discussion of other findings

If the database were to have fields related to medical history, medications, and neuropsychological test scores, there would be a significant ability for hypothesis-generation. The data could be extracted from tables with specific queries and a put into SPSS for statistical analysis that could yield strong retrospective data for hypothetical bases used to design prospective studies.

Conclusion

A target population-specific database can be an exceptional tool when used to facilitate the accrual of geriatric subjects with dementia for clinical research because it can address some of the most significant, non-subjective obstacles to their accrual. Recruiting clinic patients from a database that have been pre-qualified in queries using inclusion and exclusion criteria, whether it be medical history or institutionalization, can significantly speed the process of screening and yield a group of potential subjects well suited to complete the study. A recruitment strategy that includes directly contacting the caregivers of patients generated from a database list of clinic patients also solves the issue of limited media access to the target population.

The database currently being used at the internship practicum site would need modifications to be an effective recruitment tool. In particular, the addition of medical history, medications, and neuropsychological test scores could transform it from a tracking device for patients with dementia to a powerful recruitment aid that has the added benefit of hypothesis-generating ability. Furthermore, were there to be a registry of these databases created, there could be a cooperative effort within the research community to reconcile the disparity between the numbers of geriatric subjects, with or without dementia, who participate in clinical trials versus the numbers that are needed to secure a representative population to produce more generally applicable and valid results.

Summary

It is proposed that developing disease-specific or target population-specific databases can address many of the obstacles to the accrual of a representative population of geriatric subjects with dementia for participation in clinical research. A review of current literature and recruitment data from previous studies conducted at the internship site indicate that the most significant impediments to recruitment of the target population are likelihood of poor compliance, strict exclusionary criteria, and difficulty reaching potential subjects with marketing efforts.

Recruitment based upon lists of potential subjects generated by database queries using inclusion and exclusion criteria, whether it be medical history or compliance indicators, can significantly speed the process of screening for recruitment because it addressed the most significant impediment to successful accrual. A strategy that includes directly contacting the caregivers of patients from a database-generated list of clinic patients also addresses and resolves the issue of limited media access to the target population.

When employing a database for the purpose of generating a list of pre-screened subjects for direct contact, the two main regulatory issues to consider are:

(1) HIPAA regulations and informed consent requirements related to the use of private health information for the creation of a database of patients with dementia; and

(2) Institutional policies regarding recruitment marketing based upon a list of potential subjects generated from a database of patients.

If patients' private health information is de-identified prior to entry into the database and a master list of corresponding names and identification numbers are kept in a separate and secure location, informed consent is not required prior to use of health information for these purposes. Recruitment marketing based upon lists generated by a database complies with institutional policy because marketing would be for services provided by the Health Science Center at no charge. Therefore, each of these elements required by the HHS, FDA, and IRB to use the existing database as a recruitment tool is satisfied.

After taking inventory of the fields and characteristics of the existing database of patients at the practicum site, it was evident that many data points that would facilitate recruitment of the target population were not present. This specific population is most likely to be included in clinical research for dementia medications or research studies of the disease processes that cause dementia. Hence, the addition of fields to capture data regarding more relevant medical history, concomitant medications, and neuropsychiatric test scores could transform the site's database from a tracking device for patients with dementia to a powerful recruitment aid that has the added benefit of hypothesis-generating ability. Furthermore, were there to be a registry of these databases created, there could be a cooperative effort within the research community to reconcile the disparity between the numbers of geriatric subjects, with or without dementia, who participate in clinical trials versus the numbers that are needed to secure a representative population to produce more generally applicable and valid results.

CHAPTER III

The Internship Experience

The internship and practicum project activities took place in an established geriatric practice that provides care to more than 2,000 patients over the age of 65. Research studies and clinical trials conducted at this site are specifically aimed at either testing the efficacy of medications and treatments in the elderly or researching disease processes predominantly found within the older population. This geriatric practice is lead by Dr. Janice Knebl with the assistance of Barbara Harty, who is a seasoned geriatric nurse practitioner, IRB board member, clinical coordinator, and my mentor during the internship.

The overall objective of the internship was to build a functional knowledge of how to manage research with human subjects. The internship experience spanned several domains within the field of clinical research management: clinical coordination, contract management, institutional research management, and data/records management. Within the course of the internship and implementation of the practicum project there were more than 1040 hours logged working within these areas of concentration in order to achieve that goal. The following is a narrative account of those experiences that details the Internship/Activity Log submitted as Appendix A of this report.

Clinical Coordination

Training and Certifications. At the beginning of the internship, it was necessary to compete HIPAA, Collaborative IRB Training Initiative (CITI), and e-Procurement training in order to participate in research with human subjects as a clinical coordinator

for this site. The CITI training, in particular, was an excellent review of the Clinical Research Management course. Furthermore, the training program included ongoing access to an updated resource for any question imaginable regarding research with human subjects, which was useful throughout the internship and will be for years to come. The eProcurement program is an accounting and tracking program for supplies, equipment, subject stipends, and account payments that coordinators at the institution use. Training provided insight into typical accounting practices as well as difficulties frequently encountered by research coordinators.

Coordinator Meetings. The site holds regular monthly meetings for coordinators so that they can discuss various aspects of the job that presented challenges. These meetings also include the department heads for the Office of Clinical Trials and the Office for the Protection for Humans Subjects, as well as support staff from the Grants and Contracts office. This was one of the most insightful experiences of the internship because the management challenges that are not so obvious to someone beginning a career in clinical research were highlighted and resolved by seasoned members of the profession. Among the most pressing of these challenges was budget development and negotiation, financial tracking of monies in from the sponsors and reconciliation of expense accounts, and coordination of efforts by study staff, support personnel, and the IRB. When issues were identified as being problematic, I either took notes on the problems and resolutions to file away for future incorporation into clinical research management or I developed a plan of action or reference for immediate use by other members of the research team, such as:

- A Coordinators' Recruitment and Marketing Strategy, Appendix B

- A Coordinator's Common Cost Sheet, Appendix C, and
- A Coordinator's Contacts and Reference Sheet, Appendix D

This opportunity allowed me to instantly become a part of a working team and benefit from years of experience in clinical research management without making the mistakes and enduring the challenges that come with that experience.

Regulatory and Administrative. The majority of the internship experience was related to regulatory and administrative duties— trial initiation, in particular. For instance, as sponsors contact the clinic to solicit participation in studies, they submit protocols and study requirements for review. One of the most important things that a site can do to ensure the success of a study is to carefully review these requirements and conduct a thorough feasibility study to determine if the research goals can be met with the resources available. This includes balancing a number of aspects related to study coordination, such as:

(1) Length of time allowed for recruitment versus the number of subjects required for enrollment.

(2) Duration of participation versus usefulness of therapy to the subjects, as long trials have high attrition rates and potential subjects seem less willing to commit to longer studies without a significant therapeutic return.

(3) Likelihood of adverse events and severity potential versus likelihood of benefit to the subjects.

(4) Benefit to risk ratio versus compensation to subjects for participation.

(5) The sponsor's recruitment goal versus the likelihood of being able to enroll that number of subjects. This is a multi-faceted issue that can depend upon all of the following:

- Access to the target population
- Presence of a trust relationship with target population
- Adequate population pool
- Special recruiting challenges associated with the given population pool (family influence; high rate of co-morbidity, decreased mobility, impaired cognitive ability, or rate of institutionalization within the target population; likelihood of ability to comply with protocols).

(6) Strictness, nature, and number of inclusion and exclusion criteria versus prevalence of disease processes in the target population.

(7) Projected difficulty of recruitment versus budget for recruitment and sponsor support programs for recruitment.

(8) Time commitment required for execution of the protocols versus time available to devote to the study.

(9) Cost in time, personnel, supplies, and institutional overhead versus the initial budget proposal submitted by the sponsor and history of flexibility for that sponsor.

In order to conduct an adequate feasibility study, a coordinator must first review the protocol in detail, break it down in terms of supplies, personnel, costs, tasks, resources needed, etc., and correspond with the sponsor to get all questions answered regarding the study protocols and requirements. During the course of the internship I

reviewed three studies to this level of inspection and presented full reports to my mentor for review and discussion.

A site visit by the sponsor is another component of the pre-initiation phase of clinical research. This is an excellent opportunity to assess compatibility between sponsor expectations and the site ability to conduct the research to that level of expectation. A successful site meeting necessitates preparation by the coordinator so that remaining questions and requirements can be addressed and the sponsor's questions regarding regulatory details can be answered readily. I had the opportunity to participate in all of the preparation leading up to and attend an initial site visit as an orientation to the site and coordinator's responsibilities.

Once a site visit takes place and both the sponsor and site agree to proceed with negotiations, customarily, a budget proposal is submitted by the sponsor to the site. The site's coordinator must also prepare an expected budget that includes:

- Personnel time
- Recruitment time
- Cost of advertising and recruitment materials
- Equipment needed (if not supplied by the sponsor)
- Medical supplies
- Facility related costs
- Medical consultants and procedures associated with the protocol if subjects need to be referred to other physicians, radiology, or other healthcare providers for evaluations during the study
- Labs charges for specimen collection, specific tests, etc.

- Shipping costs or special cold or biohazard shipping supplies
- Subject compensation
- Institutional/site administrative overhead

Once the budget is prepared, it is typically divided by the number of subjects to be recruited as stipulated by the proposed clinical trial agreement (CTA) for a per subject budget. Other times the budget may be presented as a per-subjects visit and procedure accounting. In either case, the site's IRB fees must be added to the total and the budget proposal can be assessed. These budgets usually require active negotiation between the site and sponsor. I had the opportunity to review, develop, and negotiate two clinical trial budgets for the site under the guidance and supervision of my internship mentor.

Once the sponsor and site agree upon a budget, a recruitment strategy should be determined to serve as the basis for developing recruitment materials, as all materials must be submitted to the IRB for approval as a part of an IRB application packet. When all recruitment materials are prepared and the appropriate paperwork is signed and collected, a copy of the budget, protocols, the IRB application, Conflict of Interest forms, CVs, CITI certificates, and the CTA are sent to a contracts manager for IRB preparation. Simultaneously, the start-up paperwork required by the sponsor, including a signed copy the CTA, completed FDA form 1572, Conflict of Interest forms, CVs, laboratory normal values, protocol agreement, and a list of IRB members, must be gathered and returned to the sponsor. During the internship I gathered and completed these forms for two clinical trials, routing them appropriately after mentor review and approval.

A significant amount of pre-trial preparation consists of devising a plan for implementation of the protocols by reviewing all of the requirements and establishing a

system of checks and balances to insure that steps of the process are not missed. This generally includes development of line item check sheets, recruitment logs, and, oftentimes, official source documents for subject-specific information that will be turned in to the sponsors.

- Schedule of Events, Appendix E
- Study Recruitment Requirements, Appendix F
- Study Intake Forms, Appendix G

Sometimes a coordinator can complete all of the preceding activities in anticipation of trial start-up just to have the trial be either suspended for an indefinite period of time or cancelled. This happened at the site after all of the preparatory steps had been completed when a sponsor pushed back the trial start date for 4 months once and indefinitely a second time. It is also possible to go through the preceding steps before determining that it would be best to withdraw from further participation in a study before returning a copy of IRB approval and a signed CTA to the sponsor. Such was the case in one of the studies that was processed by the site. In this particular case, the time until enrollment cut-off was shortened, the category of subjects required was changed to a more difficult group to recruit, and coordinator conference calls with other sites illuminated significant impediments to the accrual of subjects, despite coordinators doubling their recruitment campaign efforts. When a trial is cancelled for any reason, a letter of cancellation must be submitted to the IRB and Office of Clinical Trials. A "Notification of Cancellation" was written and submitted by me in both cases for these two studies.

Recruitment, Subject Visits, and Day-to-day Management. For studies that are successfully initiated, recruitment is often the most critical aspect of clinical coordination. During this internship I was able to develop recruiting strategies and marketing materials for two studies. However, the studies were either cancelled or suspended, and I was not able to participate in active recruitment for either of them. Unfortunately, this also robbed me of the opportunity to participate in the Informed Consent process, subject visits, trial management, reporting, and study closeout for the trials I was intended to help manage. Because there are many other trials taking place in the same department, I was able to participate in all of these activities at some time during the internship and to some degree, but not routinely for one study. Nonetheless, I was exposed to every aspect of the clinical coordinator's position. During the course of my internship, I contributed to the team most in the areas of strategy development, construction of implementation tools and resources, and trial initiation activities. In the end, I came away feeling confident that I could successfully manage a clinical research trial independently.

Contract Management

Due to trial suspensions and a cancellation, the initial plan to participate in daily management of subject visits was altered to include a number of other activities in order to fulfill the time required with relevant trial management experience. The bulk of that time and experience was satisfied in contracts management doing IRB submission preparations and revisions for the Office of Clinical Trials.

Initial IRB Submissions. After coordinators collect the required IRB paperwork, such as the protocol, Investigator's Brochure, CVs, training certifications, Conflict of

Interest forms, CTA, budget, and recruitment materials, they send them to a contracts manager, who is responsible for getting the IRB submission packet in order. This process consists of the following:

- Electronic IRB application preparation
- Writing the Protocol Synopsis
- Writing an Informed Consent for the study
- Writing a HIPAA/Use of Protected Health Information Addendum for the Informed Consent
- Collecting the required materials that will accompany the IRB submission, such as letters of agreement to participate for any associated facility, copies of protocols for any physical or psychological test, procedure, or evaluation that will be done in the course of the study, and all fore-mentioned paperwork supplied by the coordinators.
- Preparing 20 copies of the submission packet for IRB members and one for the chairman that includes CVs, certifications for key personnel, etc.

Throughout my time in this role, I prepared five submissions under the supervision of a contracts manager.

Once a study is reviewed by the IRB, they return a Board Action statement that lists any requests for modifications to the protocol, synopsis, consent form, or any other inclusions or omissions that they feel are necessary for the protection of human research subjects. These modifications must be submitted to the IRB as red-line edited versions of the originals that clearly show all changes. This version is submitted with a clean copy of

the revised documents for final IRB approval. I completed two of these IRB Request for Modifications during the internship.

Sponsor-initiated Changes in Protocols. It is also very common for sponsors to make modifications to protocols during a study. In this event, the Contracts Manager must prepare a cover letter to the IRB that lists every change, where it is found, and whether or not it will require modifications to the synopsis, consent, or other documents. The documents are then red-line edited to show the changes and submitted to the IRB. The IRB then decides if the changes can be made under an "expedited review" or if the quorum must vote on the approval of those changes. Either way, the process is the same as the initial review process. An IRB Board Action statement is issued with requests for any modifications necessary, and the documents are again edited and submitted as needed. I successfully completed one sponsor request for modifications to the protocol for the Office of Clinical Trials.

The experiences I had in contracts management was very valuable because it allowed me to get very familiar with the procedures and terminology that the IRB scrutinizes. I am now able to review protocols and foresee where the IRB will contend and know how to negotiate these points with a sponsor prior to even submitting a contract to the Office of Clinical Trials or submitting a protocol to the IRB. I am also able to review Informed Consent forms and research synopses to determine where modifications would be required before an approval could be issued.

Institutional Management of Research

Institutional Approval of Research. The internship site is governed by the institutional regulations of the University of North Texas Health Science Center. Within the institution, clinical trial agreements are routed to many departments for review before the university will allow that research to be conducted on the premises. After a contract, or CTA, is successfully negotiated by the coordinator and contract manager, a specific routing form is made to accompany the CTA to all appropriate departments and personnel. The CTA must be reviewed by the Director of the Office of Clinical Trials, the Dean of TCOM, the institution's legal council, the Principle Investigator, the Associate Dean for Clinical Research, the Associate Vice President for Research and Biotechnology, and the Executive Vice President for Finance and Administration. During the internship, one of the sponsors offered a $2000 incentive to the site if they could complete the entire contract and budget negotiation, IRB submission, and contract routing and return all of the trial initiation documentation and FDA application within 30 days. Under the supervision of my mentor and the contracts manager, I personally prepared, collected, an hand-delivered the appropriate documentation to each of the institutional representatives, IRB, and sponsor within that time frame for the incentive bonus—despite a 2-week delay by the sponsor's legal department on approving the Informed Consent before IRB submission. Not only was this a huge challenge, it was an excellent opportunity to become familiar with each department, their roles in the approval process, institutional policy, and potential sources of delay in the process.

Institutional Review Board Approval of Research. The IRB for the site meets once monthly for approximately 4 hours to review potential research studies, changes to protocols, annual reviews, and adverse events. I attended two of these meetings during my internship. During both meetings, I participated in two capacities:

a. Observer of the process. Watching the interaction of the IRB members afforded me the privilege of insight into the different perspectives and types of concerns members from the community, clinicians, researchers, legal representatives, and administrators have when reviewing the same research proposals.

b. Representative of proposed research. At each meeting there was a submission that I had prepared for the site for review. When the IRB reviewed the projects, I stepped up as the representative to answer any questions on the protocol, recruitment strategy, and regulatory documentation. My mentor was at these meetings as an IRB member and observed my performance from that standpoint.

Data and Records Management

Archiving Data. Prior to the start of my internship there were two studies that had been closed out. The institution requires that study materials, including subject records and regulatory documentation, must be securely stored for 7 years after closeout. The archiving process consists of filling out the proper paperwork, itemization of study materials on a Records Transmittal form, delivery to the Records Management department, and filing the receipt of records received. I completed this process for both sets of study materials at the site.

Data Entry and Records Management. Implementation of the practicum project required a detailed review of archived study records from previous trials at the institution in an effort to collect recruitment data that could help identify possible barriers to the recruitment of geriatric subjects or substantiate existing theories on what factors contribute to the special challenges associated with recruitment and retention of geriatric subjects in clinical research. In doing so, subject records from all previous studies done at the university over the past 7 years that included subjects over the age of 65 were reviewed and data was compiled on the number of subjects contacted, pre-screened, screened, enrolled, and withdrawn from these studies, as well as reasons for refusal to participate, screen failure, and withdrawal. This process was profoundly important in helping me understand the intricacy of recruitment and retention of this special population, as well as the records archiving and storage procedures for clinical trials data.

In lieu of time spent participating in subject visits for the suspended trial, I also logged over 100 hours performing duties in data entry and records management to assist the site with ancillary functions of clinical research. For example, new patients coming into the clinic needed to be entered into either one or both of the existing research databases in geriatrics or psychology. I coordinated with scheduling to get the names of patients recently seen and retrieved their charts from medical records to be entered into the database. Including these patients in the database required a de-identification process that is common to all human research studies by assigning them an identification number stored in a separate data set and only using the assigned identification number in the actual database. Entering data in the database exposed me to quality-control concepts, such as inter-rater reliability measures and the importance of clearly defined terminology.

It was very helpful for me to become familiar with these processes and with procedures related to records management, storage, and tracking, as these are essential elements of successful data coordination in any research study that involves the use of human subjects and/or databases.

APPENDICES

APPENDIX A: INTERNSHIP TIME/ACTIVITY LOG

Date	Activity	From-To	Hours	Initials
7/17	Committee meeting	2-3	1	
8/1-8/28	Research, review, preparation of materials, e-mails	varied	20+	
8/4	Protocol review	2-6	4	
8/6	Question prep for pre-trial meeting	4-7	3	
8/7	Pre-trial meeting/ site visit with Novartis	9-12	3	
8/30	Meeting with Dr. Gwirtz	9:05-9:45	0:40	
8/30	Meeting with Dr. Dimitrijevich	9:50-10:35	0:45	
8/30	Meeting with Carla Lee and *Designation of Committee* filed	10:40-11:20	0:40	
8/30	Budget preparation	1-5:45	4:45	
8/31	Time Log (hand-written and electronic) created	9-10:30	1:30	
9/1	IRB, ORB, HIPAA, and various resources explored on UNTHSC website	3-5:30	2:30	
9/1	Budget proposal sent to Barb and several e-mails in correspondence	varied	1	
9/4	Research for running study: recruiting and staff training	9:30-12:45	3:15	
9/5	Status letter to Dr. Knebl and Barb and 3 other e-mails to Barb	varied	1	
9/5	39 resources set up in RefWorks for research proposal/dissertation	2-6:45	4:45	
9/6	Outline for research proposal created	10-4:35	6:35	
9/6	Read resources/researched/began writing research proposal	6-8	2	
9/7	Met with Barb and made Recruiting/Retention Info sheet	9:15-12:15	3	
9/7	Worked on research proposal	1:30-4:45	3:15	
9/8	Met with Barb throughout day, pulled past studies, compiled study data	9:15-5:15	8	
9/9	Research proposal	3-7:20	4:20	
9/10	Research proposal	2-8:30	6:30	
Total of Hours: 85.30+				

Date	Activity	From-To	Hours	Initials
9/11	Meeting with Dr. Gwirtz	9-9:35	0:35	
9/11	Project- contacting CDER, NIH, AARP, CISCRP, CDC, & more	9:45-5:15	7:30	
9/12	E-mails to recruiting companies for information	11-1:15	2:15	
9/14	Project: NIH reference department comm./links, research proposal	10:45-6:30	7:45	
9/15	Project and research proposal	8:45-12	3:15	
9/15	Project and research proposal	1-6:15	5:15	
9/16	Research proposal	11:45-9:30	9:45	
9/17	Research proposal	12:30-7:30	7	
9/18	Project research, proposal, e-mails to Novartis, AARP, etc.	9:30-4:55	7:25	
9/19	Research proposal, basis of dissertation, and project R&D	2-4:15	2:15	
9/19	Research proposal, basis of dissertation, and project R&D	9-10:30	1:30	
9/20	Research proposal, basis of dissertation, and project R&D	7-10:45	3:45	
9/21	Research proposal, basis of dissertation, and project R&D	7:30-11:00	3:30	
9/21	Research proposal, basis of dissertation, and project R&D	3-7:15	4:15	
9/22	Research proposal and correspondence	7:45-11:30	3:45	
9/23	Dissertation	3-7	4	
9/24	Dissertation	12-2:30	2:30	
9/24	File folder for communication and references	9:30-11:30	2	
				37
Total of Hours: 78.15				

Date	Activity	From-To	Hours	Initials
9/25	Meeting with Dr. Gwirtz	9-9:40	0:40	
9/25	Correspondence	9:45-10:15	0:30	
9/26	Practicum project/recruiting proposal R&D	8:45-3	6:15	
9/27	Practicum project/recruiting proposal R&D	9-3:30	6:30	
9/28	Practicum project/recruiting proposal/dissertation R&D	10:45-2:30	3:45	
9/28	Practicum project/recruiting proposal/dissertation R&D	5-7:15	2:15	
9/29	Practicum project/recruiting proposal/dissertation R&D	9-4:15	7:15	
8/2	Meeting with Dr. Gwirtz	9-9:10	0:10	
8/2	Practicum project/recruiting proposal/dissertation R&D	9:15-3:00	5:45	
8/2	Practicum project	4-5	1	
8/2	Proposal prep for meeting	8-10	2	
8/3	Archived records review for project	12-4	4	
8/4	Archived records review for project	12:30-4:45	4:15	
8/5	Archived record review for project and sent proposals to com. members	1-3:55	2:55	
8/6	Communications, research proposal delivered to mailboxes, reading	9:30-1:00	3:30	
8/7	Project objectives, *Potential Subject* form made, *Revisions* form made	12-4:30	4:30	
8/8	Practicum report/dissertation and project development	9-11:45	2:45	
Total of Hours: 58				

Date	Activity	From-To	Hours	Initials
8/9	Meeting with Dr. Gwirtz	9-9:45	0:45	
8/9	Recruiting Project- Databases	9:55-1:00	3:05	
8/11	Printing, E-mails, project-databases, and meeting prep	9-1:30	4:30	
8/11	Meeting prep and meeting, etc.	3-6:30	3:30	
8/14	Review of Editing comments and suggestion	11-3	4	
	*Very ill for 5 days of this week and PA interview day on 8/16			
8/17	Revisions- editing proposal and bibliography, etc.	8:45-3:15	6:30	
8/18	Revisions to project design, etc. and e-mails	10:30-3:45	5:15	
8/19	Project/dissertation development, database searches	9-2:30	5:30	
8/19	Database searches & literature review	10-11:45	1:45	
8/23	Locating archived studies, database search, project development	9-12	3	
8/23	Locating archives, meetngi with D. Shingleton, project development	2-6:30	4:30	
8/24	Meeting with Dr. Gwirtz	9-9:45	0:45	
8/24	Project development	10-4	6	
8/26	CRM meeting with Gladhue, Review new protocols & meet w/ Fairchild	7:30-3	7:30	
8/27	HIPAA, IC, and IRB Submission forms, meeting w/ Wendy	10:30-4:30	6	
8/29	Preparing Conflict of Interest and HIPAA addendum for new protocols	9-2:30	5:30	
Total of Hours: 68:05				

Date	Activity	From-To	Hours	Initials
10/30	Meeting with Dr. Gwirtz	9-10	1	
10/30	Protocol synopsis for Studies 1 & 2 for AD research, lunch lecture	10-6:15	8:15	
10/31	Research project development- regulatory docs for Consortium studies	8:30-3	6:30	
11/1	Correspondence	9-10	1	
11/1	HIPAA training, research study initiation	11-7	8	
11/2	HIPAA and PHI forms created, CITI training	8:30-5	8:30	
11/2	CITI training on-line	9-10:15	1:15	
11/3	CITI training, correspondence	8:45-2	5:15	
11/4	Recruitment proposal	9-12	3	
11/6	Meeting with Dr. Gwirtz	9-9:55	0:55	
11/6	Protocol Synopsis template developed, meetings, and correspondence	10-6:20	8:20	
11/7	Lesson on business plans for studies, introduction to grant work	3:45-5:15	1:30	
11/8	Regulatory docs, research	8:30-3:15	6:45	
11/9	Collecting Letters of Invitation and development of mailing materials	7:30-7	11:30	
11/10	2 Telephone scripts and 2 Letters of Invitation written, IC edit	7:15-6	10:45	
11/11	Protocol synopsis redone to reflect merged protocols	6:30-5:45	11:15	
11/12	Informed Consent rewritten to reflect merged protocols and editing	6:45-5:30	10:45	
11/13	IRB packet prep, meeting with Dr. Gwirtz, meeting Wendy for IRB	7:15-6:45	11:30	
11/15	Research new proposal	2-8	6	
Total of Hours: 111:15				

Date	Activity	From-To	Hours	Initials
11/20	AD and Depression project ad research, correspondence	7:45-3:30	7:45	
11/22	Meeting with Dr. Gwirtz	9-2:45	5:45	
11/24	Amgen CIF and W9, budget review,	9-7	10	
11/25	Amgen protocol, ICF, Assent forms	10-6	8	
11/27	Meeting with Dr. Gwirtz, Amgen regulatory docs, etc.	7-5	10	
11/28	Amgen, cost spreadsheet for CRCs, committee meeting at 2	7:15-5:45	10:30	
11/29	Databases research, MDS review	7:45-5:15	9:30	
11/29	Time log updated and cross-referenced	6:30-7:15	0:45	
11/29	Quest correspondence about lab costs	7:45-8:30	0:45	
11/29	Revising budget	12:30-1:45	1:15	
12/4	Amgen application process, coordinator charge sheet, meetings	7:15-6:35	11:20	
12/5	Office scouting, credentialing, protocol review, 1st IRB meeting	7:00-5:30	10:30	
12/6	Database project research and development, correspondence	7:45-5:30	9:45	
12/7	ePro training, Amgen trial, project	10-7:10	9:10	
12/8	Meeting with Dr. Gwirtz, Amgen IRB submission application	7:30-5	9:30	
12/9	Amgen study- Informed consent, synopsis, HIPAA addendum, app.	10-5:30	7:30	
12/10	Amgen study- IC, synopsis, CV, IRB certs, COI forms, app.	8-4:45	8:45	
12/11	Database training, meeting w/ Wendy for IRB application, NH ads	8:30-5:45	9:15	
Total of Misc. Hours:			**140:45**	

Date	Activity	From-To	Hours	Initials
12/12	Meet Wendy for changes required for Amgen submission & copies, etc.	8-4:45	8:45	
12/13	Coordinators' meeting	10-6	4	
12/15	Coordinators' References started,	7-1	4	
12/16	Database project	9:30-12:30	3	
12/17	Business plan, recruit plan, database	10a-11:20p	13:20	
12/18	IRB revisions for AD	10-11:45	1:45	
12/18	IRB revisions for AD	3-4	1	
12/19	IRB revisions for AD	9:30-7	9:30	
12/20	Amgen correspondence, NH letters, lab set-up	7-6:30	11:30	
12/27	Database project and correspondence for trials	10:15-2:15	4	
12/29	Database project and correspondence for trials	9:30-2:30	5	
	Total of Misc. Hours: 63:50			

Date	Activity	From-To	Hours	Initials
1/2	Correspondence with Quest and account set-up questions, e-mails, etc	8:45-11	2:15	
1/3	Coordinators' References	7:30-11:30	4	
1/4	Coordinators' References	10-4	6	
1/6	Coordinators' References	9-12:30	3:30	
1/8	Tegaserod arrives! Protocol review and comments	8-9:45	1:45	
1/8	Tegaserod arrives! Protocol review and comments	10:30-5:15	5:45	
1/9	Pre-submission prep and IRB meeting	7:15-5	9:45	
1/10	Negotiating contract from CTA and budget	7:15-6:30	11:15	
1/11	Budget preparation and negotiations	8-4:30	8:30	
1/12	Database project meeting with Dr. Hall and Amgen correspondence	7:15-4:15	9	
1/12	Tegaserod contract tutorials (Wendy) on routing, legal, etc.	8-10p	2	
1/13	Contract preparation and Letter of Invite, CV, 1572	9a-11p	14	
1/14	COIs here and for Novartis file, corr., budget, etc. Novartis/Amgen	1:15-8p	8:45	
1/15	Tegaserod ICF, HIPAA,	8:15a-11:30p	15:30	
1/16	NH comm. for Amgen approval, recruiting plan, feasibility study	9-5	8	
1/17	IRB revisions for Amgen- synopsis	9-5:15	8:15	
1/18	Amgen conference and IRB revisions Amgen	8:30-6	9:30	
1/19	Discussions on feasibility, write-up, and Dropping Amgen study	8-11:50	3:50	
1/19	Tegaserod ICF, IRB app., Synopsis	3p-4a	13	
1/20	Database project	10:30-3:15	4:45	
1/21	Database project and Tegaserod ads and review of docs	9:30-7p	9:30	
	Total of Misc. Hours: 158:30			

Date	Activity	From-To	Hours	Initials
				SH
1/22	Letter of Cancellation Amgen, doc signing, Assent, meet Dr. Gwirtz	8-5:15	9:15	
1/23	Tegaserod set-up and comm., IRB re-submit. AD study	7:45-4:30	8:45	
1/24	Re-organize filing system, communications, research	7-5:20	10:20	
1/25	Coordinators meeting, lab cost sheet, comm..	7-11	4	
1/26	Assisting in writing protocol and revisions to synopsis, consent, etc	7-4:45	9:45	
1/27	Database project	1-3	2	
1/28	Database project, protocol collaboration and editing	9-7:30	10:30	
1/29	OCT meeting with Wendy to review changes and cover letter, etc.	7-5:15	10:15	
1/30	Novartis communication, Quest and Fed-ex accounts	7-10	3	
1/31	Novartis consent, budget, and CTA communications,	6:45-4	9:15	
2/1	Protocol change redline-packet preparation	8:15-6:30	10:15	
2/2	Protocol change redline-packet preparation, status update on all studies	7-7:30	12:30	
2/3	Prep for Q&A at IRB for protocols, learning site's database	7:15-9:30	2:15	
2/5	COIs,CITI, CV, etc. collected, routing contract for Novartis	7:15-5:00	9:45	
2/6	Re-organize office and cabinets for chart storage, comm. Novartis	8:30-6	9:30	
2/7	Learning records management procedures and OTC contract handling	7-10	3	
2/8	Pulling charts, learning data entry, making charts, routing contract	8-11	3	
2/8	Pulling charts, learning data entry, making charts, routing contract	1-6:45	5:45	
2/9	Learning neuro-psych database for chart entry, pulling charts	2-6:45	4:45	
2/11	Writing protocols for procedures for next intern, research	7:45-6:50	10:45	↓
				BR
	Total of Misc. Hours: 148:20			

Date	Activity	From-To	Hours	Initials
				BV
2/13	Pulling charts for entry	2:30-6:15	3:45	
2/14	Data entry	12:15-4:30	4:15	
2/15	Writing protocols for procedures for next intern and TARC	10:45-4:30	5:45	
2/16	Meeting with Wendy at 2-4 for protocol changes packet, revisions	2:7:15	5:15	
2/17	Data entry and make new tracking records for charts	10:15-7:30	9:15	
2/18	Database merger between neuropsych and MDS databases	9:45-6	8:15	
2/20	Coordinators' meeting with Troutman, strategy report	2-7:30	5:30	
2/22	Monthly Coordinators' meeting in OCT, data entry	7:30-9	1:30	
2/23	Database merger between neuropsych and MDS databases	12-4:30	4:30	
2/25	Database merger between neuropsych and MDS databases	6:30-5	10:30	
2/26	Data entry	2:30-5	2:30	
2/27	Pulling charts and data entry, protocol book completion	9:45-5	7:15	
3/2	Database merger between neuropsych and MDS databases	11-4:45	5:45	
3/4	Address and emergency contacts found and entered into enrollment log	12:30-5	4:30	
3/6	Address and emergency contacts found and entered into enrollment log	10:45-4	5:15	
3/7	IRB communications and sponsor contact	8:30-10:30	2	
3/8	Address and emergency contacts found and entered into enrollment log	7-9	2	
3/9	Database merger between neuropsych and MDS databases	11-4	5	
				BV
	Total of Misc. Hours: 92:45			

	Activity	From-To	Hours	Initials
3/13	Address and emergency contacts found and entered into enrollment log	7-9	2	
3/14	Address and emergency contacts found and entered into enrollment log	7-9	2	
3/15	Address and emergency contacts found and entered into enrollment log	7-9	2	
3/18	Address and emergency contacts found and entered into enrollment log	1-4	3	
3/20	Address and emergency contacts found and entered into enrollment log	12:30-3:15	2:45	
3/27	Address and emergency contacts found and entered into enrollment log	7:30-9:30	2	
3/29	Address and emergency contacts found and entered into enrollment log	8-10	2	
4/4	Neuropsych reports reviewed for enrollment	1:30-4:30	3	
4/6	Neuropsych reports reviewed for enrollment and database merger	11-4	3	
4/13	Database merger between neuropsych and MDS databases	11-3	4	
4/14	Database merger between neuropsych and MDS databases	8:30-3	6:30	
4/15-4/23	Completion of internship hours and focus on report, meetings with Dr. Gwirtz, and defense.			
Total of Misc. Hours: 32:15+				

APPENDIX B:

COORDINATORS' RECRUITING AND MARKETING STRATEGIES

Potential Subject Pools:

- All patients in PCC exam/waiting rooms viewing ad
- Physician referrals from within the PCC
- New patient, follow-up, and annual exams
- Locally affiliated facilities
- Medical code list from billing department
- Support groups— on-line or local meetings
- DPS local list of persons in age range and desired zip codes for mass mailings
- Staff/students/referrals through the University's news letter and postings
- Community at large though local radio, news, and postings
- Specialized publications, i.e. Senior Times, Diabetes Beat, OA Today, etc.

Methods of Marketing:

- Mailings, to include:
  - Letter of introduction and request for participation.
  - Phone number for message line if participants have any questions or want to schedule appointments.
- Phone contact if no reply from letter to follow-up one week after letter of invitation is sent.
- Message lines set up for potential subjects to contact study coordinators.
- Referrals during patient visits
- Sponsor's study introduction letter to physicians sent to outlying clinics
- Flyers in exam/waiting rooms at the PCC and in local facilities.
- University postings on campus and in *Daily News.*
- Local advertisement via radio, newspaper, support group meeting presentations, and postings, such as bus stop pull-tab sign (nationally the single most effective public recruitment advertisement method).

Patient Care Center Networking:

1. Contact floor managers for standing agreement on cross-referral system and permission to post recruitment materials.
2. Flyers in patient exam rooms and waiting rooms at the PCC.
3. Send initial notice of trial and procedures to nurses and physicians to introduce them to studies and remind them that they can pre-screen subjects and call coordinators for same-day patient Q&A session with study staff.
4. Bi-weekly reminders of study recruitment if no referrals from physician with appropriate patient base.

5. Incentive program: Thank you note, fruit/cookies, kudos at division meeting, etc. for those referring.

Strategies for effective recruitment of Patient Care Clinic patients:

New Patient clinic visit recruiting

1. Put note on entry page of chart reminding nurse and physician to pre-screen and refer potential subjects by calling the coordinator for same-day Q&A session/enrollment with study staff.
2. Potential subjects will receive consent immediately and/or set appointment for screening visit OR
3. Contact eligible subjects by letter, followed by phone call one week later if no reply from letter.
4. Schedule visit for Q&A, consent, screening, sample collection, etc.
5. Keep track of all problems encountered, including reason for refusal to participate for future evaluation of the success of the current strategy.

Review of follow-up, sick patient, and annual exams

1. Identify all potentially eligible subjects from the PI's existing patient base who will be due a follow-up, sick (for contact after current illness), or annual evaluation within the coming week (front desk will print list of upcoming appointments for you to pre-qualify).
2. Coordinate possible Q&A, consent, and evaluation times for promising subjects with practitioners.

Strategies for effective recruitment of locally affiliated facility patrons or residents:

1. Contact administrator for introduction and permission to recruit
2. Flyers posted at facility
3. Visit staff to introduce them to study
4. Referral network set up with staff.
5. Maintain cal-in line for potential subjects AND/OR
6. Contact eligible subjects by letter, followed by phone call one week later if no reply from letter.
7. Schedule visit for Q&A, consent, and evaluations.
8. Keep track of all problems encountered, including reason for refusal to participate.
9. Incentive program: Letters of commendation or Thank You card for participation to referring staff and supervisor, cookies/fruit.

Strategies for effective recruitment of support group members:

1. Notify chairperson of intent to present study and provide something at next meeting.
2. Present research and offer invitation through group new or at meeting.
3. Collect referrals and schedule appointments for consent and evaluations.
4. Keep track of all problems encountered, including reason for refusal to participate.

Strategies for effective recruitment of TxDOT subjects:

1. Request list of possible subjects from desired zip codes that are within the age group needed.
2. Contact eligible subjects by letter, followed by phone call one week later if no reply from letter.
3. Schedule visit for Q&A, consent, pre-screening, evaluation, and enrollment.
4. Keep track of all problems encountered, including reason for refusal to participate.

Strategies for effective recruitment medical billing subjects:

1. Contact Dennis Shingleton for call to the billing office to grant access.
2. Pull up all patients from the PCC who have had a billing code for condition being studied.
3. Contact eligible subjects by letter, followed by phone call one week later if no reply from letter.
4. Schedule visit for Q&A, consent, pre-screening, evaluation, and enrollment.
5. Keep track of all problems encountered, including reason for refusal to participate.

Tracking

- Recruitment log that includes name and contact information, attempts to contact information, date, method of contact, outcome, and reason for refusal.

Bi-Weekly review of strategy success:

- Review comments from previous month by the referring staff, recruitment tracking forms, and other staff to adjust strategy as needed.

APPENDIX C: COORDINATOR'S COMMON COST SHEET

Procedures			
Complete physical	227	Weight, height	20
Vital signs	20	Guiac x 3	96
Blood draw	23	EKG	67
Blood handling	36	CT	x
Carotid ultrasound	614	MRI	x
Medical History taken	23	X-rays	x
Personnel Hourly Rates			
Principle investigators	126	Nurse/Infusion nurse	27
Clinical coordinators	46		
Current F&A			
IRB Prep & Submission	3000	Informed Consent	96
Amendments each	100	Re-consenting	46
Periodic Reviews each	100	Overhead	25%
Lab Charges & Test Codes for Quest Account #xxxxx			
B_{12} 7065	55		
CBC 1759	4.30	Ferritin- serum 457	30
CRP 17401	20	Folate 466 or 467	30
Creatinine- serum 37091	30	PT/PTT 4914	15
Electrolytes 34392	14.29	Rheumatoid panel 17669	65
Fibrinogen 461	15	Reticulocytes 793	6
Iron- serum 571	10	Sedimentation rate 809	10
Haptoglobin 502	20	SMAC 10231	2.50
Hemoglobin 510	3.75		
Lipid Panel 7600	30	TIBC (total iron binding) 7573	19.40
Manual differential 465	8	TSH 899	10
Supplies			
EKG electrodes (100)	7.65	Dry ice	x
Gloves (100)	5.95	Ream of paper	3.25
Vacutainer Sets 21 guage (50)	72.80		
IV Solution NaCl 1000cc bag	36.65		
22" IV caths (50)	145		
20-ml syringes (40)	15.80		
Sterile water preps (25-pack)	25.65		
Pharmacy IV Prep fee (for prep of specific infusion)	40		

APPENDIX D:

Clinical Coordinators' Common Contacts and Account Information

Coordinators

Barbara Harty- Geriatrics
Office in PCC #4-302 at ext. 2193
Fax #817-735-5441
bharty@hsc.unt.edu

Christopher Hayes- Surgery
Office in PCC-584 at 817-735-5476
chayes@hsc.unt.edu

Cynthia Jimenez- Rheumatology
Office in PCC #4-387 at 817-735-0317
cjimenez@hsc.unt.edu

Della Weis-
Office in CBH540 at 817-735-0304
Fax# 817-735-0276
fweis@hsc.unt.edu

Enisa Arslanagic- Internal Medicine
Office in PCC 4-376 at ext. 5159
earslanagic@hsc.unt.edu

Jessica Alexander- Alzheimer's Consortium
Office in "the blue house" at ext. 0275
Fax # 817-735-0167
Cell # 817-xxx-xxxx
jealexan@hsc.unt.edu

Sandra Powell- Pediatrics/Internal Medicine
Office in PCC #4-380 at 817-735-0591
Fax # 817-735-2098
spowell@hsc.unt.edu

Clinical Trials Support Staff

Billing Staff for Internal Medicine:
Marla Collier (or Hope)
Office in PCC #4-349 at ext. 2646

Budget Approval/Finance & Administration:
Steve Russell
Office in EAD #826 at ext. 2525
srussell@hsc.unt.edu

Chief of Staff and Director of Office of Clinical Trials:
Dennis Shingleton
Office in EAD #856 at ext. 2672
dshingle@hsc.unt.edu

Clinical Trial Administrative Specialist
Romona Gibson
Office of Clinical Trials in CBH-140 at ext. 2358
rgibson@hsc.unt.edu

Contract Administrator:
Wendy Hammons-Stoecker
Office of Clinical Trials in CBH-141 at ext. 5474
Fax # (817) 735-0292
whammons@hsc.unt.edu

Director OPHS:
Brian Gladue
Office in CBH-142 at 817-735-5083
bgladue@hsc.unt.edu

Grants & Contract for Payee/Funding:
Sarah Panepinto
Office of Clinical Trials in CBH-145 at 817-735-2561
spanepin@hsc.unt.edu

Industrial Storage/ITS (archived trial materials):
Steve Woodall
Office in LIB 122A at ext. 5011
Fax #817- 735-2494
swoodall@hsc.unt.edu
Provide date and protocol number to retrieve materials

IRB Chairman:
Jerry McGill
Office in ENX 106 at 817- 735-2496
mcgillj@hsc.unt.edu

Legal Affairs for Review of Contracts:
Jon McGough
Office in EAD #210 at 817-735-5028
Fax #817-735-0433
jmcgough@hsc.unt.edu

Legal Representative for Institution:
Marc Hahn, DO
Office in EAD #864 at ext. 2416
mhahn@hsc.unt.edu
Assistant is Corrie

Vice President of Research:
Glenn Dillon
Office of Clinical Trials in CBH 145 at ext. 2055
gdillon@hsc.unt.edu
Assistant is Nancy at ext. 5484

Support Services

Courier service:
Fed Ex # 800-463-3339
Account #xxx-xx

Imaging:
Radiology Associates (X-rays, CT, and MRI)
3400 Camp Bowie Blvd. Ste. 100
Fort Worth, TX 76107
(817) 885-7739 or 321-0405
Account manager is Laurie

Monticello Imaging (specialized MRI)
3712 W. 7th St.
Fort Worth, TX 76107
(817) 377-3800
Account manager is Terry and Dr. Paul Morris for contracts

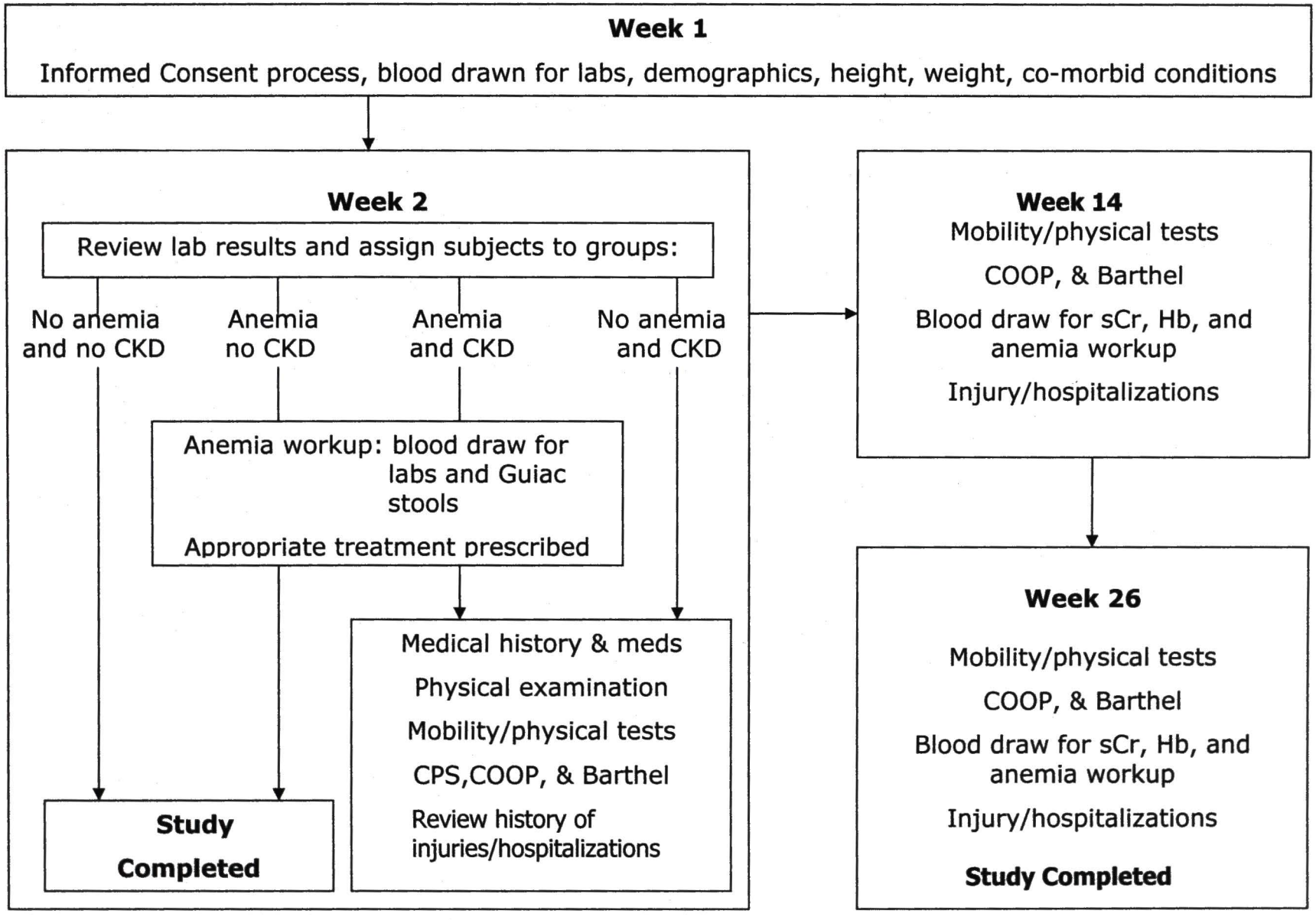
Laboratory:
Quest Diagnostics
Account #xxxxx for geriatrics and #xxxxx for 2nd floor central clinic
Downstairs lab at (817) 731-0518 managed by Leena
Routed to central lab at 4770 Regent Blvd., Irving (972) 916-3200
Account representative- Robyn McNeill at (817) xxx-xxxx
robyn.x.mcneill@questdiagnostics.com
District manager- Monica Richmond at (800) 824-6152

Pharmacy (Infusion prep or delivery of supplies):
Dan Hooper
GSB 147A at ext. 2248

Miscellaneous Accounts and Information

Tax ID/EIN #xx-xxxxxxx

APPENDIX E: SCHEDULE OF EVENTS 1



APPENDIX F:

Study Recruitment Requirements

Whole Genome Project	CVD, Infammatory, & AD
Include: Age 55 – 105 Subjects with probable or possible AD Controls without signs/symptoms of AD	Include: Previous qualifications AND Clinical Dementia Rating of 1 or 2 OR MMSE score $\geq$ 11 Controls with CDR = 0
Screen potential subjects Using health history, Hachinski AND MMSE/CDR	Screen potential subjects using CDR
Exclude: Hachinski Ischemic Score > 4 History of major cortical infarction, diagnosed either by neuroimaging or clinical stroke with persistent focal neurologic deficit	Exclude: Concomitant neurological disease Chronic inflammatory disorders Urinary infections Current cancer
Recruit:	Recruit from other study participants:
125 AD subjects →	25 of the AD subjects
25 non-AD subjects →	Same 25 non-AD subjects

APPENDIX G: STUDY INTAKE FORMS

Study Subject Information

Subject Name_____

Date of Birth: _____-_____-_____

I. Contact Information

Address of Subject _____

_____

_____

Name of Caregiver_____

Telephone_____**Cell**_____

Name of Legal Representative_____

Address of Legal Representative_____

_____

_____

Telephone_____**Cell**_____

Alternate Contact_____

_____

_____

II. Demographics

***Age: _____ (Must be over 55)**

Sex: ☐ Male ☐ Female

Primary Language: ☐ English ☐ Other ☐ Spanish ☐ Unknown

Race: ☐ White ☐ Indian/Alaskan ☐ Black ☐ Asian/Pac. Islander ☐ Hispanic ☐ Other

Education:

Highest grade or number of years of regular school completed _____

Marital Status:

- ☐ Married
- ☐ Widowed
- ☐ Divorced
- ☐ Separated
- ☐ Never Married
- ☐ Other, e.g. not married but cohabitating
- ☐ Missing or unknown

Residence:

- ☐ Private residence
- ☐ Retirement community
- ☐ Assisted living/boarding home/ adult family home
- ☐ Skilled nursing facility/nursing home
- ☐ Other
- ☐ Missing/unknown

Medical History
And *Exclusionary Criteria

I. Cardiovascular

CAD □ Yes □ No
PVD □ Yes □ No
Hypertension □ Yes □ No
Hyperlipidimeia □ Yes □ No
Angina □ Yes □ No
AMI □ Yes □ No
Date: _____-_____-_____
***CVA** □ Yes □ No
TIA □ Yes □ No
Other □ Yes □ No
Diagnosis: _____

II. Inflammatory

***Rheumatoid arthritis** □ Yes □ No
***Multiple sclerosis** □ Yes □ No
***Polymyalgia rheumatica** □ Yes □ No
***Chronic or current UTI** □ Yes □ No
***Other acute** □ Yes □ No

Diagnosis: _____

III. Other

***Cancer** □ Yes □ No (Cannot be current)

Type: _____

***Hachinski test:**

Abrupt onset □ 2
Stepwise deterioration □ 1
Fluctuating course □ 2
History of strokes □ 2
Somatic complaints □ 1
Focal neurological signs □ 2
Relative preservation of personality □ 1

Evidence of associated atherosclerosis □ 1
History of hypertension □ 1
Nocturnal confusion □ 1
Emotional incontinence □ 1
Focal neurological symptoms □ 2
Depression □ 1

***Total score:** _____ **(Must <u>not</u> be > 4)**

Study Subject Database Intake Form

**Exclusionary Criteria*

Date of initial evaluation: _____-_____-_____

MMSE at initial evaluation: _____

Date of most recent evaluation: _____-_____-_____

MMSE at most recent evaluation: _____

Did the subject meet clinical criteria for dementia at most recent evaluation? ☐

Yes ☐ **No**

If not, what was the diagnosis?

- ☐ **Not demented control subject, no neurological disorder**
- ☐ ***Not demented, but has a neurological disorder**
- ☐ **Questionable dementia or cognitive impairment**
- ☐ ***Down Syndrome, but not demented**
- ☐ **Other**
- ☐ **No diagnosis made**
- ☐ **Missing/unknown**

At what age did the subject develop dementia? _____

Was the primary clinical dementia diagnosis Alzheimer's disease at the most recent evaluation?

- ☐ **Alzheimer's disease (NINCDS probable AD or DSM IV dementia of Alzheimer's type)**
- ☐ **Alzheimer's disease with other conditions or variations in course**
- ☐ ***Non-Alzheimer's dementia**
- ☐ **Missing/unknown**

Does the subject meet criteria for Lewy bodies, Lewy body variant Alzheimer's disease, or diffuse Lewy body disease? ☐ **Yes** ☐ **No**

If diagnosis of non-Alzheimer's dementia, what is the etiology?

- ☐***Frontal lobe dementias**
- ☐***Parkinson's disease dementia**
- ☐**Huntington's disease**

☐Progressive supranuclear palsy

☐*Alcohol related dementia

☐Corticobasal degeneration

☐Communicating, obstructive, or normal pressure hydrocephalus

☐*Vascular dementia

☐Dementia with Lewy bodies

☐Prion-associated dementia

☐Human immunodeficiency virus encephalopathy

☐Primary progressive aphasia

☐Posterior cortical dysfunction

☐*Down syndrome

☐*Dementia due to multiple non-Alzheimer's etiologies

☐*Dementia due to other general medical conditions

☐Other/not specified

☐Missing/unknown

Does the subject have a history of *stroke? ☐ Yes ☐ No

Does the subject have a history of *Parkinson's? ☐ Yes ☐ No

Did the subject have depression at the most recent evaluation? ☐Yes ☐ No

Did the subject have delirium at the most recent evaluation? ☐Yes ☐ No

Do parents, children, or siblings have dementia? ☐ Yes ☐ No ☐ Unknown

How many first degree relatives are reported to have dementia? _____

Is the subject from a multiple birth? ☐ Yes ☐ No ☐ Unknown

Has apolipoprotein-E genotyping been done? ☐ Yes ☐ No

Are data from neuropsychological (not MMSE) test results available?

☐ Yes ☐ No

Data from the following neuroimaging studies are accessible:

☐CT-Computed tomography

☐PET-Positron emission tomography

☐SPECT-Single photon emission computes tomography

☐MRI-Magnetic resonance imaging

Neuropsychological tests performed:

Global cognitive functioning/status

□ MMSE Score: _____

Date of last: _____-_____-_____

□ CDR Score: _____

Date of last: _____-_____-_____

Attention

□ Digit Span Score: _____

Date of last: _____-_____-_____

□ Trails A Score: _____

Date of last: _____-_____-_____

Executive function

□ Trails B Score: _____

Date of last: _____-_____-_____

□ Clock Drawing Score: _____

Date of last: _____-_____-_____

Memory

□ WMS Logical Memory I Score: _____

Date of last: _____-_____-_____

□ WMS Logical Memory II Score: _____

Date of last: _____-_____-_____

Language

□ Boston Naming Score: _____

Date of last: _____-_____-_____

□ FAS Verbal Fluency Score: _____

Date of last: _____-_____-_____

Pre-morbid IQ

□ AMNART Score: _____

Date of last: _____-_____-_____

□ WTAR Score: _____

Date of last: _____-_____-_____

□ WRAT-3 Score: _____

Date of last: _____-_____-_____

□ Reading Recognition Score: _____

Date of last: _____-_____-_____

Depression

□ Geriatric Depression Scale (GDS) Score: _____

Date of last: _____-_____-_____

*Hachinski test score: _____ (Must not be > 4)

Date of last: _____-_____-_____

What is the source of subject data?

□Clinical core

□Satellite

□Center-affiliated study

□Other

□Missing/unknown

Date of last contact: _____-_____-_____

Status of subject:

□Active—further in-person visits expected

□Active—further visits expected on phone or other

□Deceased—autopsy pending

□Deceased—autopsy complete with neuropathology information available

□Deceased—autopsy complete with neuropathology information not available

□Inactive—deceased with no autopsy

□Inactive—no further data expected, but alive at last contact

Last known vital status: ☐ Alive ☐ Dead

Date of death: _____-_____-_____

Has an autopsy been performed? ☐ Yes ☐ No

Has an antemortem brain autopsy been performed? ☐ Yes ☐ No

What was the primary neuropathological diagnostic classification?

- ☐ *Normal brain
- ☐ Alzheimer's disease- definite
- ☐ Alzheimer's disease- probable
- ☐ *Alzheimer's disease- possible
- ☐ *Idiopathic Parkinson's disease with cortical and/or subcortical Lewy bodies
- ☐ Dementia with Lewy bodies and AD
- ☐ Dementia with Lewy bodies without significant AD changes
- ☐ *Vascular dementia
- ☐ Pick's diseases
- ☐ Lobar atrophy without Pick's bodies
- ☐ Hippocampal sclerosis
- ☐ Progressive supranuclear palsy
- ☐ Corticobasal degeneration
- ☐ *Prion-associated dementia
- ☐ *Down syndrome
- ☐ Other
- ☐ *Stroke or cerebrovascular disease, but not vascular dementia
- ☐ Autopsy report pending
- ☐ Missing/unknown

What is the secondary neuropathological diagnostic classification?

- ☐ None
- ☐ *Alzheimer's pathology, but insufficient for AD diagnosis
- ☐ *Idiopathic Parkinson's disease with cortical and/or subcortical Lewy bodies
- ☐ Dementia with Lewy bodies and AD
- ☐ Dementia with Lewy bodies without significant AD changes
- ☐ *Vascular dementia
- ☐ Pick's diseases

☐ **Lobar atrophy without Pick's bodies**

☐ **Hippocampal sclerosis**

☐**Progressive supranuclear palsy**

☐**Corticobasal degeneration**

☐**Prion-associated dementia**

☐***Down syndrome**

☐**Other**

☐***Stroke or cerebrovascular disease, but not vascular dementia**

☐ **Autopsy report pending**

☐**Missing/unknown**

Is banked frozen brain tissue accessible? ☐ **Yes** ☐ **No**

Is formalin-fixed brain tissue accessible? ☐ **Yes** ☐ **No**

Are paraffin-embedded blocks of brain tissue accessible? ☐ **Yes** ☐ **No**

Is banked post-mortem cerebrospinal fluid accessible? ☐ **Yes** ☐ **No**

Is banked antemortem cerebrospinal fluid accessible? ☐ **Yes** ☐ **No**

Is banked DNA accessible? ☐ **Yes** ☐ **No**

Is banked serum accessible? ☐ **Yes** ☐ **No**

LITERATURE CITED

1. Avorn J. Including elderly people in clinical trials. British Medical Journal. 1997 Oct 25;315(7115):1033-4.

2. Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, et al. The causes and effects of socio-demographic exclusions from clinical trials. Health Technol Assess. 2005 Oct;9(38): iii,iv, ix-x, 1-152.

3. Beasley, D. (2006). Recruiting Special Patient Populations: Common barriers to enrollment can be overcome by using targeted recruitment strategies. Applied Clinical Trials, online. Retrieved September 5, 2006 from http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=334572&sk=&date=&pageID=2

4. Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: A descriptive study of published reports. British Medical Journal. 1997 Oct 25;315(7115):1059.

5. Cohen-Mansfield J. Recruitment rates in gerontological research: The situation for drug trials in dementia may be worse than previously reported. Alzheimer Dis Assoc Disord. 2002 Oct-Dec;16(4):279-82.

6. Ershler WB. Capecitabine use in geriatric oncology: An analysis of current safety, efficacy, and quality of life data. Critical Reviews in Oncology/Hematology. 2006/4;58(1):68-78.

7. Fiske A, Gatz M, Aadnoy B, Pedersen NL. Assessing age of dementia onset: Validity of informant reports. Alzheimer Dis Assoc Disord. 2005 Jul-Sep;19(3):128-34.

8. Fitzpatrick AL, Fried LP, Williamson J, Crowley P, Posey D, Kwong L, et al. Recruitment of the elderly into a pharmacologic prevention trial: The ginkgo evaluation of memory study experience. Contemp Clin Trials. 2006 Jul 4.

9. Gismondi PM, Hamer DH, Leka LS, Dallal G, Fiatarone Singh Meydani SN. Strategies, time, and costs associated with the recruitment and enrollment of nursing home residents for a micronutrient supplementation clinical trial. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2005;60(11):1469-74.

10. Godlovitch G. Age discrimination in trials and treatment: Old dogs and new tricks. Monash Bioeth Rev. 2003 Jul;22(3):66-77.

11. Guidance for Institutional Review Boards and Clinical Investigators 1998 Update. Retrieved March 17, 2007, from http://www.fda.gov/oc/ohrt/irbs/appendixc.html

12. Hebert R, Dubois MF, Wolfson C, Chambers L, Cohen C. Factors associated with long-term institutionalization of older people with dementia: Data from the canadian study of health and aging. J Gerontol A Biol Sci Med Sci. 2001 Nov;56(11):M693-9.

13. HIPAA Security Guidance for Remote Use of and Access to Electronic Protected Health Information Retrieved March 17, 2007, from http://www.cms.hhs.gov/SecurityStandard

14. Keith SJ. Evaluating characteristics of patient selection and dropout rates. J Clin Psychiatry. 2001;62 Suppl 9:11,4; discussion 15-6.

15. Kim SY, Caine ED, Currier GW, Leibovici A, Ryan JM. Assessing the competence of persons with alzheimer's disease in providing informed consent for participation in research. Am J Psychiatry. 2001 May;158(5):712-7.

16. Kornblith AB, Kemeny M, Peterson BL, Wheeler J, Crawford J, Bartlett N, et al. Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. Cancer. 2002 Sep 1;95(5):989-96.

17. Leber PD, Davis CS. Threats to the validity of clinical trials employing enrichment strategies for sample selection. Control Clin Trials. 1998 Apr;19(2):178-87.

18. Mitchell SL, Sullivan EA, Lipsitz LA. Exclusion of elderly subjects from clinical trials for parkinson disease. Arch Neurol. 1997 Nov;54(11):1393-8.

19. NIH 1999 Almanac- Legistative Chronology. Retrieved March 17, 2007, from http://www.nih.gov/about/almanac/archive/1999/historical-data/legislative.html

20. Peterson ED, Lytle BL, Biswas MS, Coombs L. Willingness to participate in cardiac trials. Am J Geriatr Cardiol. 2004 Jan-Feb;13(1):11-5.

21. Schenk DB, Gilman S. What do people at risk for alzheimer disease think about surrogate consent for research? Neurology. 2006 Jun 13;66(11):1785-6.

22. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the US food and drug administration. J Clin Oncol. 2004 Nov 15;22(22):4626-31.

23. University of North Texas Health Science Center HIPAA Training on-line. Retrieved March 3, 2007 from https://intranet.hsc.unt.edu/HIPAATrain