LEVEL OF UNDERSTANDING OF PARTICIPATION IN A CLINICAL TRIAL BY ALZHEIMER'S SUBJECTS AND ITS CORRELATION TO THEIR NEUROPSYCHOLOGICAL TEST SCORES: A PILOT STUDY

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

By

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Fort Worth, Texas

November, 2009

ACKNOWLEDGEMENT

I am overwhelmed with gratitude as I think of all the people who have helped me work on this project. Words are powerless as I begin thanking all of them.

First of all, I want to humbly thank Dr. Janice Knebl and Ms. Barbara Harty, my on-site mentors for being the guiding light throughout my internship. Despite her extremely busy schedule, Dr.Knebl was always there to give her valued opinions about my project work and to encourage me. I cannot thank her enough. I want to express my deepest gratitude towards Barb, my friend, philosopher and guide. No matter what, she always provided constant direction and helped me learn a lot. With her around, work was always fun and there was never a dull moment!

Words are not enough to thank Dr. Patricia Gwirtz, my Graduate Advisor and Major Professor. Thank you Dr. Gwirtz for being so patient and making time in your incredibly busy schedule to help me put together this report and my presentation. You have done a lot for me throughout my Masters program. My special thanks to Dr.Stokely for her suggestions and valued opinions to help me achieve my goal.

I am sincerely thankful to Maninder Malik for being there to teach me the various tasks at the internship site. It was because of her that I was able to learn a lot and she made the transition really easy.

I would also like to thank Dr. Rosalie Uht for letting me have flexible work timings and thus making a contribution to the completion of this project. I am very grateful to Dr. Michelle Harvey for helping me design my project, Kimberly Brown for her words of encouragement and guidance, my colleague Elaine Gregg for all her kindness and caring. Heartfelt thanks to Tiffany Murdock who made scheduling all appointments with Dr.Gwirtz so easy!

I will remain highly indebted to my parents for all they have done for me. Aai (my mother), I cannot thank you enough for having the faith in me and being the strongest support I have ever had. I am here today and have achieved what I have ONLY because of you. You are the reason for what I am. My deepest gratitude to my sisters and brothers-in-law, Gouri-Jayant and Ashwini-Vinay for being my support system in the United States. You all have done a lot for me and never let me feel homesick.

Heartfelt thanks to Deepa, Smrithi, Amruta, Pooja, Amol, Sanjay, Jessi and all my friends in Fort Worth and India for being my family and being there for me through all the ups and downs.

Finally, I thank the Almighty for giving me the strength and the courage to fulfill my dreams!

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CHAPTER I

INTRODUCTION

In partial fulfillment of curriculum requirement for Masters in Clinical Research Management, I conducted a six month internship between June 1, 2009 and October 31, 2009 at the Department of Internal Medicine, Division of Geriatrics at the University of North Texas Health Science Center. I worked under the supervision of an on-site mentor, Dr. Janice Knebl D.O., M.B.A and Clinical Research Coordinator Barbara Harty, R.N., M.S.N., G.N.P. During my internship, my site dealt with two ongoing clinical trials on Alzheimer's disease. I got the opportunity to assist in conducting the Phase III, multicenter, randomized, double blind, placebo controlled, parallel group, efficacy and safety trial of Bapineuzumab in patients with mild to moderate Alzheimer disease (AD) who are either carriers or non-carriers of Apolipoprotein E4. According to the study protocol, the carrier and non-carrier arms of the study were divided in two separate groups, differing in the drug dosage regimen. This clinical trial, sponsored by Janssen Alzheimer's Immunotherapy, is being conducted across seven countries. The trial is still actively enrolling subjects. I was also able to assist in recruitment of subjects for the Balance Study, "The effect of Osteopathic Manipulative Treatment on the Postural Stability in the Elderly" and the For Hers project, "Mitochondrial Estrogen Receptors, Health and Disease"

From the principle of respect for persons (1), humans as research subjects should be given the opportunity to choose whether they will participate in clinical research/human subjects research. This is accomplished through the process of informed consent. This process encompasses not only the informed consent document but also, importantly, verbal discussions with the potential

subject. The informed consent is considered a critical component of any research involving human subjects. The Belmont Report also discusses the voluntary nature of informed consent and explains that the information must be complete, understandable and presented in an unhurried fashion (1). It is the investigator's responsibility to ensure that the subject understands all the information presented in the informed consent document. Informed consent must be obtained from the subject or, if appropriate, the subject's legally-authorized representative (LAR) under circumstances that minimize the possibility of coercion or undue influence. The information should be in a language that is understandable to the subject, which may necessitate translation of advertisements, the informed consent document (ICD), and other study-related materials, and/or, if necessary, having someone on site who can answer questions (2).

Neurological disorders like Alzheimer's Disease can cause cognitive impairment that diminishes or eliminates a person's ability to understand and consent to participation in research. Cognitive impairment would render a person incompetent to make their own decisions about participation in research if it eliminates the person's ability to understand, make choices about or communicate a decision regarding participation in a particular research project (3). Investigation into areas like Alzheimer's Disease, by its nature requires the involvement of the cognitively impaired. Special protections to safeguard the welfare and rights of cognitively impaired subjects must be applied because these subjects are particularly vulnerable.

When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the

nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits (1).

BACKGROUND

Ethics in clinical research:

Scientific research has produced substantial social benefits, but it has also posed some serious ethical questions. Public attention was drawn to these questions by reported unethical use of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner (1).

The fifth and sixth principles in the Basic Principles section of the Declaration of Helsinki (4) spell out the perspective of the Declaration with respect to the appropriate relationship between individuals who serve as subjects in research and the goals of science and society. These principles read:

- "Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society"

- "The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject" (4).

However, the Declaration of Helsinki contains rules that are difficult to interpret and may not apply to complex situations.

The Belmont report identified three basic ethical principles important for the conduct of research involving human subjects (1). These three are comprehensive and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. Their objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects (1). These principles are relevant to the ethics of research involving human subjects: the principles of respect for persons, beneficence and justice (1).

1. Respect for Persons**:** Respect for persons incorporates at least two ethical convictions. First, individuals should be treated as autonomous agents. Second, persons with diminished autonomy are entitled to additional protection. The principle of respect for persons includes two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy. The extent of protection depends upon the risk of the harm and the likelihood of benefit**.**

   In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations,

however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most challenging cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence: Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

   In any research involving human subjects, it is important to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

3. Justice: An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the

principle of justice is that equals ought to be treated equally. For research involving human subjects, the principle of justice is relevant when it comes to the selection of subjects. It is important to assess whether a certain class of subjects is being selected for a study just because of their easy accessibility, manipulability or compromised position or because of reasons related to the problem under study.

Clinical Research and Vulnerable Populations:

Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests (5). The central problem presented by plans to involve vulnerable persons as research subjects is that such plans may entail an inequitable distribution of the burdens and benefits of research participation. Classes of individuals conventionally considered vulnerable are those with limited capacity or freedom to consent or to decline to consent. They are the subject of specific guidelines in this document (5) and include children, prisoners and persons who because of mental or behavioral disorders are incapable of giving informed consent. Ethical justification of their involvement usually requires that investigators satisfy ethical review committees that (5):

- the research could not be carried out equally well with less vulnerable subjects;
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class– either the actual subjects or other similarly situated members of the vulnerable class;

- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;

- the risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless an ethical review committee authorizes a slight increase over this level of risk (Guideline 9); and,

- when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives.

Elderly persons are commonly regarded as vulnerable. With advancing age**,** people are increasingly likely to acquire attributes that define them as vulnerable. They may, for example, be institutionalized or develop varying degrees of dementia**.** If and when they acquire such vulnerability-defining attributes and not before, it is appropriate to consider them vulnerable and to treat them accordingly (5). The following people may be considered as vulnerable subjects (5):

1. Children
2. Economically disadvantaged
3. Educationally disadvantaged/illiterate
4. Employees
5. Physically impaired
6. Life-threatening condition/seriously debilitating illness

7. Mentally disabled/cognitively impaired
8. Non–English-speaking subjects
9. Nursing home residents
10. Pregnant women
11. Prisoners
12. University students
13. Wards of the State

Informed Consent:

The informed consent document forms the basis of any clinical research. According to 21CFR (Code of Federal Regulations) 50.25, following information (6) shall be provided to each subject in an informed consent document:

1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2) A description of any reasonably foreseeable risks or discomforts to the subject.
3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

9) *Additional elements of informed consent.* When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

10) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

11) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law (6).

Conducting clinical trials with the cognitively impaired population:

Neurological disorders like Alzheimer's disease can cause cognitive impairment that diminishes or eliminates a person's ability to understand and consent to participation in research. Even for these persons, however, the principle of respect for persons from the Belmont Report requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. It also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm. The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best

interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest (1).

When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits (1).

Alzheimer's Disease:

Alzheimer's is a disease of the brain that damages brain cells causing problems with thinking, memory and behavior. Alzheimer's Disease (AD) is believed to develop due to multiple factors rsather than a single one. Age is believed to be the greatest risk factor for developing Alzheimer's (7).

In the United States alone, every 70 seconds someone develops Alzheimer's. In 2009, it is estimated that there are as many as 5.3 million Americans living with Alzheimer's. This includes 5.1 million people age 65 years and older and 200,000 people under age 65 years with early-onset Alzheimer's disease. It is predicted that by 2010, there will be nearly a half million new cases of Alzheimer's each year and by 2050, there will be nearly a million new cases annually (8).

Believed to be the seventh leading cause of death in the United States, Alzheimer's is not a part of the normal aging process (7). It is a progressive and fatal disease. The factors that cause

Alzheimer's begin to damage the brain years before the symptoms begin to appear (8). The brain of an Alzheimer's patient has fewer nerve cells and synapses compared to a healthy brain. Abnormal microscopic structures called "plaques" and "tangles" are considered as hallmarks of Alzheimer's disease. They were first described by a German neuropsychiatrist Alois Alzheimer in 1906. The plaques are formed from protein fragments called *amyloid peptide (abeta)* that accumulate between the brain cells, while the tangles are formed from the *Tau protein* (7). According to the amyloid hypothesis, accumulation of abeta in the brain is the principle cause of AD pathogenesis (2).

Over the past 15 years, scientists have made tremendous progress in Alzheimer's research thus contributing to a better understanding of the disease process of AD. Several prescription drugs are currently approved by the U.S. Food and Drug Administration (FDA) to treat people who have been diagnosed with AD. These drugs may either prevent or delay the symptoms but none of them stops the disease progression (7). Scientists continue to make advances and currently there are several hundreds of clinical trials being conducted to explore new therapeutic approaches (9).

Conducting clinical trials with Alzheimer's disease sufferers:

Since this disease involves some degree of cognitive impairment, it compromises the ability of the research subject to provide a valid informed consent. Thus, research involving this population presents ethical challenges (10).

It is required that prospective research subjects appoint someone to make decisions for them regarding their involvement in research *if and when* they are unable to do so. It is important for the appointed surrogate or a legally authorized representative (usually a family member or a

trusted friend) to know the research subject (AD patient) well enough and to have received sufficient instructions from the research subject to make the same decisions about research participation that he/she would make (10).

In addition, it is important to assess the decisional capacity of demented people before enrolling them in any research study (11). Various practical instruments have been designed for this purpose, but the choice which is generally considered most reliable is the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) (12).

Various outcome measures used in Alzheimer's clinical trials: The following neuropsychological tests are commonly used in Alzheimer's research to test brain functioning and memory.

1) Mini-Mental State Examination: The MMSE is used to detect and track the progression of cognitive impairment associated with Alzheimer's disease (11). The MMSE is a fully structured scale that consists of 30 points grouped into seven categories: orientation to place (state, county, town, hospital, and floor), orientation to time (year, season, month, day, and date), registration (immediately repeating three words), attention and concentration (serially subtracting 7, beginning with 100, or, alternatively, spelling the word world backward), recall (recalling the previously repeated three words), language (naming two items, repeating a phrase, reading aloud and understanding a sentence, writing a sentence, and following a three-step command), and visual construction (copying a design) (11). The MMSE is scored by the number of correctly completed

items; lower scores indicate poorer performance and greater cognitive impairment. The total score ranges from 0 to 30 (perfect performance) (11).

2) Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): ADAS was designed to measure the severity of the most important symptoms of AD. Its subscale ADAS-cog is the most popular cognitive testing instrument used in clinical trials for Alzheimer's. It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of AD. The scores range from 0 to 70 points, with higher scores indicating a greater degree of impairment (13).

3) Neurological Test Battery (NTB): The NTB represents a useful cognitive measure for clinical trials to assess cognitive change in patients with mild to moderate AD or potentially mild cognitive impairment. The components of NTB index memory and/or executive function (14). It also provides an index of global cognitive function by drawing on the many cortical areas required to support language, attention (digit span forward-the examiner reads out sets of numbers and the subject is asked to say them right back to the examiner), visual perception, verbal memory, working memory (digit span backward-the examiner reads out sets of numbers and the subject is asked to say those numbers backwards to the examiner), and list learning.

4) Disability Assessment of Dementia Scale (DAD): The DAD has been found to be a reliable and valid instrument to assess functional disability in early Alzheimer's disease

(15). In this test, the subject's caregiver is asked questions to assess if the subject is able to perform daily activities like household chores, preparing a meal, shopping etc (15).

5) Clinical Dementia Rating-Sum of Boxes (CDR-SOB): The Washington University Clinical Dementia Rating Scale (CDR) is a global assessment instrument that yields global and Sum of Boxes (SOB) scores, with the global score regularly used in clinical and research settings to stage dementia severity. The CDR-SOB provides a more general index compared to the global score (16). CDR-SOB is proved to be very useful in staging dementia severity as it is a more sensitive test (16). The CDR-SOB tests the subject in the areas like memory, orientation, judgment & problem solving, community affairs, home &hobbies and personal care (16).

CHAPTER II

SPECIFIC AIMS AND METHODS USED FOR INTERNSHIP PRACTICUM REPORT

Specific Aim 1:

To determine whether subjects with Alzheimer's type dementia understand the meaning of participating in a "research" study. If so, what is their level of understanding?

Studies that have been done so far have either assessed the decision-making capacity of Alzheimer's subjects before they are enrolled in a clinical trial (17) or used hypothetical research study situations (18). Although Alzheimer's subjects may not be considered fully capable of providing informed consent**,** the ethical principle of respect for persons requires that they know they are participating in a "research study" and understand what these words mean.

Significance:

The informed consent is considered a continuous process throughout the period of any research study and hence, it is important to determine if the subjects realize what their rights are as "research study" participants (1). This practicum study will help to evaluate the comprehension by the Alzheimer's subjects of being in a "research study". This study will help to answer the question whether having a one-time informed consent in a trial involving Alzheimer's subjects is appropriate or is there a need to repeatedly have a shorter version of it, summarizing the major and key points about the study. The results will determine if there is a need to improve the

informed consent process in Alzheimer's trials, thus providing additional safeguards for this vulnerable population.

Specific Aim 2:

To evaluate the correlation between the level of understanding of participation in a clinical trial by Alzheimer's subjects and their latest scores on neuropsychological tests.

Neuropsychological tests are generally used as the primary endpoints in an Alzheimer's clinical trial. They test the executive functioning of the brain and memory (15, 11, 14). This pilot study will determine whether the subject's neuropsychological test scores, which are an index of their memory and cognitive capacity, reflect the retention of their understanding of the clinical trial they are participating in.

Methods used:

This pilot study involved subjects that are currently participating in a pharmaceutical clinical trial that has a total duration of two years. All subjects had already been enrolled in the clinical trial for approximately one year. Specifically, my practicum project was performed with participants that are enrolled in the UNTHSC IRB (Institutional Review Board) approved Phase 3 trial of Bapineuzumab sponsored by Janssen Alzheimer's Immunotherapy (IRB protocol # 2008-036 & 2008-037) and the Phase 3 open-label study of Exelon patch sponsored by Novartis (IRB protocol # 2007-56) which are being conducted at the Patient Care Center, University of North Texas Health Science Center, Fort Worth. Currently, there are a total of 5 subjects enrolled

in these two studies. All five subjects were included in my project. Since this is a pilot study, a small sample size is appropriate for the study.

Methods for Specific Aim 1:

A structured interview was conducted with subjects (questionnaire attached) when they came for their scheduled study visits as part of either the Janssen and Novartis study. This interview was designed to assess if the subjects understand what it means to be a part of the Janssen/Novartis study. The interview was conducted as soon as the subject came in and before the Janssen/Novartis study procedures were conducted for that particular visit. All subjects were accompanied by their caregiver/LAR. Each participant was interviewed twice during the study period (July 2009-November 2009) to determine if there was any change in their scores. The interview was scored with a minimum score of 0 and a maximum score of 16. (Detailed scoring system is shown in the attached questionnaire). The answers were recorded in writing by the interviewer.

The subject's caregiver/LAR was asked to sign the Caregiver Research Participation Agreement. The subject was not informed about participation in the practicum project study to facilitate natural responses to the questions in the interviews. The consent procedure with the subjects was waived since the study involved no more than minimal risk. However, since this is a vulnerable population, the subject's caregiver/LAR was informed about this study and was asked to authorize the subject's participation.

Methods for Specific Aim 2:

The interview scores will then be used to correlate to the latest scores of the subjects on the following neuropsychological tests:

Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), Neurological Test Battery (NTB)-Rey Verbal Learning and category fluency test, Disability Assessment for Dementia(DAD) and Clinical Dementia Rating (CDR)-sum of boxes for the Janssen study subjects and MMSE and ADAS-Cog for the Novartis study subjects. These tests were administered to the subjects by trained professionals during their routine study visits as a part of the Janssen study and Novartis study. The latest scores on the neuropsychological tests for the Janssen study subjects were accessed from the Medidata Database. This is a database supplied by the sponsor to securely enter all test scores. The scores for the Novartis study subjects were accessed through the Investigator portal. These databases are accessible only to the key personnel and are password-protected. The subject's sponsor-assigned ID numbers were used for data analysis to protect subject's privacy. The subjects were debriefed after the completion of this pilot study. They were given the opportunity to ask questions about any new information generated through this study. They also had the opportunity to withdraw and have their data removed.

Pearson's correlation coefficient was calculated using the in-built statistical tool in Microsoft Excel.

Human Subjects Protection:

Since this study involves human subjects, it was approved from UNTHSC Institutional Review Board (IRB). (Approved on 07-21-09. IRB protocol # 2009-086).

CHAPTER III

RESULTS AND CONCLUSION

(1) Results of the structured interview:

All subjects were scored based on the answers they provided to the specific questions asked. (Detailed scoring system is shown in the attached questionnaire)

- All subjects scored 0%- 28% in the interview.
- The subjects had same scores in both interviews.
- All subjects gave the same answers in both interviews.

All subjects have been in their respective clinical trials for approximately one year of two. These subjects visit the clinic regularly at an interval of 6 weeks for the Janssen study and once every 3 months for the Novartis study. Even then, these subjects have a very poor knowledge of what it means to be a clinical trial participant as reflected by their interview scores. Interestingly, all subjects answered the same answers during both the interviews. This shows consistency in the results.

I also observed that the caregivers had an idea that their loved one (subject) would not be able to answer the questions in the interview. This was seen through their reaction when I explained my proposed study to them.

In general, subjects were unable to answer questions and looked at their caregivers for help or pointed to the caregiver to answer the question asked to them.

(2) Correlation of interview score with each test score:

The subject's interview score was compared with their latest scores on various neuropsychological tests that test executive function of the brain and memory.

Lowest possible interview raw score: 0, Maximum possible raw score for the interview: 16.

Table 1 represents the subject's latest scores on the MMSE. Subjects with an increase, decrease or no change in MMSE scores (compared to Baseline) scored below 28% on the interview. MMSE scores track reduction in cognition (11). Thus, it is difficult to say that MMSE scores are directly proportional to the interview scores.

Table 1: Mini-Mental State Examination (MMSE):

Subject #	% Average Interview Score	MMSE Raw Score	
		Baseline	Recent
246-1005	25	16	17
246-1007	28	20	17
246-1008	0	22	19
246-1010	28	20	20
0534-06	0	18	18

Lowest possible MMSE raw score: 0, Maximum raw score: 30

The ADAS-Cog is more sensitive and tests specific brain functions (13). The scores presented in Table 2 suggest impairment in the subject's cognitive ability i.e. higher the scores more the impairment and vice versa (13). Subjects with increased, decreased or constant impairment (compared to baseline) scored below 28% on the interview. Thus, the ADAS-Cog scores also do not correlate directly with the interview scores.

Table 2: Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog):

Subject #	% Average Interview Score	ADAS-Cog Raw Score (Impairment)	
		Baseline	Recent
246-1005	25	31	28
246-1007	28	23	26
246-1008	0	22	26
246-1010	28	23	17
0534-06	0	26	27

Lowest possible ADAS-Cog raw score: 0, Maximum raw score: 70

In the NTB-Rey verbal learning test, all subjects showed in a decline in the scores for immediate recall of words. This data is shown in Table 3. However, interestingly, 3 of 4 subjects showed an increase in scores for the delayed recall of words and 1 subject had constant scores (compared to baseline). Also 3 of 4 subjects showed an increase in scores on the Category Fluency test and 1 showed a sharp decrease in scores.

Table 3: Neurological Test Battery (NTB):

Subject#	% Avg Interview Score	NTB (% Avg Rey Verbal Learning)				NTB	
		Immediate recall		Delayed recall (Total Correct)		Category Fluency Test (%)	
		Baseline	Recent	Baseline	Recent	Baseline	Recent
246-1005	25	28	20	36	30	7	10
246-1007	28	26	16	26	36	20	23
246-1008	0	28	3	46	46	23	5
246-1010	28	27	22	33	40	25	30

Lowest possible Rey Auditory Verbal Learning and Category Fluency Test raw score: 0

Maximum Possible raw score for immediate recall: 105, delayed recall: 30, category fluency test: 39.

The DAD scores are shown in Table 4. These scores show an increase in disability in all subjects.

The percent impairment is indicated by the CDR-SOB scores as shown in Table 4. One subject showed sharp increase in impairment and three showed a fairly constant impairment score.

Table 4: Disability Assessment for Dementia (DAD) & Clinical Dementia Rating (CDR):

Subject #	% Avg Interview Score	DAD Score (%)		CDR-SOB (% impairment)	
		Baseline	Recent	Baseline	Recent
246-1005	25	77	85	25	27
246-1007	28	77	75	27	55
246-1008	0	77	82	22	27
246-1010	28	82	77	22	25

Lowest possible raw score for DAD and CDR-SOB: 0, Maximum possible raw score for DAD: 40 and for CDR-SOB: 18

The Pearson's Correlation coefficient (r) is an index of linear correlation between two variables (-1 : strong negative correlation, 0: no correlation, +1: strong positive correlation)

Table 5: Pearson Correlation Coefficient (r) for the interview score and each neuropsychological test score:

Test	Pearson Correlation Coefficient (r)
MMSE	-0.17
ADAS-Cog	-0.4
NTB (Immediate Recall Test)	0.95
NTB (Delayed Recall Test)	-0.73
NTB (Category Fluency Test)	0.75
DAD	0.28
CDR-SOB	0.33

Discussion:

This practicum study emphasizes the importance of the informed consent document in any clinical research. Informed consent is a process and starts from the recruitment of the subject until the end of the clinical trial (1). It is crucial to take into consideration the importance of making sure that the subject really understands what is written in the informed consent document. The doctrine of informed consent includes an assumption of disclosure of information, comprehension of the information, and voluntary participation. The Belmont Report acknowledges that comprehension of the information provided may be limited for certain groups of individuals, especially children and the cognitively impaired. The informed consent document is intended to protect research participants by ensuring that they are aware of the risks, benefits, alternatives, and what the research will involve (1). In general, the informed consent document is long and contains a lot of information that can be overwhelming for the subject and the caregiver. Thus, it is important to not assume that the subject has understood all that information and what it will take to participate in that particular clinical trial.

Alzheimer's subjects may not be capable of making independent decisions, but they should be aware of what is being done with them as participants of the clinical trial /research study. The Belmont Report states that lines between the two concepts of research and treatment tend to be blurred, and it must be clear to the participant what the nature of the intervention is. Even though they give their assent to participation in a clinical trial before enrollment, it cannot be considered as a long-term consent as cognitive ability decreases with the progression of the disease (19). While this consent may reflect the individual's wishes at the time, it cannot be considered in the same light as a non-impaired participant. It is possible that the individual may understand the

terms of study at the time of consent; however, this understanding may decline and one cannot be certain that the participant will want to continue involvement or understand that they may remove themselves from the study at any time.

The informed consent procedure in Alzheimer's clinical trials might benefit from periodic reassessment as attempted in this pilot study. Since there is involvement of a "vulnerable" population in Alzheimer's clinical trials, special safeguards are required. There may be a need to have the key points of the specific trial re-read to the subjects, perhaps at each study visit. A brief script might be used for this purpose. Specifically, the correct answers to the questions in our interview questionnaire might serve as key points important to be told to the subject at each visit.

Visual aids might also be helpful for conveying the key elements in the specific informed consent.

This study further emphasizes the importance of a caregiver/study partner in an Alzheimer's trial. The caregiver/LAR is usually a member of the subject's family or a close friend (19). Making any type of decisions may become difficult for the Alzheimer's patient due to decline in cognitive ability (19). Jointly, with the caregiver, the Alzheimer's subjects make a decision to participate or not in a specific clinical trial. Thus, the caregiver caries a huge responsibility of weighing the benefits and risks of any research study.

Immediate recall test of the Neurological Test Battery (NTB) shows a strong positive correlation with the interview score as indicated by the Pearson's correlation coefficient (r). Thus, it may be an indicator of the level of understanding of the Alzheimer's subjects.

A major limitation of this practicum study is that it was conducted with a very small sample size and thus, makes it difficult for the results to be statistically significant. Hence, I would like to do this study with a larger sample size to be able to detect any trend, if present.

In addition, it would be interesting to ask the caregivers the same interview questions asked to the subject.

The inclusion of age-matched controls who were participating in a non-AD research study, would improve this study by controlling for age-related medical confusion that was not disease-specific.

CHAPTER IV

INTERNSHIP EXPERIENCE

The six-month clinical research internship that I undertook was located at the University of North Texas Health Science Center in the Patient Care Center, specifically in the Department of Internal Medicine, Division of Geriatrics. The geriatric department provides specific care to patients over the age of 65 years and offers services, such as family conferences, to help cope with age-related diseases. Many clinical trials are conducted at this site which target typical age-related problems such as AD and rheumatoid arthritis. The trial of interest for me was specifically aimed at testing the safety and efficacy of the investigational drug, Bapineuzumab, in elderly patients with mild to moderate AD. The geriatric division is led by Dr. Janice Knebl DO, MBA. Her assistant, Barbara Harty, Geriatric Nurse Practitioner, serves as the clinical research coordinator in several dementia related diseases. Ms. Harty is also a member of the UNTHSC Institutional Review Board, an assistant professor and my educator during my internship. During my internship, two industry sponsored AD clinical trials and two investigator initiated studies were ongoing.

Through this internship, I obtained the working knowledge and valuable experience on how human clinical trials are conducted and the roles of a principal investigator, research coordinator and the Institutional Review Board (IRB). During my internship I learned and performed day-to-day activities expected from a clinical research coordinator (CRC). These include subject screening, recruitment, preparation and management of a clinical trial. The clinical trial that contributed to my experience was a Phase-3, multicenter, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety trial of Bapineuzumab. This trial was conducted in

patients with mild to moderate Alzheimer disease who are carriers and non-carriers of Apolipoprotein E4. This clinical trial was complex and allowed me to truly learn the details involved in clinical research management. Duties expected were both direct and indirect with regards to study subjects. Direct duties included subject-coordinator rapport, such as recruitment, sample collection, adverse event reporting, informed consent process, vital signs assessment and monitoring during infusion visits and follow-up phone-calls. Other direct duties involved IRB, clinical monitor and study sponsor interactions. Indirect duties included protocol implementation, administrative duties, filing of case reports, management of study related files, inventory accountability, training and monetary/budget information. Some direct indirect duties are explained in detail below.

Training and Certification:

To participate in research with human subjects the UNTHSC IRB requires the comprehension and completion Collaborative IRB Training Initiative (CITI). **Health Insurance Portability and Accountability Act** (HIPAA) training is also required to have access to private patient information.

The UNTHSC Office of Clinical trials require Study Manager training for stipend compensation and doctor fee distribution, in which I obtained.

Upon sample collection, particularly blood samples, training was offered and completed for proper processing, shipping and packaging.

Occasionally, our study sponsor provided live training on documentation, protocol and procedure changes in which I attended via internet or phone. The study sponsor also provided Medidata training, a program specifically designed for data input of any trial related material.

Subject Recruitment and Screening:

Potential subjects often came from UNTHSC geriatric clinic doctor referrals, active patients of the Texas Alzheimer's Research Consortium (TARC) or by study recruitment ads. I quickly learned how to screen potential subject's medication chart for trial eligibility. If a subject met clearance through inclusion/exclusion criteria, Ms. Harty demonstrated how to explain the concept of a clinical trial without placing pressure to join the study. She stressed that the drug was investigational and that participation was strictly voluntary. If necessary, Ms. Harty offered advice and detailed explanation of AD progression. If a subject was unable to join our study, their names were kept for further studies if permission was granted.

Implementation of Study Protocol Procedures:

During my internship, I was fortunate to observe Ms. Harty efficiently explain the details of the informed consent. She verbally gave the subject adequate information concerning the study, allowed for the subjects to consider all options and answered any questions the subject may have. A copy of the informed consent was given to each subject.

At each visit, I assisted Ms. Harty in collecting, processing and packaging blood samples for laboratory analysis. Guidelines were followed according to study sponsor and the secondary laboratory packaging of biological samples regulations.

During certain study visits, an electrocardiogram (EKG) was obtained. I reviewed and received training to successfully perform an EKG and to transmit the results.

At the end of each study, I ensured that the subject and caregiver would receive their stipend supplementation. Ms. Manider Malik, Ms. Harty's assistant, provided adequate training on the use of Study Manager for subject stipend request. Study Manager is a program used by UNTHSC Office of Clinical Trials that tracks monetary activities such as subject and doctor compensation.

Management Duties:

Subject binder preparation was an important component of assuring that the visit was properly conducted. I was taught to place all necessary documents, workbooks and study visit kits together before each patient arrived. I would hand all materials to the corresponding doctors as per protocol procedure. By doing so, I inadvertently learned to keep track of inventory, such as laboratory kits, airway bills, shipping cartons, test booklets, source documents, subject binders, EKG cards and any other study related material.

Our study sponsor frequently asked for weekly updates regarding the study. As a result, a weekly fax was sent to them that included significant information of our enrollment status.

Ms. Harty also kept me well informed of changes out study sponsor may have required. Some emails required necessary action in which I completed quickly. All items ensured successful completion of our study.

Occasionally, our study subject would inform us of unexpected events. A copy of the Seriuos Adverse Event (SAE) was sent to our IRB as well. If a subject missed a study visit due fell out of the study window, a protocol deviation had to be filed. Protocol deviations had to be sent to both out study sponsor and IRB and approval must be attained before commencing with the study. During my internship, many unforeseen circumstances occurred allowing for practice of filing such documents.

Regulatory Duties:

IRB Interaction:

During my internship, I had the opportunity to participate in many different IRB regulatory administrative duties. During my internship, the study was scheduled up for a continuing review. If a study is approved with continuing review, it means that the study contains a moderate risk level and the IRB wishes to review the study, in this case, every six months. I was also fortunate to attend an IRB meeting in which I witnessed various protocols being analysed before approval.

SAEs that occurred outside of our specific site were also reported to us and subsequently our IRB. I learned firsthand how to complete and submit off-site SAEs to our IRB.

For my practicum report, I participated directly in my own submission of an expedited review.

Protocol and Procedural Modifications:

Because a clinical trial is investigating a new drug, it is common for the study sponsor to make modifications to the protocol, procedure and even the informed consent. During my internship, I had the opportunity experience changes in protocol design, informed consent and other documents. This provided powerful insight of how a study sponsor might intervene if the investigational drug becomes too perilous.

Study Sponsor and Clinical Monitor Communication:

I observed and even participated in several outreaches to both our study sponsor and clinical monitor regarding issues that arose with our clinic site. Such problems included protocol deviations and SAE reporting. In my observation, both the study sponsor and clinical monitor were quick in responding to our queries.

During the course of my internship, I was able to participate in a clinical monitor visit. I was able to witness the expectation, hard work and effort necessary to become a clinical monitor. My management training I received during my internship allowed for a very smooth visit with our monitor.

Meetings:

My internship allowed me to attend departmental, institutional, study sponsor and coordinator meetings. During these meeting I learned of the problems that were faced with other studies and how to properly address such issues.

APPENDIX A

DAILY JOURNAL

June 1, 2009:

1) 9:00 a.m: Committee meeting with Dr. Gwirtz, Dr.Stokely and Barbara. Barbara explained the Bapenuzimab study that I was going to be involved in. We discussed a potential thesis idea for me (general idea: safety reports).
2) 11:00 a.m: Elan Bapineuzumab American Association of Neurology Presentation Meeting. This was a web teleconference. Various aspects of the Phase II study were presented including the results, SAEs and their significance.
3) Preparation of visit 6 of subject scheduled on June 2. Went through the subject folder to make sure materials needed for the visit were in place.

June 2, 2009:

1) Visit 6 procedures performed:
    1) Dr. Hall administered the MMSE.
    2) Dr.Knebl performed the neurological testing
    3) Clean urine sample collected.
    4) Barbara drew blood: 1 tube for hematology, 1 for chemistry.

5) Take tubes to the research lab to process according to specifications. EKG performed on study patient in exam room. Transfer the EKG data over the phone. Wait for the operator to give OK sign for the EKG.
6) Informed consent signed by the study patient and the caregiver again after Barbara explained the change in dosage in the drug, as modified by the sponsor.
7) Packaging: write the patient no. and initials on all tubes. Placed the tubes and slides in given ziplock. Prepared the gel pack. Wrapped the ziplock with the tubes in the gel pack and placed in the kit. Called UPS to schedule the pickup.
8) Added the visit to the patient profile in medidata as taught by Maninder.
9) Processed the patient stipend request using study manager. Sent a mail to Denise in OHRP about each patient stipend processing .(separate mail for each patient)
10) Attended the monthly IRB meeting from 2 p.m to 4:30 p.m. Observed 6 protocols for continuing review and one protocol for full board review. It was good to observer the real version of an IRB meeting.

June 3, 2009:

Read through the study materials like informed consent, protocol to note the details of the Elan study. Went through the regulatory binder.

June 4, 2009:

1) Visit 7 procedures performed:
    1) Patient visit at 8:30 a.m. Dr. Hall performed the Neuropsychology Test Battery (NTB), Alzheimer's Disease Assessment Scale-Cognitive Behavior (ADAS-Cog) and Neuropsychiatric Inventory (NPI) with the patient.
    2) Lisa Alvarez performed DAD and CDR with the caregiver. She asked the caregiver questions about the patient's behavior. Past events (so that she could cross check with the patient).
    3) Barbara performed the Dependence Scale (DS), Resource Utilization in Dementia (RUD) LITE, Health Utilities Index (HUI), Quality of Life Alzheimer's Disease Scale (QoL-AD) with the caregiver and QoL-AD with the patient.
    4) Barbara also went over the informed consent with the patient and the caregiver to explain the change in dosage. She asked if the patient still wanted to participate after knowing the change. Patient and caregiver signatures taken on the new informed consent.
2) Folders and tubes prepared to be given for the For Hers project.
3) Preparation for monitor visit on June 9. Went through all patient folders to make sure everything is in place. Separated out the documents to be signed by Dr.Knebl and Barbara.

June 5, 2009:

Went through the regulatory binders for Bapi study 301 & 302. Made sure all documents are in the right tabs. Made sure necessary documents had Dr.Knebl's and Barbara's signatures. Also Medidata has the up-to-date information about all subjects.

June 8, 2009:

Learnt how to write a safety report. The safety report (report of a SAE at any of the sites included in the study) is to be submitted to the UNTHSC IRB. Also a copy of the safety report is to be filed in the study binders.

June 9, 2009:

1) Visit no. 7 (infusion) of subject. Observed the physical and neurological testing administered by Dr.Knebl. Learnt how to package blood samples and ship on dry ice.
2) SAE on site was reported. It was vasogenic edema (asymptomatic). Sent the necessary paperwork to the sponsor. Filled out adverse event form of UNTHSC IRB and sent to Deb.Ceron.
3) Entered Visit 7 details into Medidata and study manager.
4) Sent an email to Rhonda Dennis to process the stipend request.

June 10, 2009:

Preparation for monitor visit. Made sure all documents are in place in all subject binders, regulatory binders.

June 11, 2009:

Monitor visit.

June 12, 2009:

Discussed the corrections suggested by the monitor. But overall he was happy with our site!

June 15, 2009:

Meeting with Dr.Knebl and Barbara at 9 a.m to discuss my thesis topic. The topic discussed at the committee meeting did not seem meaningful. Dr.Knebl suggested a new topic.

June 16, 2009:

1) Attended Sandra's defense at 8 a.m.
2) Study visit no. 8 of subject. Dr.Hall performed the MMSE (Mini Mental State Examination). Barbara collected blood and urine samples. I processed and packaged the samples under Maninder's supervision and shipped via USPS. Sent an email to Rhonda Dennis for stipend request form.
3) Literature review for thesis.

June 17, 2009:

1) Maninder and I went to Deb Ceron's office to discuss the discrepancies in the continuing review. We discussed all the issues and finally resolved them!
2) Literature review.

June 18, 2009:

Completed two safety reports sent by the sponsor. Sent necessary documents to UNTHSC IRB.

June 19, 2009:

1) Completed the medidata and study manager details of visit 8 for subject no. 246-1008.
2) Visited Carolyn Polk's office to go through theses of past CRM students.
3) Literature review.

June 22, 2009:

1) Sent the missing regulatory documents to PRA international (CRO) for the study. (Barabara's CV, Medical License, Financial disclosure forms)
2) Sent the same set to Tina Mc Call in Office of Clinical Trials.
3) Met with Dr.Gwirtz at 10:00 a.m to discuss the new topic for my thesis.
4) Visit no. 8. Dr. Hall performed MMSE. Barabara took vital signs and drew blood.Packaged blood samples and sent by UPS. Any adverse events and change in medications were recorded.

5) Prepared for visit no. 7 for June 23 for patient 246-1010.
6) Literature review.

June 23, 2009:

1) Meeting with Dr.Knebl to discuss my doubts about the thesis with her.
2) Visit no. 7. I observed Dr.Hall administer the Adas-Cog, NPI and NTB. I also observed Lisa Alvarez administer RUD-LITE and QOL tests with caregiver and the subject. Barabara took the vital signs and went over the new informed consent with both the caregiver and the subject. Any adverse events and change in medications were noted.
3) I entered the visit no. 8 details that took place on June 22 in medidata.
4) I entered the visit details in study manager. I sent an email to Rhonda Dennis for request to process stipend request form for today's visit.
5) I called Covance supplies to order new kits and shipping boxes.
6) Sent the follow-up SAE form to UNTHSC IRB for the adverse event reported at our site for subject.

June 24, 2009:

1) Literature review for research proposal.
2) Attended seminar on "Bioterrorism" at James.L.West with Barbara and Maninder.

June 25, 2009:

1) Entered visit no. 7 details in medidata.

2) Prepared the follow-up report for on-site SAE to be submitted to UNTHSC IRB. Took signatures from Dr.Knebl.
3) Worked on research proposal.

June 26, 2009:

Literature review

June 27, 2009:

Attended the "Alzheimer's Awareness Tour" organized by the Alzheimer's Association with Maninder at Hyatt Place, Dallas From 9 a.m to 11:30 a.m. They screened a part of the documentary "The Alzheimer's Project" created by HBO. At the end, Maninder and I answered questions from the audience on clinical trials and in particular we spoke about the Elan Study. It was a good experience!

June 29, 2009:

1) Attended the "Bapineuzamab PIII IVRS training" through a virtual meeting and teleconference. They gave training on subject randomization.

June 30, 2009:

1) Maninder showed how subjects are screened for the Elan study. I screened 30 patients to look for potential subjects for the study. I made a list of the qualified and disqualified patients.

July 1, 2009:

1) I screened some more subjects for the study.
2) Worked on research proposal.

July 2, 2009:

1) Meeting with Dr.Harvey to discuss my project. I explained my ideas to her. She made a few suggestions.
2) Literature review.

July 3, 2009:

1) Study subject from Novartis study scheduled. Barb took the vital signs and handed over the medications to her.
2) Barb explained how to complete the Drug Accountability Log.
3) Meeting with Dr.Harvey at 11:30 a.m

July 6, 2009:

1) Maninder and I screened patients for enrollment in Elan study.
2) I discussed the corrections in the questionnaire for my project suggested by Dr.Knebl with Barb.
3) Barb and I discussed the IRB research proposal in detail. She suggested corrections.
4) Brad, the monitor called to update on the transfer of subject to Wisconsin.
5) Attended the monthly Geriatrics division meeting at 12:00 p.m.
6) Worked on research proposal.

July 7, 2009:

1) Completed safety report. Maninder gave instructions.
2) Discussed with Barb all the doubts for the IRB submission.
3) Took signatures from Dr.Knebl on documents
4) Sent a fax to Elan

July 8, 2009:

1) Completed safety reports
2) Took signatures from Dr.Davanloo
3) Filed all new documents in the regulatory binder.
4) Worked on IRB submission
5) Discussed my doubts with Kimberly Brown

July 9, 2009:

1) Completed training on packaging and shipping hazardous goods.
2) Prepared schedule for visits of all subjects with Maninder's guidance
3) Discussed my doubts for IRB submission with Barb.
4) Prepared the packet for IRB submission.

July 10, 2009:

1) Worked on research proposal
2) Went to the library
3) Submitted the IRB application

July 13, 2009:

1) Completed safety report. Took signatures from Dr.Knebl. Sent to Deb Ceron in IRB office
2) Updated regulatory binder.

July 14, 2009:

1) Completed safety report
2) Worked on IRB proposal
3) Worked on research proposal

July 15, 2009:

1) Worked on research proposal
2) Screened subjects for Elan study

July 16, 2009:

1) Worked on research proposal
2) Updated the subject binders

3) Discussed the safety report I had completed with Maninder. She explained the mistakes I had made.

July 17, 2009:

1) Modified the safety report according to Maninder's suggestions.
2) Sent the documents to Deb Ceron
3) Submitted final documents for my expedited review application to Jill in IRB office.

July 20, 2009:

1) Signatures taken from Dr.Knebl on documents (change of study personnel and COI) and submitted to Jill in IRB office.
2) Screened subjects for Elan study
3) Dr.Knebl told me about the new projects I will be handling during my internship.
4) Faxed the MRI sheet to Radiology Associates.
5) Prepared for visit 8 for tomorrow.
6) Maninder, Lisa Alvarez and I discussed about the new therapies in clinical trials for Alzheimer's. Lisa told us about the International Alzheimer's Conference she recently attended in Vienna.

July 21, 2009:

1) Picked up IRB approved materials for my project. Yay!!
2) Conducted interview with subject.
3) Visit 8 for subject #246-1008
4) Processed blood samples
5) Called UPS to schedule a pick-up for blood samples.
6) Safety report

July 22, 2009:

1) Completion of safety report.
2) Entered visit details of July 21 in Medidata.
3) Went through subject binders to make sure all information was entered in Medidata. (preparation for monitor visit in August)
4) Maninder taught me how to randomize subject.

July 23, 2009:

1) Went through subject binders and resolved queries in medidata.
2) Maninder, De Raan and I had a meeting about the balance study and the updates.

3) Safety report.

July 24, 2009:

1) Safety report.

2) Went through subject binder.

July 27, 2009:

1) Safety report completion

2) Preparation for visit on 28th July.

July 28, 2009:

1) Visit no. 9 for subject

2) Entered all data into Medidata software.

3) Sent Rhonda Dennis an email about stipend request.

4) Entered data into Study Manager

July 29, 2009:

1) Took signatures from Dr.Davanloo
2) Sent documents to Deb Ceron in IRB
3) Safety reports
4) Meeting with Jim Moss

July 30, 2009:

1) Safety report
2) Copied entire subject binder for a subject being transferred to another site
3) Sent all documents to Wisconsin

July 31, 2009:

1) Screening of a new subject.
2) Packaged and sent blood work
3) Safety report

Aug 3, 2009:

1) Safety report
2) Sent safety report to Deb in IRB
3) Screened 50 patients for Balance study and sent the names of potential subjects to Dr.Patterson's Assistant
4) Attended Geriatrics Division monthly meeting at noon.
5) Observed Barb perform phone screening for the Elan study.
6) Updated 1572 form for the Novartis study.

Aug 4, 2009:

1) Filed the safety reports received from IRB in the regulatory binder.
2) Completed safety report.
3) Screened 25 patients for the balance study.

Aug 5, 2009:

1) Safety report completion
2) Screening for Balance study.

Aug 6, 2009:

1) Safety report
2) Screening for balance study
3) Filing documents in the subject folders

Aug 7, 2009:

1) Safety report
2) Screening for balance study
3) Observed the data collection for balance study in the clinical research unit of the osteopathic medicine division.

Aug 10, 2009:

1) Safety reports.
2) Preparation of visit 9 on Aug 11
3) Spoke to CRA about doubts we had.

Aug 11, 2009:

1) Visit 9 for a subject.
2) Packaged blood sample.
3) Called UPS to schedule a pickup.
4) Sent e-mail to Rhonda Dennis for stipend request
5) Entered all the visit data into Medidata.
6) Entered data into Study Manager.

Aug 12, 2009:

1) Safety report
2) Went through subject binders to get ready for monitor visit.
3) Clinical Research Coordinator's meeting.

Aug 13, 2009:

1) Safety report
2) Screening for Balance study
3) Went through subject binders for monitor visit

4) Took Dr.Knebl's signatures

Aug 14, 2009:

1) Safety reports.
2) Went through subject binders for monitor visit
3) Balance study screening

Aug 17, 2009:

1) Safety report.
2) Went through Regulatory Binder to make sure everything was ready for monitor visit
3) Called subject to confirm visit
4) Screening visit for a new subject

Aug 18, 2009:

1) Took Dr.Knebl's signatures
2) Sent safety report to Den Ceron
3) Filed all the documents into respective subject binders.

Aug 19, 2009:

1) Safety report
2) Screening visit for a new subject
3) Packaged and sent the blood sample
4) Screened for balance study
5) Preparation for visit on Thursday
6) Spoke to Brad (CRA)

Aug 20, 2009:

1) Study Visit
2) Packaged blood and scheduled shipping via Fedex
3) Entered all the study details in medidata
4) Entered data into Study Manager
5) Emailed Rhonda Dennis to process stipend request
6) Filled out the Medical Exemption Form and faxed it to Elan
7) Brad's (CRA) visit.
8) Mailed screening informed consent to the patient seen on Aug 19th.

Aug 21, 2009:

1) Safety report.
2) Sent it to Deb Ceron
3) Screened for Balance Study
4) Discussed the data in all subject binders with the CRA (Brad)
5) Resolved all queries with Brad.

Aug 24, 2009:

1) Safety report. Took Dr.Davanloo's sign and sent to Deb Ceron
2) Made a new binder for new subject that has been entered into the study.
3) Discussed scheduling for new subject with Barb
4) Data collection for the For Hers Project
5) Prepared documents for Screening Visit-Part 2 for new subject

Aug 25, 2009:

1) Balance study screening
2) Sent the new informed consent to Wendy for IRB approval

Aug 26, 2009:

1) Screening for balance study
2) Completed on-site SAE form and took signatures from Dr.Knebl
3) Discussed the SAE (on-site) situation with Dr.Knebl
4) Completed the SAE form for Elan.
5) Spoke to Brad (CRA)

Aug 27, 2009:

1) Sent the On-Site SAE form to Deb Ceron
2) Sent the SAE form to Elan risk management and pharmacovigilance group.
3) Screening for Balance Study.
4) Spoke to Brad (CRA)

Aug 28, 2009:

1) Safety report
2) Filed documents
3) Screening for Balance study

Aug 31, 2009:

1) Safety report
2) Screening for Balance study
3) Preparation for visit on 1st Sept.

Sep 1, 2009:

1) Visit 9 for subject
2) Entered visit data in Medidata
3) Entered visit data in study manager
4) Emailed Rhonda Dennis for stipend request form processing

Sep 2, 2009:

1) Screening for Balance study.

Sep 3-Sep 4, 2009:

Did not go to office because I was out of state.

Sep 7, 2009:

Labor Day holiday!

Sep 8, 2009:

1) Safety report
2) Worked on the suggestions given by Dr.Knebl to improve research proposal
3) Took signatures from committee members and submitted research proposal to the Graduate Office
4) Discussed with Lisa the status of For Hers project
5) Sent documents to Radiology Associates.
6) Sent email to clarify doubts about new recruitment materials for the ICARA study.
7) Preparation for visit on Sep 9, 2009.

Sep 9, 2009:

1) Subject Visit
2) Entered all data in Medidata
3) Entered visit details in study manager
4) Emailed Rhonda for stipend request form processing

5) Collected IRB approved revised ICFs from Office of Clinical Trials

6) Filed documents in their respective binders.

Sep 10, 2009:

1) Subject visit for screening

2) Packaged and sent blood sample.

3) Filed safety reports

Sep 11, 2009:

1) Screening for Balance Study

2) Sent an email to Dr.Knebl to give update on Balance Study

3) Worked on thesis writing

Sep 14, 2009:

1) Screening for Balance study

2) Attended the board review.

3) Updated study files

4) Discussed the For Hers project with Dr.Knebl

Sep 15, 2009:

1) Screening for Balance study
2) Sent an email to Tina in Office of Clinical Trials to clarify the IRB's doubt about our new email ad.
3) Sent the new approved advertising materials for our study by fax.

Sep 16, 2009:

1) Balance study screening

Sep 17, 2009:

1) Balance study screening
2) Safety report
3) Updated study files
4) Spoke to Brad to give updates

Sep 18, 2009:

1) Updated regulatory binder
2) Safety reports
3) Screening for Balance study

Sep 21, 2009:

1) Screening for balance study
2) Preparation for visit on Sep 22

Sep 22, 2009:

1) Visit # 10
2) Entered visit details in Medidata
3) Sent email to Rhonda Dennis for stipend request
4) Entered visit details in study manager
5) Safety reports-completed and sent to Deb Ceron
6) Screening for Balance Study
7) Sent email to committee members to decide defense date

8) Worked on thesis writing

Sep 23, 2009:

1) Screening for Balance study
2) Updated regulatory binder
3) Worked on thesis writing

Sep 24, 2009:

1) Updated regulatory binder
2) Updated subject binder
3) Safety report
4) Worked on thesis writing

Sep 25, 2009:

1) Safety report
2) Updated regulatory binder
3) Balance study screening

Sep 28, 2009:

1) Updated AE log for subject
2) Balance study screening
3) Ordered Apo E kits
4) Worked on thesis writing

Sep 29, 2009:

1) Safety report
2) Balance study screening
3) Spoke to Brad about my doubts
4) Subject screening
5) Packaged and sent blood

Sep 30, 2009:

1) Safety report
2) Sent email to Tina in IRB
3) Updated Medidata

Oct 1, 2009:

1) Sent new materials for IRB approval
2) Safety report
3) Updated subject binders

Oct 2, 2009:

1) Safety report
2) Faxed approved email ad to recruitment specialist
3) Worked on thesis writing

Oct 5, 2009:

1) Updated regulatory binder
2) Safety report
3) Thesis writing

Oct 6, 2009:

1) Safety report

2) Spoke to Brad

3) Screening for Balance study

4) Thesis writing

Oct 7, 2009:

1) Safety report

2) Updated regulatory binder

3) Worked on thesis

Oct 8, 2009:

1) Updated subject binder

2) Screening for Balance study

Oct 9, 2009:

1) Scheduled MRI for subject

2) Screening for Balance study

Oct 12, 2009:

1) Updated regulatory binder
2) Safety report
3) Worked on continuing review-progress report

Oct 13, 2009:

1) Safety report
2) Worked on thesis

Oct 14, 2009:

1) Safety report
2) Worked on progress report

Oct 15, 2009:

1) Safety report
2) Updated regulatory binder

Oct 16, 2009:

Did not go to office

Oct 19, 2009:

1) Safety report
2) Met with the new Director of Clinical Trials- Dr.Bergamini
3) Updated regulatory binder
4) Prepared for visit 9 on Oct 20th
5) Spoke to Brad (CRA) to discuss the re-dosing for subject coming in on Oct 20th

Oct 20, 2009:

1) Subject visit
2) Entered all visit data in Medidata
3) Updated visit in Study Manager
4) Sent email to Rhonda for stipend request process

Oct 21, 2009:

1) Safety report

2) Worked on thesis writing

Oct 22, 2009:

1) Worked on continuing review and submitted it to Tina in the Office of Clinical Trials

2) Worked on thesis writing

Oct 23, 2009:

1) Safety Report

2) Updated subject binders and regulatory binders

APPENDIX B

INTERVIEW QUESTIONNAIRE

Subject ID no:

1) Do you know the name of this place?

2) Do you know why you have come here today?

3) Do you know if you have come to the clinic today for your usual medical care (such as a a check up) or are you involved in a research study?

4) Do you know what the research study is about?

5) Do you believe that you can refuse to participate in the research study?

6) As a participant in this research study, do you know if you are receiving the study medication or the placebo (sugar pill or salt water infusion)?

7) As a participant in this research study, do you receive the study medication in pill form or as an injectable (in your vein)?

8) Are you taking part in this research study in the hope that the study medication with help you or other patients with Alzheimer's disease?

- Scoring: 0-unable to answer/ wrong answer, 1-partial correct answer, 2-correct answer.
- Total score:0-16
- Score of at least a 50% would suggest that the subject has a reasonable knowledge of the meaning of being in a research study.
- A partial correct answer is expected only for question # 1 and # 4:
- # 1: correct answer- University of North Texas Health Science Center

  Partial correct answer- doctor's office, medical facility
- # 4: correct answer- Testing a new drug for Alzheimer's disease

  Partial correct answer- testing a drug for my memory problem

APPENDIX C

IRB DOCUMENTS

UNIVERSITY of NORTH TEXAS
HEALTH SCIENCE CENTER at Fort Worth
★
Education, Research,
Patient Care and Service

DATE: 21 July 2009
TO: Janice Knebl, DO, MBA

Office for the Protection of Human Subjects
3500 Camp Bowie Boulevard
Fort Worth, Texas 76107-2699

PROTOCOL: # 2009-086

Level of Understanding of Participation in a Clinical Trial by Alzheimer's Subjects and its Correlation to Their Neuropsych Test Scores: A Pilot Study

IRB BOARD ACTION AND NOTICE OF APPROVAL

The Institutional Review Board (IRB) has reviewed your protocol under Expedited Review Procedures and has granted approval under the provisions of 45 CFR 46.110 (b) (1) Category (7).

Approval is effective July 21, 2009 through July 21, 2010

You are responsible for complying with all UNTHSC IRB and OPHS policies, decisions, conditions and requirements. You are responsible for insuring that the research is implemented as specified in the approved protocol. Unless otherwise authorized by the UNTHSC-IRB, you are responsible for obtaining and documenting informed consents in accordance with applicable Federal Regulations (45 CFR 46 and 21 CFR 50) using ONLY the IRB approved consent forms designated for this protocol.

You must report to the Chair of the IRB any changes affecting the protocol upon which this certification is based. **No changes may be made without prior approval by the IRB** except those necessary to eliminate immediate hazards.

Should your project period extend beyond this expiration date, you must submit a Progress Report for Continuing Review to the IRB. You must allow sufficient time for the request for renewal to be reviewed and approved **before expiration of the current approval.** Be sure to *prepare for a renewal 2 months prior to the protocol expiration date.* If the project is finished before the approval expiration date, you must submit a final Progress Report (Continuing Review) either at the time the project is completed or before the expiration.

The Office for the Protection of Human Subjects (OPHS) will send out a reminder notice for your Progress Report (Continuing Review), however it is the responsibility of the Principal Investigator to prepare such a report in order for continuing review to occur BEFORE the expiration date.

Sincerely,

Brian Gladue, PhD
Chair, UNTHSC Institutional Review Board

UNIVERSITY of NORTH TEXAS HEALTH SCIENCE CENTER at Fort Worth
TEXAS COLLEGE OF OSTEOPATHIC MEDICINE
INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS

BOARD ACTION

IRB PROJECT #: 2009-086 DATE SUBMITTED: July 2009

PRINCIPAL INVESTIGATOR: Janice Knebl DO, MBA

PROJECT TITLE: Level of Understanding of Participation in a Clinical Trial by Alzheimer's Subjects and its Correlation to Their Neuropsych Test Scores: A Pilot Study

PROTOCOL #:

DEPARTMENT: Internal Medicine TELEPHONE EXTENSION:

In accordance with UNT Health Science Center policy on the protection of human subjects, the following action has been taken on the above referenced project:

Approval, when given, is **only** for the project as submitted. **No changes** may be implemented without first receiving IRB review and approval.

✓ Project has received approval through July 21, 2010.

✓ Informed Consent approved as submitted on July 21, 2009 (partic. agreemt. x2). You **MUST** use this version (attached) rather than previously approved versions. In addition, only consent documents which bear the official UNTHSC IRB approval stamp can be used with subjects.

____ Study Protocol dated _____ approved as submitted.

✓ Protocol Synopsis approved as submitted on July 21, 2009.

____ Amendment _____ to the protocol approved as submitted.

____ Based upon the recently completed Continuing Review (IRB Form 4), project has received continued approval through _____.

____ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "highlighted" copy and one "clean" copy of the revised protocol synopsis, informed consent and advertisements to the IRB for review. YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.

____ Consideration of the project has been tabled pending resolution of the issue(s) outlined below.

____ Project is disapproved for the reason(s) outlined below.

____ Completion of project is acknowledged and all required paperwork has been received.

✓ Special Findings:

The following materials were approved as submitted: protocol synopsis, caregiver research participation agreement (i.e Novartis Pharmaceuticals), caregiver researcher participation agreement (i.e. Elan Pharmaceuticals), and debriefing script.

Chairman, Institutional Review Board

7-24-09

Date

IRB Form 2 revised 12-03 MA 04-1487

PROTOCOL SYNOPSIS

Title of Research Activity:

Level of understanding of participation in a clinical trial by Alzheimer's subjects and its correlation to their neuropsych test scores: a pilot study.

Name of Principal Investigator:

Dr.Janice Knebl, DO, MBA

Name of co-investigator:

Barbara Harty, NP, MSN

Name of student investigator:

Deepti Patki

A. Specific Aims-

(1) To determine whether subjects with Alzheimer's type dementia understand the meaning of participating in a research study. If so, what is their level of understanding?

(2) To determine the correlation of the level of understanding of the subjects with their neuropsych test scores.

B. Background and Significance-

Although Alzheimer's subjects are not considered fully capable of providing consent, they have the right to know what it means to participate in a research study. Studies that have been done so far have assessed the capacity of Alzheimer's subjects to provide informed consent before enrolling them in the research study or using hypothetical situations (Scott. Y.M. et.al, 2002). This study will evaluate the comprehension by the Alzheimer's subjects of being in a "research study" after participating in one and being half-way through it. This study will further evaluate whether their latest neuropsych test scores correlate with their level of understanding. This study will help to answer the question whether having a one-time informed consent in a trial involving Alzheimer's subjects is a good idea or is there a need to repeatedly have a shorter version of it, summarizing the major points about the study. The results will determine if there is a need to improve the informed consent process in Alzheimer's trials, thus providing additional safeguards for this vulnerable population.

C. Preliminary Studies-

None

D. Investigator Experience- Dr.Knebl, Chief of Geriatrics Division, UNTHSC has served as a Principle Investigator in multiple drug trials involving Alzheimer's subjects for over 15 years. She is also the Medical Director of Long term care facilities.

E. Experimental Design and Methods-

1) Methods and Procedures-This study will involve participants that are enrolled in the UNTHSC IRB approved Phase 3 trial of Bapineuzumab sponsored by Elan Pharmaceuticals (IRB protocol # 2008-036 & 2008-037) and the Phase 3 open-label study of Exelon patch sponsored by Novartis (IRB protocol # 2007-56) being conducted at the Patient Care Center, University of North Texas Health Science Center, Fort Worth. The subject's caregiver will be asked to sign the consent form if he/ she thinks the subject will be willing to participate in this study. The subject will not be told about participation in this study. The aim of this study is to assess whether the subjects know that they are currently participating in a "research study" at the UNTHSC. Hence, the researchers would like to have natural responses to the questions in the interview. Informing subjects that they will be asked questions about the clinical trial they are participating in will defeat the purpose of this study. The consent procedure with the subjects can be waived since this study involves no more than minimal risk. However, since this is a vulnerable population, the subject's caregiver will be informed about this study and will be asked to authorize the subject's participation.

   A structured interview will be conducted with subjects (questionnaire attached) when they come for their scheduled study visits for the Elan and Novartis study. This interview is designed to assess if the subjects understand what it means to be a part of the Elan/Novartis study. The interview will take place as soon as the subject comes in, before the Elan/ Novartis study procedures are conducted for that particular visit. All subjects will be accompanied by their caregiver. The interview will be conducted two times in all during the study period to determine if there is any change in the scores. The interview will be scored with a minimum score of 0 and a maximum score of 16. (Detailed scoring system is in the attached questionnaire). The answers will be recorded in writing by the interviewer. These scores will then be used to correlate to the latest scores of the subjects on the following neuropsych tests:

   Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), Neurological Test Battery (NTB)-Rey Verbal Learning and category fluency test, Disability Assessment for Dementia(DAD) and Clinical Dementia Rating (CDR)-sum of boxes for the Elan study subjects and MMSE and ADAS-Cog for the Novartis study subjects. These tests are administered to the subjects by trained professionals during their routine study visits as a part of the Elan study and Novartis study. The latest scores on the neuropsych tests for the Elan study subjects will be accessed from the Medidata Database. This is a database supplied by the sponsor to securely enter all test scores. The scores for the Novartis study subjects will be accessed through the Investigator portal. These databases are accessible only to the key personnel and are password-protected. (Copies of the tests to be used are attached)

   The subjects will be debriefed after the completion of this study. They will have the opportunity to ask questions about any new information generated through this study. They will also have the opportunity to withdraw from this study and have their data removed.

2) Data Analysis and Data Monitoring- This study will not involve any statistical analysis since it is a pilot study with a small sample size. However, descriptive analyses will be performed from the data collected.

3) Data Storage and Confidentiality- The randomized subject identification numbers already assigned by the sponsor (Elan and Novartis) will be used. All research data will be stored in a locked cabinet in room PCC 2-302. Only the key personnel will have access to this data. No data will be released.

4) Setting- All interviews will be conducted in the Patient Care Center clinic area in a private exam room. The privacy and confidentiality of subjects will be maintained. Only the caregivers and the interviewer will be present during the interview with the subject. The room will be locked during the interview.

5) Laboratory methods and facilities- N/A

6) Estimated Period of Time to Complete the Study-Overall time required for the study (start to completion) is 4 months. The study includes 2 visits, each visit lasting for 30 minutes.

F. Human Subjects-

1) This study will include Alzheimer's subjects enrolled in the Elan study and Novartis study approved by the UNTHSC IRB.

2) Sample size- 10

3) Inclusion criteria- Subjects already enrolled in the Phase III Alzheimer's Disease trial of Bapineuzumab sponsored by Elan Pharmaceuticals and the Phase III open-label study of Exelon Patch sponsored by Novartis being conducted at UNTHSC, Fort Worth. These subjects are diagnosed with dementia of the mild to moderate Alzheimer's type. Children will not be included in this study since children cannot develop dementia of the Alzheimer's type.

4) The participants can be male/female, 50-89 years old and of any race. This study is designed to assess the level of understanding of participation in a clinical trial by people with Alzheimer's disease and hence, it is necessary to have this vulnerable population for the study.

5) Source of study population: Subjects enrolled in the Elan study and Novartis study being conducted at UNTHSC, Fort Worth. These subjects come from the UNTHSC Geriatrics Clinic and the community.

6) There are no plans for recruitment since subjects that are enrolled in the Elan and Novartis study will be asked if they would like to participate in the study.

G. Risk/Benefit Assessment-

1) This research study involves minimal risk. There is no direct benefit to the subject.

2) Outcomes from this study may help provide insights into the informed consent process in a trial involving Alzheimer's subjects. This study might be able to show the need to improve the informed consent process.

3) This study may help to determine if the subjects really understand what it means to participate in a research study. If not, the informed consent process involving this vulnerable population could be modified for their

better understanding and may provide additional safeguards in a study involving this vulnerable population. This study is significant since the informed consent is an important part of any human research study. There are no alternative approaches for the subjects. The Alzheimer's subjects will not be consented before their participation in this research study in order to accomplish the research objective. However, they will be debriefed after the completion of this study and will be given the opportunity to withdraw from the study and have their data removed. The caregiver will act on behalf of the subject and will authorize the subject's participation in this study.

4) Potential risks: The subjects may feel some frustration if they are not able to answer questions asked in the interview. No adverse reactions are expected from this study. The informational risk is minimized since all research data will be kept secured in locked cabinets accessible only to the key personnel.

H. **Payment/Compensation-** No compensation will be provided to the subject.

I. **Subject Costs-** None.

J. List of Key Personnel-

1) Dr.Janice Knebl, DO, MBA: Supervision of the entire study. Guidance for data analyses.

2) Barbara Harty, GP, MSN: Supervision of data collection

3) Deepti Patki, MS: Will be responsible for conducting the interview and administering the research participation agreement.

K. Literature Cited-

1) Alison Wichman, MD, and Alan L. Sandler, DDS. Research involving subjects with dementia and other cognitive impairments: Experience at the NIH, and some unresolved ethical considerations. Neurology, 1995; 45:1777-1778
2) Barbara Resnick, PhD, CRNP, FAAN, FAANP, 1 Ann L. Gruber-Baldini, PhD. Reliability and Validity of the Evaluation to Sign Consent Measure. The Gerontologist, 2007; Vol.47, No.1; 69-77
3) Cahill, Maura; Wichman, Alison. Research Involving Persons with Cognitive Impairments: Results of a Survey of Alzheimer Disease Research Centers in the United States. Office of Human Subjects Research, National Institutes of Health, Bethesda, Maryland, U.S.A., January/March 2000; Volume 14(1): 20-27
4) Dilip Jeste, MD, Barton.W.Palmer, PhD. A New Brief Instrument for Assessing Decisional Capacity for Clinical Research. Arch Gen Psychiatry. 2007; 64(8):966-974
5) Dinesh Mittal, M.D. Barton W. Palmer, Ph.D. Comparison of Two Enhanced Consent Procedures for Patients With Mild Alzheimer Disease or Mild Cognitive Impairment, Am J Geriatr Psychiatry, February 2007; 15:2
6) Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State ": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975; 12:189–198
7) Jason Karlawish, M.D., Scott Y. H. Kim, M.D., Ph.D. The Views of Alzheimer Disease Patients and Their Study Partners on Proxy Consent for Clinical Trial Enrollment, Am J Geriatr Psychiatry, March 2008; 16:3

8) Jessica Wilen Berg. Legal and Ethical Complexities of Consent with Cognitively Impaired Research Subjects: Proposed Guidelines. Journal of Law, Medicine & Ethics, 1996; 24 : 18-35
9) John Harrison, C. Psychol, PhD; Sonia L. Minassian, DrPH. A Neuropsychological Test Battery for Use in Alzheimer Disease Clinical Trials, Arch Neurol. 2007; 64(9):1323-1329
10) Salvini Porro G. Clinical research from the point of view of caregivers. Ital.J Neurol.Sci.Suppl. al n. 1997; 5:57-58
11) Scott Y.H. Kim, M.D., Ph.D., Christopher Cox, Ph.D., Eric D. Caine, M.D. Impaired Decision-Making Ability in Subjects With Alzheimer's Disease and Willingness to Participate in Research. Am J Psychiatry, 2002; 159:797–802
12) Sid E. O'Bryant, PhD, Stephen C Waring, DVM, PhD. Staging Dementia using Clinical Dementia Rating Scale Sum of Boxes Scores: A Texas Alzheimer's Research Consortium Study. Arch Neurol, 2008; 65 (8): 1091-1095
13) Susan Slaughter, Dixie Cole, Eileen Jennings and Marlene A Reimer. Consent and Assent to Participate in Research from People With Dementia. Nursing Ethics, 2007; 14 (1)
14) The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The Belmont Report: Ethical Principles and Guidelines for the protection of Human Subjects of Research, April 18, 1979.
15) http://books.google.com/books?id=w1yPmehSZ2cC&lpg=PA213&ots=Vjygr59I9x&dq=Disability%20assessment%20DAD&pg=PA255

Attachments:

I. Consent Forms
II. Study Documents- questionnaire for the interview, script for debriefing subjects, copy of tests used.
III. Evidence of Human Subject Training for the student investigator. The CITI training certificates for Principle Investigator and Co-Investigator are already on file with UNTHSC IRB.
IV. Conflict of Interest Form completed and signed by each key personnel.

UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER

Caregiver Research Participation Agreement

Title: Level of understanding of participation in a clinical trial by Alzheimer's subjects and its correlation to their neuropsych test scores: a pilot study

Name of the Principle Investigator: Dr. Janice Knebl, DO, MBA

Name of the Co- Investigator: Barbara Harty, R.N., M.S.N

Name of the person conducting the interview: Deepti Patki

The University of North Texas Health Science Center (UNTHSC) is conducting a research project to evaluate the level of understanding of participation in a clinical trial by Alzheimer's subjects and to determine its correlation to their neuropsych test scores. There will be no direct benefit for participation in this research study. If you would like your loved one (subject) to participate in this research study, he/she will be asked to complete a short face-to-face interview (30 minutes) with a member of our research staff, two times during the period of this study. This study will take place from July 2009-November 2009. The interviewer will ask your loved one questions about what it means to participate in the Phase III study of Bapineuzumab sponsored by Elan Pharmaceuticals that he/she is currently participating in at the UNTHSC. The interview will take place on the day of the scheduled Bapineuzumab study visits. None of your/ your loved one's personal identifying information such as name and address will be recorded in the study data. Results from this study will not report any of your/ your loved one's personal information. No compensation will be provided for participation in this study. In order to accomplish the research objective and to get natural responses to the questions on the interview, we will not tell your loved one about his/her participation in this study. However, after the completion of this study, they will be debriefed as to the purpose of the study and will be given adequate time to ask questions and/or withdraw their participation from this study.

If you do not want your loved one to participate in this study, this will in no way affect you or your loved one's medical treatment at the UNTHSC clinic/ participation in the clinical trial. Participation in this research study is completely voluntary

My name is _____ and I am a **caregiver** to an Alzheimer patient. I have read (or have been told) the above and agree to have my loved one take part in this research study.

Caregiver's signature:_____ Date:_____

Signature of Person Obtaining Consent_____ Date_____

HIPAA COMPLIANCE INFORMATION

Protocol Title: Level of understanding of participation in a clinical trial by Alzheimer's subjects and its correlation to their neuropsych test scores: a pilot study

Principal Investigator: Dr.Janice Knebl, DO, MBA

ADDENDUM TO INFORM CONSENT FORM FOR AUTHORIZATION OF PARTICIPATION OF YOUR LOVED ONE IN A HUMAN RESEARCH STUDY (HIPAA AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION IN RESEARCH)

This form and the attached research consent form need to be kept together.

Purpose of this form:

You have been asked to authorize the participation of your loved one (subject) in a research study. The consent form for this study describes the subject's participation, and that information still applies. This addendum is required by the federal "Health Insurance Portability and Accountability Act" (HIPAA). The purpose is to get your permission (authorization) to use health information about your loved one that is created by or used in connection with the research.

Authorization to Use Health Information:

The investigator named above and their assistants will be allowed to see and to use your loved one's health information for this research study. We may share this health information with people at the Health Science Center who help with the research.

We are asking your permission for your loved one's participation in the research described in the attached consent form. To do this research, we need to collect health information that identifies your loved one. The information we might use or disclose includes: supporting information from your loved one's research records to include the scores of his/her neuropsych tests. For your loved one to be in this research, we need your permission to collect and share this information.

Term of Authorization:

If you sign this form, we will collect your loved one's health information until the end of this research study. We may collect some information from your loved one's medical records even after his/her direct participation in the research project ends. We will keep all the information as long as necessary in case we need to look at it again. We will protect the information and keep it confidential.

Initials of Caregiver_____

Date _____

Refusal to Sign/Right to Revoke:

If you sign this form, you are giving us permission to collect, use and share your loved one's health information. You do not need to sign this form. If you decide not to sign this form, your loved one cannot be in this research study. You need to sign this form and the attached consent form if you want your loved one to be in this research study. We cannot do the research if we cannot collect, use and share your loved one's health information. If you change your mind later and do not want us to collect or share this health information, you need to send a letter to the researcher listed on the attached consent form. The letter needs to say that you have changed your mind and do not want the researcher to collect and share your loved one's health information:

Dr.Janice Knebl
Dept of Internal Medicine
University of North Texas Health Science Center
855, Montgomery Street,
Fort Worth, Texas 76107.

Questions regarding your privacy rights:

Any questions? Please ask Dr. Janice Knebl by calling 817-735-2200. You can also call the Institutional Review Board, University of North Texas Health Science Center at Fort Worth, at 817-735-0409 with questions about the research use of your loved one's health information. The researcher will give you a signed copy of this form.

By signing this form, I am giving permission for the personal health information about _____ to be collected and used as described above by the researchers and staff for the research study described in this form and the attached consent form. I will be given a copy of this authorization form after I have signed it.

Name of Caregiver (print)	Signature	Date

Name of Person Conducting Informed Consent Discussion (print)	Signature	Date

Initials of Caregiver_____

Date _____

UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER

Caregiver Research Participation Agreement

Title: Level of understanding of participation in a clinical trial by Alzheimer's subjects and its correlation to their neuropsych test scores: a pilot study

Name of the Principle Investigator: Dr. Janice Knebl, DO, MBA

Name of the Co- Investigator: Barbara Harty, R.N., M.S.N

Name of the person conducting the interview: Deepti Patki

The University of North Texas Health Science Center (UNTHSC) is conducting a research project to evaluate the level of understanding of participation in a clinical trial by Alzheimer's subjects and to determine its correlation to their neuropsych test scores. There will be no direct benefit for participation in this research study. If you would like your loved one (subject) to participate in this research study, he/she will be asked to complete a short face-to-face interview (30 minutes) with a member of our research staff, two times during the period of this study. This study will take place from July 2009-November 2009. The interviewer will ask your loved one questions about what it means to participate in the Phase III open-label study of Exelon patch sponsored by Novartis Pharmaceuticals that he/she is currently participating in at the UNTHSC. The interview will take place on the day of the scheduled Exelon patch study visits. None of your/ your loved one's personal identifying information such as name and address will be recorded in the study data. Results from this study will not report any of your/ your loved one's personal information. No compensation will be provided for participation in this study. In order to accomplish the research objective and to get natural responses to the questions on the interview, we will not tell your loved one about his/her participation in this study. However, after the completion of this study, they will be debriefed as to the purpose of the study and will be given adequate time to ask questions and/or withdraw their participation from this study.

If you do not want your loved one to participate in this study, this will in no way affect you or your loved one's medical treatment at the UNTHSC clinic/ participation in the clinical trial. Participation in this research study is completely voluntary

My name is _____ and I am a **caregiver** to an Alzheimer patient. I have read (or have been told) the above and agree to have my loved one take part in this research study.

Caregiver's signature:_____ Date:_____

Signature of Person Obtaining Consent_____ Date_____

HIPAA COMPLIANCE INFORMATION

Protocol Title: Level of understanding of participation in a clinical trial by Alzheimer's subjects and its correlation to their neuropsych test scores: a pilot study

Principal Investigator: Dr.Janice Knebl, DO, MBA

ADDENDUM TO INFORM CONSENT FORM FOR AUTHORIZATION OF PARTICIPATION OF YOUR LOVED ONE IN A HUMAN RESEARCH STUDY (HIPAA AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION IN RESEARCH)

This form and the attached research consent form need to be kept together.

Purpose of this form:

You have been asked to authorize the participation of your loved one (subject) in a research study. The consent form for this study describes the subject's participation, and that information still applies. This addendum is required by the federal "Health Insurance Portability and Accountability Act" (HIPAA). The purpose is to get your permission (authorization) to use health information about your loved one that is created by or used in connection with the research.

Authorization to Use Health Information:

The investigator named above and their assistants will be allowed to see and to use your loved one's health information for this research study. We may share this health information with people at the Health Science Center who help with the research.

We are asking your permission for your loved one's participation in the research described in the attached consent form. To do this research, we need to collect health information that identifies your loved one. The information we might use or disclose includes: supporting information from your loved one's research records to include the scores of his/her neuropsych tests. For your loved one to be in this research, we need your permission to collect and share this information.

Term of Authorization:

If you sign this form, we will collect your loved one's health information until the end of this research study. We may collect some information from your loved one's medical records even after his/her direct participation in the research project ends. We will keep all the information as long as necessary in case we need to look at it again. We will protect the information and keep it confidential.

Initials of Caregiver_____

Date _____

Refusal to Sign/Right to Revoke:

If you sign this form, you are giving us permission to collect, use and share your loved one's health information. You do not need to sign this form. If you decide not to sign this form, your loved one cannot be in this research study. You need to sign this form and the attached consent form if you want your loved one to be in this research study. We cannot do the research if we cannot collect, use and share your loved one's health information. If you change your mind later and do not want us to collect or share this health information, you need to send a letter to the researcher listed on the attached consent form. The letter needs to say that you have changed your mind and do not want the researcher to collect and share your loved one's health information:

Dr.Janice Knebl
Dept of Internal Medicine
University of North Texas Health Science Center
855, Montgomery Street,
Fort Worth, Texas 76107.

Questions regarding your privacy rights:

Any questions? Please ask Dr. Janice Knebl by calling 817-735-2200. You can also call the Institutional Review Board, University of North Texas Health Science Center at Fort Worth, at 817-735-0409 with questions about the research use of your loved one's health information. The researcher will give you a signed copy of this form.

By signing this form, I am giving permission for the personal health information about _____ to be collected and used as described above by the researchers and staff for the research study described in this form and the attached consent form. I will be given a copy of this authorization form after I have signed it.

Name of Caregiver (print)	Signature	Date

Name of Person Conducting Informed Consent Discussion (print)	Signature	Date

Initials of Caregiver_____

Date _____

Debriefing Script/ Information Sheet

I would like to tell you that with your caregiver's permission, you were a part of a research study entitled "Level of Understanding of Participation in a Clinical Trial by Alzheimer's Subjects and its Correlation to their Neuropsych Test Scores: A Pilot Study." Dr. Knebl is the primary researcher on this study, and I am a student researcher who has been helping her with this study.

Additionally, I would like to discuss with you in more detail the study you just participated in. Do you have any questions before I begin to tell you about what we did in this study?

As you may know, scientific methods may require in certain circumstances that subjects in research studies not be given complete information about the research they participated in until after the research is completed. In studies like these we cannot always tell you everything before you begin your participation; we do want to tell you everything now that the study is completed.

We don't always tell people everything at the beginning of a study because we do not want to influence their responses to the study. Now, I would like to explain exactly what we were trying to study in this investigation. In this study, we were trying to determine whether you are able to understand what it means to participate in a clinical trial or a research study such as the Bapineuzumab/ Exelon patch study that you are currently participating in at the UNTHSC, Fort Worth. In order to do that, over the past couple of visits we have conducted a short interview with you (including the one you just took). Your answers to the questions on the interview were scored with a minimum score of 0 and a maximum score of 16. A score of at least 50 % means that you had an understanding of your participation in a clinical trial. As you know, we perform neurological tests (tests that evaluate your memory and how your brain works) with you every time you come in for your routine Bapineuzumab/Exelon study visits. We have used your scores on these brain tests and your interview scores to see if there is any type of relationship between these two items.

(At this point the correlation between the interview scores and the neuropsych test scores will be told to the subjects, if any.)

Because other people in our clinic might also be participating in this same type of study, we are asking that you not share the information we just discussed; because if other people knew the true nature of the experiment, it might affect how they answer questions on the interview.

Now that the study has been explained to you, do you have any additional questions for me? Also, I wanted to see if you would agree to allow the investigator, Dr. Knebl, to use the data that we collected from your participation in this study? Please know that if you choose to allow us to use your data or not, it will not affect the care you receive at this clinic by Dr. Knebl at any time.

Also, I want you to know that none of the results from this data will use your personal identifying information such as name and address.

I hope you enjoyed your experience!

If you have any questions later, please feel free to contact me:

Dr.Janice Knebl
Dept of Internal Medicine
University of North Texas Health Science Center
855, Montgomery Street,
Fort Worth, Texas 76107.

Do you have any final questions and/or comments about anything we've talked about?

Thank you again for your participation!

APPENDIX D

NEUROPSYCHOLOGICAL TESTS

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

ADMINISTRATION GUIDELINES

The DAD is administered through an interview with the caregiver.

There is no specific expertise required for administering this assessment. Health professionals such as occupational therapists and nurses have the necessary qualifications.

This instrument can be administered in any setting and does not require any material for administration other than the questionnaire and a pencil. It is preferable to do it in a quiet environment alone with the caregiver.

Administration of the DAD is not time consuming; it takes approximately 15 minutes.

The DAD is a measure of the actual performance in ADL of the individual as observed over a period of 2 weeks previous to the time of the interview.

In addition, the instrument assesses what the individual is doing and not what he/she is or might be capable of doing.

These activities are evaluated as performed without any assistance or reminder being provided from caregivers. These informations must be kept in mind when administering the instrument so that questions are formulated and clarified in this sense.

Questions should be asked as stated in the questionnaire and if clarifications are needed they should be given in a language that is understandable by the caregivers.

Questions should be given as follows: "During the past 2 weeks, did Mr./Ms. X, without help or reminder . . . undertake to wash himself/herself or to take a bath or shower?"

It is essential to use the exact wording in order to respect content validity. Elements in brackets should be read. The choice of answer (Yes, No, N/A) should be specified at the beginning of the interview and should be repeated throughout.

There is no strict order to follow for the administration of the items. For example, one may prefer to start the interview with instrumental ADL instead of basic ADL.

SCORING GUIDELINES

Each item can be scored: 1 point = YES, 0 point = NO, or non applicable = N/A

A **YES** indicates that the person has performed the activity without help or reminder in the last 2 weeks even if it was only performed once.

A **NO** signifies that the person did not perform the activity without help or reminder. Therefore, if a person has performed the activity with some assistance from the caregiver, verbal or physical, he/she is scored as a NO. Comments, however, could be added to this item to guide intervention planning if desired.

If the item assessed is **N/A** because, for example, the individual never did it before the occurrence of AD, or did not have the opportunity to do it in the past 2 weeks, it is scored as N/A so that he/she is not penalized.

Information on the respondent and his/her relationship to the person assessed is also gathered in the initial part of the questionnaire. In addition, information on any sensory-motor disturbance, which could influence performance in ADL, is recorded enabling this to be taken into account when interpreting the results.

Authors: L. Gauthier and I. Gelinas
Collaborators: M. McMintyre, S. Gauthier, H. Laberge, and S. Wood Dauphinee

DISABILITY ASSESSMENT FOR DEMENTIA (DAD)

Administration Guidelines

Interview the **caregiver** to measure the actual performance of the patient over the previous 2 weeks. The activities must be performed by the patient without any assistance or reminder. Therefore, to ensure the caregiver answers each question correctly begin with:

"During the past 2 weeks, did the patient, without help or reminder, . . . "

Scoring
Yes = performed activity in last 2 weeks if only once
No = did not perform activity or performed with some assistance or reminder
N/A = individual never previously performed this item or did not have the opportunity to do it in the past 2 weeks. Therefore, it is not relevant.

	Hygiene	Yes	No	N/A
Initiation	Undertake to wash himself/herself or to take a bath or shower			
	Undertake to brush his/her teeth or care for his/her dentures			
	Decide to care for his/her hair (wash and comb)			
Planning and Organization	Prepare the water, towels, and soap for washing, taking a bath or shower			
Effective Performance	Wash and dry completely all parts of his/her body safely			
	Brush his/her teeth or care for his/her dentures appropriately			
	Care for his/her hair (wash and comb)			

	Dressing	Yes	No	N/A
Initiation	Undertake to dress himself/herself			
Planning and Organization	Choose appropriate clothing (with regard to the occasion, neatness, the weather and the color combination)			
	Dress himself/herself in appropriate order (undergarments, trousers/dress, shoes)			
Effective Performance	Dress himself/herself completely			
	Undress himself/herself completely			

	Continence	Yes	No	N/A
Initiation	Decide to use the toilet at appropriate times			
Effective Performance	Use the toilet without "accidents"			

	Eating	Yes	No	N/A
Initiation	Decide that he/she needs to eat			
Planning and Organization	Choose appropriate cutlery and seasonings when eating			
Effective Performance	Eat his/her meals at normal pace and with appropriate manners			

DISABILITY ASSESSMENT FOR DEMENTIA (DAD) (continued)

	Meal Preparation	Yes	No	N/A
Initiation	Undertake to prepare a light meal or snack for himself/herself			
Planning and Organization	Adequately plan a light meal or snack (ingredients, cookware)			
Effective Performance	Prepare or cook a light meal or snack safely			

	Telephoning	Yes	No	N/A
Initiation	Undertake to telephone someone at a suitable time			
Planning and Organization	Find and dial a telephone number correctly			
Effective Performance	Carry out an appropriate telephone conversation			
	Write and convey telephone messages adequately			

	Going on an Outing	Yes	No	N/A
Initiation	Undertake to go out (walk, visit, shop) at an appropriate time			
Planning and Organization	Adequately organize an outing with respect to transportation, keys, destination, weather, necessary money, shopping list			
Effective Performance	Go out and reach a familiar destination without getting lost			
	Safely take the adequate mode of transport (car, bus, taxi)			
	Return from the shops with the appropriate items			

	Finance and Correspondence	Yes	No	N/A
Initiation	Show an interest in his/her personal affairs such as his/her finances and written correspondence			
Planning and Organization	Organize his/her finance to pay his/her bills (checks, statement, bills)			
	Adequately organize his/her correspondence with respect to stationary, address, stamps			
Effective Performance	Adequately handle his/her money (make change)			

	Medications	Yes	No	N/A
Initiation	Decide to take his/her medications at the correct time			
Effective Performance	Take his/her medications as prescribed (according to right dosage)			

	Leisure and Housework	Yes	No	N/A
Initiation	Show an interest in leisure activity(ies)			
	Take an interest in the household chores that he/she used to perform in the past			
Planning and Organization	Adequately plan and organize household chores that he/she used to perform in the past			
Effective Performance	Complete household chores adequately as he/she used to perform in the past			
	Stay safely at home by himself/herself when needed			

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking? ☐ Yes ☐ No

1a. If yes, is this a consistent problem (as opposed to inconsistent)? ☐ Yes ☐ No

2. Can he/she recall recent events? ☐ Usually ☐ Sometimes ☐ Rarely

3. Can he/she remember a short list of items (shopping)? ☐ Usually ☐ Sometimes ☐ Rarely

4. Has there been some decline in memory during the past year? ☐ Yes ☐ No

5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion) ☐ Yes ☐ No

6. Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event? ☐ Usually ☐ Sometimes ☐ Rarely

7. Does he/she forget pertinent details of the major event? ☐ Usually ☐ Sometimes ☐ Rarely

8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)? ☐ Usually ☐ Sometimes ☐ Rarely

9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

   Within 1 week: _____

   _____

   _____

   Within 1 month: _____

   _____

   _____

10. When was he/she born? _____

11. Where was he/she born? _____

12. What was the last school he/she attended? _____

    Name _____

    Place _____

    Grade _____

13. What was his/her main occupation/job (or spouse's job if subject was not employed)? _____

14. What was his/her last major job (or spouse's job if subject was not employed? _____

15. When did he/she (or spouse) retire and why? _____

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Orientation Questions for Informant:

How often does he/she know of the exact:

1. Date of the Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way about familiar streets?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way about indoors?

☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:

   ☐ As good as they have ever been
   ☐ Good, but not as good as before
   ☐ Fair
   ☐ Poor
   ☐ No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):

   ☐ No loss
   ☐ Some loss
   ☐ Severe loss

3. Rate his/her ability to handle complicated financial or business transactions (e.g., balance check-book, pay bills):

   ☐ No loss
   ☐ Some loss
   ☐ Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

   ☐ As well as before
   ☐ Worse than before because of trouble thinking
   ☐ Worse then before, another reason (why) _____

   _____

   _____

5. Can he/she understand situations or explanations?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

*This item rates behavior, not appearance.

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Community Affairs Questions for Informant:

Occupational

1. Is the subject still working? ☐ Yes ☐ No ☐ N/A
   If not applicable, proceed to item 4
   If yes, proceed to item 3
   If no, proceed to item 2

2. Did memory or thinking problems contribute to the subject's decision To retire? (Question 4 is next) ☐ Yes ☐ No ☐ D/K

3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?
   ☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

Social

4. Did he/she ever drive a car? ☐ Yes ☐ No
   Does the subject drive a car now? ☐ Yes ☐ No
   If no, is this because of memory or thinking problems? ☐ Yes ☐ No

5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No

6. Is he/she able to independently shop for needs?
   ☐ Rarely or Never (Needs to be accompanied on any shopping trip)
   ☐ Sometimes (Shops for limited number of items; buys duplicate items or forgets needed items)
   ☐ Usually
   ☐ Don't Know

7. Is he/she able to independently carry out activities outside the home?
   ☐ Rarely or Never (Generally unable to perform activities without help)
   ☐ Sometimes (Limited and/or routine, e.g., superficial participation in church or meetings; trips to beauty parlor)
   ☐ Usually (Meaningful participation in activities, e.g., voting)
   ☐ Don't Know

8. Is he/she taken to social functions outside a family home? ☐ Yes ☐ No
   If no, why not? _____

9. Would a casual observer of the subject's behavior think the subject was ill? ☐ Yes ☐ No

10. If in nursing home, does he/she participate well in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in community affairs?
If not, please probe further.

Community Affairs: Such as going to church, visiting with friends or family, political activities, professional organizations such as bas association, other professional groups, social clubs, service organizations, educational programs.

_____

***Please add notes if needed to clarify subject's level of functioning in this area.**

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household chores? _____

_____

1b. What can he/she still do well? _____

_____

2a. What changes have occurred in his/her abilities to perform hobbies? _____

_____

2b. What can he/she still do well? _____

_____

3. If in nursing home, what can he/she no longer do well (H and H)? _____

_____

Everyday Activities (Blessed):

	No Loss		Severe Loss
4. Ability to perform household tasks	0	0.5	1

Please describe: _____

_____

_____

5. Is he/she able to perform household chores at the level of:
(Pick one. Informant does not need to be asked directly).

☐ No meaningful function.
(Performs simple activities, such as making a bed, only with much supervision)

☐ Functions in limited activities only.
(With some supervision, washes dishes with acceptable cleanliness; sets table)

☐ Functions independently in some activities.
(Operates appliances, such as a vacuum cleaner; prepares simple meals)

☐ Functions in usual activities but not at usual level.

☐ Normal function in usual activities.

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?
If not, please probe further.

Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple care maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography, gardening, going to theater or symphony, woodworking, participation in sports.

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

	Unaided	Occasionally misplaced buttons, etc.	Wrong sequence commonly forgotten items	Unable to dress
A. Dressing (Blessed)	0	1	2	3

	Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B. Washing, grooming	0	1	2	3

	Cleanly; proper utensils	Messily; spoon	Simple solids	Has to be fed completely
C. Eating habits	0	1	2	3

	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D. Sphincter control (Blessed)	0	1	2	3

*A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Memory Questions for Subject:

1. Do you have problems with memory or thinking? ☐ Yes ☐ No

2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

Within 1 month

1.0 – Largely correct _____
0.5 _____
0.0 – Largely incorrect _____

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

4. When were you born? _____

5. Where were you born? _____

6. What was the last school you attended?
   Name _____
   Place _____ Grade _____

7. What was your main occupation job (or spouse if not employed)? _____

8. What was your last major job (or spouse if not employed)? _____

9. When did you (or spouse) retire and why? _____

10. Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Orientation Questions for Subject:

Record the subject's answer verbatim for each question

1. What is the date today? ☐ Correct ☐ Incorrect

_____

2. What day of the week is it? ☐ Correct ☐ Incorrect

_____

3. What is the month? ☐ Correct ☐ Incorrect

_____

4. What is the year? ☐ Correct ☐ Incorrect

_____

5. What is the name of this place? ☐ Correct ☐ Incorrect

_____

6. What town or city are we in? ☐ Correct ☐ Incorrect

_____

7. What time is it? ☐ Correct ☐ Incorrect

_____

8. Does the subject know who the informant is (in your judgment)? ☐ Correct ☐ Incorrect

_____

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

Judgment and Problem Solving Questions for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing instruments)

How are these things alike?" Subject's Response

1. turnip……cauliflower _____
   (0 = vegetables)
   (1 = edible foods, living things, can be cooked, etc.)
   (2 = answers not pertinent; differences; buy them)

2. desk……bookcase _____
   (0 = furniture, office furniture; both hold books)
   (1 = wooden, legs)
   (2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)

What is the difference between these things?

3. lie……mistake _____
   (0 = one deliberate, one unintentional)
   (1 = one bad the other good – or explains only one)
   (2 = anything else, similarities)

4. river……canal _____
   (0 = natural - artificial)
   (1 = anything else)

Calculations:

5. How many nickels in a dollar? ☐ Correct ☐ Incorrect

6. How many quarters in $6.75? ☐ Correct ☐ Incorrect

7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?

   (0 = try the telephone book, go to the courthouse for a directory; call a mutual friend)
   (1 = call the police, call operator (usually will not give address)
   (2 = no clear response)

9. Subject's assessment of disability and station in life and understanding of why he/she is present at the examination (may have covered, but rate here):

   ☐ Good Insight ☐ Partial Insight ☐ Little Insight

CLINICAL DEMENTIA RATING – SUM OF BOXES (CDR-SOB)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

INSTRUCTIONS FOR ADMINISTRATION OF MINI-MENTAL STATUS EXAMINATION

ORIENTATION TO TIME AND PLACE

1. Ask the patient, "What is the year?" Then ask them about the season, the month of the year, the day of the week and the date. Give one point for each item answered correctly for a maximum of 5 points for this section. If it is near the transition between the seasons, accept either season.
2. Ask the patient, "Where are we now?" Then ask him/her to identify the country, province/territory, county or city/town, type of building and floor of the building.

REGISTRATION OF THREE WORDS

Say, "Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are . . . APPLE, TABLE, PENNY. What were those words?" Wait one second between each of the three words. Give 1 point for each correct answer for a maximum of 3 points for this section. The order of the answers does not matter. If the patient does not say all three words, repeat them again until the patient is able to repeat them all back to you. Give the patient a maximum of 5 attempts to say all three words. The score, however, should be based only on the patient's first attempt.

ATTENTION AND CALCULATION

Ask the patient, "Subtract 7 from 100 and continue to subtract 7 from each subsequent remainder until I tell you to stop. What is 100 take away 7?" After he/she gives you an answer, ask the subject to "keep going" until he/she has given you a total of five answers. Give 1 point for each correct answer for a maximum of 5 points for this section. An answer is considered correct if it is seven less than the previous answer, regardless if the previous answer was incorrect. You should score the items objectively regardless of the patient's educational level. Do not give the patient the option of spelling WORLD backwards.

RECALL OF THREE WORDS

Say, "What were those three words I asked you to remember?" Score 1 point for each correct answer for a maximum of 3 points in this section. The order of the answers does not matter. If the patient has difficulties, be encouraging but do not give any hints to the correct answer. In addition, the patient should be asked to recall the three words regardless of his or her response to the immediate registration of the three words.

LANGUAGE

Naming: Show the patient a pencil or pen and ask him/her, "What is this?" Then show a watch and ask him/her to identify it. Score 1 point for each correct item for a maximum of 2 points for this section. An answer is correct if the patient identifies the object or if he/she identifies only a part of the object.

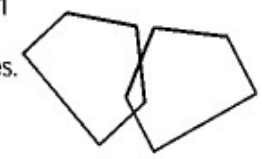
Repetition: Say, "Now I am going to ask you to repeat what I say. Ready? 'No ifs, ands, or buts'. Now you say that." If they repeat the entire phrase correctly, score 1 point for this section. Any discrepancies in the phrase should call for zero points. You may repeat the phrase if the patient has difficulties hearing or understanding you but your score should be based on the subject's first attempt at repeating the phrase. Repeat the phrase a maximum of five times.

Comprehension: Say, "Listen carefully because I am going to ask you to do something. Take this paper in your left hand, fold it in half, and put it on the floor." Score 1 point if the patient takes the paper in his/her left hand. The subject should not get a point for taking the paper in his/her right hand. Score 1 point if he/she folds the paper. The paper does not need to be folded perfectly to be considered correct. Give the patient 1 point if he/she puts the paper on the floor. The patient can get a maximum of 3 points for this section. If the patient does not take the paper at all, he/she should get zero points for this section. If the patient has a physical disability that prevents him/her from doing any of the tasks, you should still give zero points for the tasks not completed.

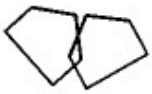
Reading: Say, "Please read the following and do what it says, but do not say it aloud." Then show him/her the "CLOSE YOUR EYES" statement. (See Appendix for the sheet of paper with this phrase printed on it.) Score 1 point if the subject closes his/her eyes. It is all right if the patient says the command aloud but do not prompt him/her to "do it" afterwards. If the subject cannot perform the command due to a vision problem or illiteracy, you should still give him/her zero points. The patient can score a maximum of 1 point for this section.

Writing: Give the patient a piece of paper and a writing utensil and say, "Please write a sentence." The patient scores a maximum of 1 point for this section if he/she writes a comprehensible sentence that contains a subject and a verb. You may ignore minor grammatical or spelling errors.

Drawing: Show the patient the design. (The design is located in the Appendix.) Then give the patient a piece of paper and say, "Please copy this design." The patient scores a maximum of 1 point for this section if he/she draws two five-sided figures that intersect to form a four-sided figure. The two figures do not have to be perfect pentagons but they should both have five sides. Furthermore, the lines need not be perfectly straight. The figure formed by the intersection, however, should have exactly four sides. A drawing should be scored as incorrect if the intersection has three or five sides or if there is no intersection al all. Patients with physical disabilities that prevent them from drawing should be given zero points for the drawing.

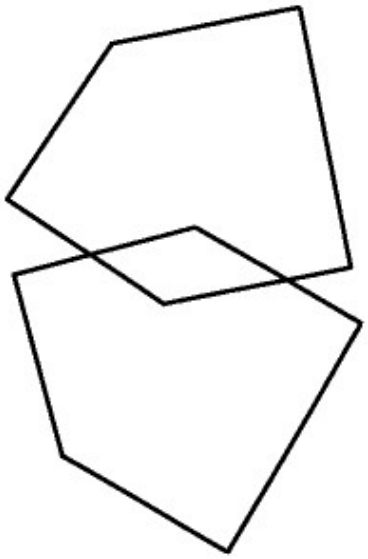


MINI-MENTAL EXAMINATION

	Patient Score	Maximum Score
Orientation To Time and Place		
What is the (year) (season) (month) (date) (day)?		5
Where are we: (country) (state/province) (city/town) (type of building) (floor)?		5
Registration of Three Words		
Name 3 objects: 1 second to say each. Use "Apple", "Table", and "Penny". Then ask the patient to repeat all 3 after you have said them. Give 1 point for each correct answer.		3
Number of trials:		
Then repeat them until he learns all 3. Count trials and record.		
Attention and Calculation		
Subtract serial sevens from 100. Stop after 5 answers (93, 86, 79, 72, 65) and give one point for each correct answer.		5
Recall of Three Words		
Ask for the 3 objects learned above. Give 1 point for each correct answer.		3
Language		
Point to a pencil or pen and a watch, and ask patient to name them.		2
Ask patient to repeat the following: "No ifs, ands, or buts".		1
Comprehension: Give the patient a sheet of paper and ask for the following: "Take a paper in your left hand, fold it in half, and put it on the floor".		3
Have patient read and obey the following instructions: "CLOSE YOUR EYES".		1
Have the patient write a sentence of his/her own choice. (The sentence should contain a subject, a verb, and make sense. Ignore spelling errors when scoring.)		1
Have the patient copy the design printed at right: (Give 1 point if all the sides and angles are preserved and if the intersecting sides form a quadrangle.) 		1
Total Score		**30**

APPENDIX

Close your eyes.



ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

The scale consists of the following components and rating scale:

RATING SCALE

* = Not assessed
0 = Not present
1 = Very mild
2 = Mild
3 = Moderate
4 = Moderately severe
5 = Severe

COGNITIVE BEHAVIOR COMPONENTS

I. Word Recall
II. Naming Objects and Fingers
III. Following Commands
IV. Constructional Praxis
V. Ideational Praxis
VI. Orientation
VII. Word Recognition
VIII. Recall of Test Instructions
IX. Spoken Language Ability
X. Word-finding Difficulty
XI. Comprehension of Spoken Language
XII. Concentration / Distractibility

ADMINISTRATION and SCORING PROCEDURES

Please refer to the accompanying administration manual for the ADAS-Cog, 1994 Revised Edition.

The first few minutes are spent in open-ended conversation in order to assess various aspects of expressive and receptive speech. Then the remaining cognitive behaviors are evaluated from report of the patient or reliable caregiver or observed during the interview. If the patient has more than a mild memory impairment, ratings on behavioral items are based on the caregiver's report. The word recall task is administered first.

The rating scale of 0-5 reflects the degree of severity of dysfunction. A rating of 0 signifies no impairment on a task or absence of a particular behavior. A rating of 5 is reserved for the most severe degree of impairment on a task. A rating of 5 is also reserved for a very high frequency of occurrence of a behavior. A rating of 1 signifies a very mild presence of a behavior or corresponds to a particular performance of a task. Ratings of 2, 3, or 4 correspond to mild, moderate, and moderately severe, respectively. Ratings on many cognitive behaviors correspond to levels of performance on task.

If total of zero is obtained for word recall, delayed word recall, or word recognition, the rater should indicate one of the following on the worksheet pages:

1 Trial administered, inappropriate response
2 Trial not administered, patient incapable
3 Trial not administered, patient refused

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

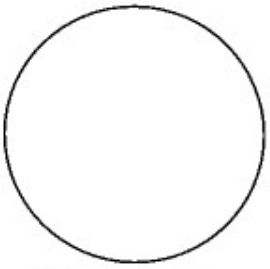
TOOLS NEEDED FOR ADAS-Cog

1. WORD RECALL – A set of cards will be issued with specific words for this visit.

2. COMMANDS – Pencil, Watch, Card

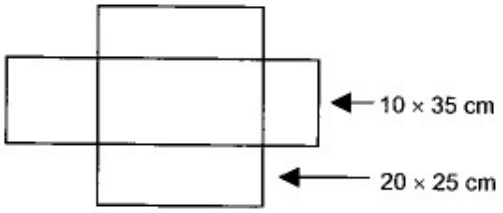
3. CONSTRUCTIONAL PRAXIS – Pieces of paper with the following drawings on them are located in the appendix:

CIRCLE

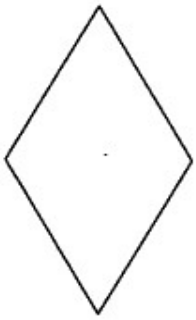


20 cm in diameter

TWO OVERLAPPING RECTANGLES

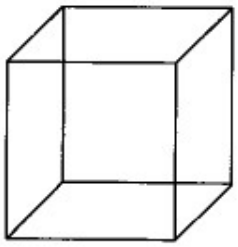


RHOMBUS



Each side 20 cm
Acute 50°
Obtuse 130°

CUBE



Each side 20 cm

4. NAMING OBJECTS AND FINGERS – The objects will be provided.

5. IDEATIONAL PRAXIS – 8½" × 11" Sheet of Paper, Long Envelope, Pencil

6. WORD RECOGNITION TASKS – A set of cards will be issued with specific words for this visit.

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

I. WORD RECALL

At the start of the first trial, the tester gives instructions similar to the following:
"I am going to show you some words, one at a time. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. We are going to do this three times".

The patient reads aloud 10 words, exposed for 2 seconds each. The patient then is asked to recall the words aloud. Three trials of reading and recalling are given.

TRIAL 1	Recalled	Not Recalled	TRIAL 2	Recalled	Not Recalled	TRIAL 3	Recalled	Not Recalled
Bottle	☐	☐	Forest	☐	☐	Girl	☐	☐
Potato	☐	☐	Temple	☐	☐	Temple	☐	☐
Girl	☐	☐	Bottle	☐	☐	Potato	☐	☐
Temple	☐	☐	Star	☐	☐	Animal	☐	☐
Star	☐	☐	Potato	☐	☐	Forest	☐	☐
Animal	☐	☐	Girl	☐	☐	Lake	☐	☐
Forest	☐	☐	Clock	☐	☐	Office	☐	☐
Lake	☐	☐	Animal	☐	☐	Clock	☐	☐
Clock	☐	☐	Lake	☐	☐	Bottle	☐	☐
Office	☐	☐	Office	☐	☐	Star	☐	☐
Total not recalled	☐		Total not recalled	☐		Total not recalled	☐	

Indicate the total number of words not recalled for each trial.

If zero words recalled for a given trial, indicate the reason below by filling in the appropriate number:

1 Trial administered, inappropriate responses

2 Trial not administered, patient incapable

3 Trial not administered, patient refused

Trial 1 ☐ Trial 2 ☐ Trial 3 ☐

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOUR (ADAS-Cog)

II. NAMING OBJECTS AND FINGERS

Say, *"Now I am going to show you a series of objects. I would like you to tell me what their names are. What is this called?"*

The patient names 12 randomly presented real objects. The first question about each object should be: *"What is this called?"* or *"What is the name of this thing?"*

If the patient responds with the object's function, say: *"Yes, that's what it does, but what is it's name?"*

If the patient does not respond, then the examiner should give the cue for that item listed below. If the patient still doesn't respond or makes an error, go on to the next object.

Objects	Standard clue that can be used to assist those patients having difficulties	Correct	Incorrect (or not named)
Flower	Grows in the garden	☐	☐
Bed	Used for sleeping	☐	☐
Whistle	Makes a sound when you blow it	☐	☐
Pencil	Used for writing	☐	☐
Rattle	A baby's toy	☐	☐
Mask	Hides your face	☐	☐
Scissors	Cuts paper	☐	☐
Comb	Used on hair	☐	☐
Wallet	Holds your money	☐	☐
Harmonica	A musical instrument	☐	☐
Stethoscope	Doctor uses it to listen to your heart	☐	☐
Tongs	Picks up food	☐	☐

Say, *"Now I am going to point to a part of your hand and I want you to tell me what it is called. What is this?"*

For the 4 fingers, if a query is necessary, say: *"What is another name for this finger?"*

The patient names the fingers on his/her dominant hand; finger:	Correct	Incorrect (or not named)
Thumb	☐	☐
Index/Forefinger/Pointer	☐	☐
Middle	☐	☐
Ring	☐	☐
Little Finger/Pinkie	☐	☐

Total Incorrect (objects and fingers) ☐

Score: 0 0-2 items named incorrectly (items : objects and fingers named)
1 3-5 items named incorrectly
2 6-8 items named incorrectly
3 9-11 items named incorrectly
4 12-14 items named incorrectly
5 15-17 items named incorrectly

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

III. FOLLOWING COMMANDS

Ask the patient to carry out the following commands. Each command should be read once. If the patient does not respond or makes an error, the tester should then give the entire command one more time. Then go on to the next command. All commands should be given to the patient. Indicate each command performed correctly or incorrectly.

	Correct	Incorrect (or not performed)
Make a fist	☐	☐
Point to the ceiling and then to the floor	☐	☐
Line up a pencil, watch, and card in that order on a table in front of the patient		
Put the pencil on top of the card and then put it back	☐	☐
Put the watch on the other side of the pencil and then turn over the card	☐	☐
Tap each shoulder twice with two fingers, keeping your eyes shut	☐	☐

Each underlined element represents a single step. Each command is scored as a whole.

Score: 0 all commands correct
1 1 command incorrect, 4 commands correct
2 2 commands incorrect, 3 commands correct
3 3 commands incorrect, 2 commands correct
4 4 commands incorrect, 1 command correct
5 all 5 commands incorrect

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

IV. CONSTRUCTIONAL PRAXIS

In the appendix, you'll find sheets of paper with the following four shapes. Show them to the patient one at a time, and instruct as follows:

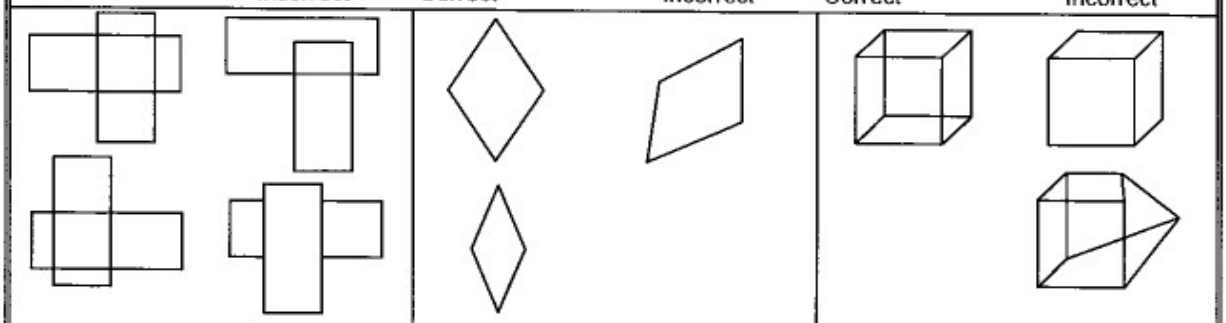
"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page" (examiner may point to shape). If patient's response is quick or sloppy, prompt with, "Take your time and try to draw it just like this one."

Allow the patient two attempts for each shape, and permit the patient to erase. If the patient cannot reproduce the figure in two attempts, the tester should go onto the next item.

A drawing should be scored as correct if the patient has reproduced all of the essential geometric features of the original. Changes in size do not count as errors. Small gaps between lines do not indicate an error, as long as the shape has been reproduced. Scoring criteria for each form (examples shown below):

1. Circle. A closed curved figure.
2. Two overlapping rectangles. Forms must be four sided, and overlap must be similar to presented form. Changes in size are not scored.
3. Diamond. Figure must be four-sided, oriented so that points are at the top and bottom, and the sides are approximately equal length.
4. Cube. The form is three-dimensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.

2.		3.		4.	
Correct	Incorrect	Correct	Incorrect	Correct	Incorrect



	Correct	Incorrect (or not drawn)
Circle	☐	☐
Two overlapping rectangles	☐	☐
Diamond	☐	☐
Cube	☐	☐

Score:

0 all 4 drawings correct
1 1 form drawn incorrectly
2 2 forms drawn incorrectly
3 3 forms drawn incorrectly
4 4 forms drawn incorrectly
5 no figures drawn, scribbles; parts of forms; words instead of forms

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

V. IDEATIONAL PRAXIS

Instruct the patient as follows:

"I want you to pretend that you have written yourself a letter. Take this piece of paper, fold it so that it will fit into the envelope, and then put it into the envelope. Then seal the envelope, address the envelope to yourself and show me where the stamp goes."

Indicate each underlined step correctly or incorrectly. If the patient forgets part of the task, or is having difficulty, the tester should repeat the instruction for the component of the task where the patient is having difficulty.

	Correct	Incorrect (or not done)
Fold a letter	☐	☐
Put the letter in an envelope	☐	☐
Seal the envelope	☐	☐
Address the envelope	☐	☐
Indicate where the stamp goes	☐	☐

Score:
- 0 all components performed correctly
- 1 failure to perform 1 component
- 2 failure to perform 2 components
- 3 failure to perform 3 components
- 4 failure to perform 4 components
- 5 failure to perform 5 components

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

VI. ORIENTATION

Before testing for orientation, the tester should be sure that no clocks, watches, or calendars are visible to the patient. Indicate each item answered correctly or incorrectly.

Score = 1 point is given for each incorrect response.

	Correct	Incorrect (or not answered)		Correct	Incorrect (or not answered)
Full name	☐	☐	**Year**	☐	☐
Day	☐	☐	**Season**	☐	☐
Date	☐	☐	**Time of day**	☐	☐
Month	☐	☐	**Place**	☐	☐

Score ☐
(maximum 8)

Acceptable answers include ± 1 day for the date, naming of upcoming season within 1 week before its onset or name of previous season for 2 weeks after its termination, within 1 hour for the time and partial name for place. First and last names, day of the week, month, and year must be exact.

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOUR (ADAS-Cog)

VII. WORD RECOGNITION

The test instructs the patient as follows:

"I am going to show you some words printed on cards. I want you to read each word out loud and try to remember it."

If the patient cannot read a word, the tester says the word out loud. However, it is important for the patient to actually look at each word and try to read it.

At the end of the learning portion of the trial, the tester instructs the patient as follows:

"Now I am going to show you another set of words. Some of the words were on the list I just showed you, and others are new. For each word, I want you to tell me whether it is one of the words I just showed you."

Then the tester shows the first word and says either:

"Is this one of the words I showed you before, yes or no?" or *"Did I show you this word before?"*

The same instruction is given before the second test word.

For the remaining test words, the tester should say,

"How about this one?"

If the patient does not remember the task (e.g., reads the words rather than responding "Yes" or "No"), then the tester should repeat or rephrase the entire question and make a note of how many times the patient had to be reminded of the task instructions. Likewise, if the patient appears to have fallen into a response set (i.e., saying "Yes" to every word or saying "No" to every word), then the test instructions should be repeated.

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

VII. WORD RECOGNITION (cont.) Bold words are the words shown before and the patient should answer YES or OLD. Italicized words are the words that the patient has not seen and the patient should answer NO or NEW. Tick the patient's responses; shading = INCORRECT responses.

	YES/ OLD	NO/ NEW	Reminder
Cost			
Nation			
Chimney			
Sparrow			
Damages			
Traffic			
Sandwich			
Service			
Shell			
Solution			
Yard			
Tube			
Body			
Ground			
Stick			
Engine			
Riches			
Gravity			
Summer			
Wisdom			
Man			
Meal			
Passenger			
Acid			

Score = total number of incorrect responses (shaded areas) or "12", whichever is smaller

Score: ☐ If Zero recognized, reason* (1—3) ☐ Total Reminders Given: ☐

*1 = Trial administered, inappropriate responses
2 = Trial not administered, patient incapable
3 = Trial not administered, patient refused

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

VIII. REMEMBERING TEST INSTRUCTIONS

Evaluate the patient's ability to remember the requirements of the word recognition task (Item VIII), based upon noting each instance of failure to remember the test instructions.

Score:	0	patient never needs extra reminders of instructions
	1	very mild – forgets once
	2	mild – must be reminded 2 times
	3	moderate – must be reminded 3 or 4 times
	4	moderately severe – must be reminded 5 or 6 times
	5	severe – must be reminded 7 or more times

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

IX. SPOKEN LANGUAGE ABILITY

Provide a global rating of the quality of speech, i.e., clarity, difficulty in making oneself understood.

Score:	0	no instance where it is difficult to understand the patient
	1	very mild – one instance of lack of understandability
	2	mild – patient has difficulty less than 25% of time
	3	moderate – patient has difficulty 25-50% of time
	4	moderately severe – patient has difficulty more than 50% of time
	5	severe – one or two word utterance; fluent, but empty speech; mute

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

X. WORD-FINDING DIFFICULTY IN SPONTANEOUS SPEECH

Rate the patient's difficulty in finding desired words, e.g., circumlocutions.

Score:	0	no evidence of word-finding difficulty in spontaneous speech
	1	very mild – 1 or 2 instances, not clinically significant
	2	mild – noticeable circumlocution or synonym substitution
	3	moderate – loss of words without compensation on occasion
	4	moderately severe – frequent loss of words without compensation
	5	severe – nearly total loss of content words; speech sounds empty; 1-2 word utterances

Score ☐
(maximum 5)

ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

XI. COMPREHENSION

Rate the patient's ability to understand speech. Do not include responses to commands.

Score:	0	no evidence of poor comprehension
	1	very mild – 1-2 instances of misunderstanding
	2	mild – 3-5 instances of misunderstanding
	3	moderate – requires several repetitions and rephrasing
	4	moderately severe – patient only occasionally responds correctly; e.g., yes/no questions
	5	severe – patient rarely responds to questions appropriately, not due to poverty of speech

Score ☐
(maximum 5)

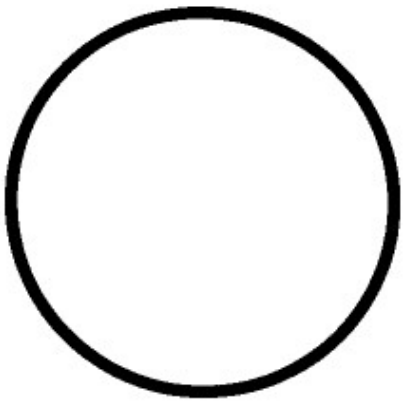
ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE BEHAVIOR (ADAS-Cog)

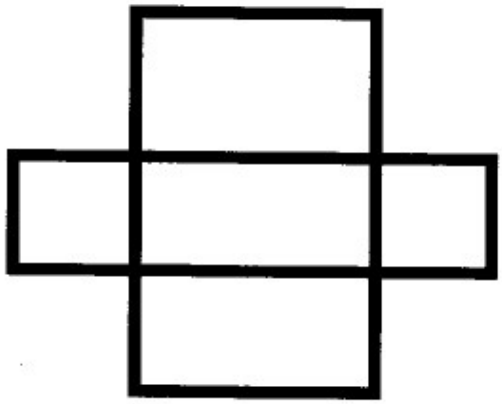
XII. CONCENTRATION/DISTRACTIBILITY

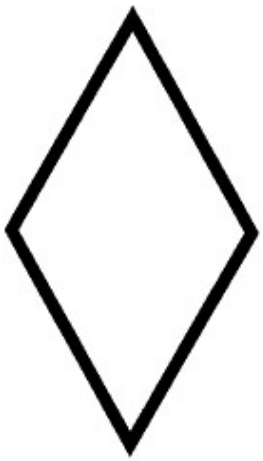
Rate the frequency with which the patient is distracted by irrelevant stimuli and/or must be reoriented to the ongoing task because the patient has lost his/her train of thought or appears to be caught up in his/her own thoughts.

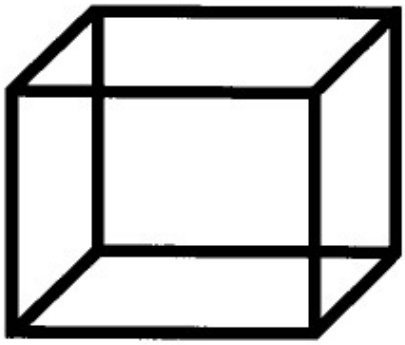
Score:	0	no evidence of poor concentration or distractibility
	1	very mild – one instance of poor concentration
	2	mild – 2-3 instances of poor concentration/distractibility; signs of restlessness and inattentiveness
	3	moderate – 4-5 instances during interview
	4	moderately severe – poor concentration/distractibility throughout much of interview
	5	severe – extreme difficulty in concentration and extremely distractible, unable to complete tasks

Score ☐
(maximum 5)









NEUROPSYCHOLOGICAL TEST BATTERY (NTB)

The scale consists of the following components:

1. Wechsler Memory Scale – Visual Paired Associates immediate test
2. Wechsler Memory Scale – Verbal Paired Associates immediate test
3. Rey Auditory Verbal Learning Test immediate test
4. Wechsler Memory Scale – Digit span
5. Controlled Word Association Test
6. Category Fluency Test
7. Wechsler Memory Scale – Visual Paired Associates delayed test
8. Wechsler Memory Scale – Verbal Paired Associates delayed test
9. Rey Auditory Verbal Learning Test delayed test

Please refer to the accompanying administration manual for the NTB.

NEUROPSYCHOLOGICAL TEST BATTERY (NTB)

3. REY AUDITORY VERBAL LEARNING TEST (RAVLT)

PART I

Instruct the patient as follows:

"I am going to read you a list of words. Listen carefully, for when I stop you are to say back as many words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can."

Read the following word list to the patient and tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

PART 2

Instruct the patient as follows:

"Now I am going to read the same list again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember, whether or not you said them before."

Read the following word list to the patient and tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

PART 3

Instruct the patient as follows:

"Now I am going to read the same list again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember, whether or not you said them before."

Read the following word list to the patient and tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

NEUROPSYCHOLOGICAL TEST BATTERY (NTB)

3. REY AUDITORY VERBAL LEARNING TEST (RAVLT) (continued)

PART 4

Instruct the patient as follows:

"Now I am going to read the same list again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember, whether or not you said them before."

Read the following word list to the patient and tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

PART 5

Instruct the patient as follows:

"Now I am going to read the same list again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember, whether or not you said them before."

Read the following word list to the patient and tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

PART 6A Time administered ☐☐☐☐ (24 hr clock)

Instruct the patient as follows:

"Now I am going to read a second list of words. Again, you are to say back as many words of this second list as you can remember. Just as before, the order in which you say the words does not matter. Just try to remember as many as you can."

Read the following word list to the patient and tick each item as and when the patient correctly recalls it.

Desk	☐	Ranger	☐	Bird	☐
Shoe	☐	Stove	☐	Mountain	☐
Glasses	☐	Towel	☐	Cloud	☐
Boat	☐	Lamb	☐	Gun	☐
Pencil	☐	Church	☐	Fish	☐
				TOTAL RECALLED (0—15)	

NEUROPSYCHOLOGICAL TEST BATTERY (NTB)

3. REY AUDITORY VERBAL LEARNING TEST (RAVLT) (continued)

PART 6B

Instruct the patient as follows:

"Now I would like you to tell me as many words as you can remember from the FIRST list of words I read to you. Again, the order in which you say the words does not matter. Just try to remember as many as you can."

Tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

NEUROPSYCHOLOGICAL TEST BATTERY (NTB)

6. CATEGORY FLUENCY TEST

Instruct the patient as follows:

"I want to see how many different types of animals you can say in one minute. Try not to repeat yourself. Begin."

Record the participant's response in the following table.

	Acceptable
1.	☐
2.	☐
3.	☐
4.	☐
5.	☐
6.	☐
7.	☐
8.	☐
9.	☐
10.	☐
11.	☐
12.	☐
13.	☐

	Acceptable
14.	☐
15.	☐
16.	☐
17.	☐
18.	☐
19.	☐
20.	☐
21.	☐
22.	☐
23.	☐
24.	☐
25.	☐
26.	☐

	Acceptable
27.	☐
28.	☐
29.	☐
30.	☐
31.	☐
32.	☐
33.	☐
34.	☐
35.	☐
36.	☐
37.	☐
38.	☐
39.	☐

Total words generated: ☐

Total acceptable words: ☐

NEUROPSYCHOLOGICAL TEST BATTERY (NTB)

9. REY AUDITORY VERBAL LEARNING TEST (RAVLT) DELAYED

PART 7

Time administered: ☐☐☐☐ (24 hr clock)

RETEST: To be administered **30** minutes after the administration of part 6A.

Instruct the patient as follows:

"A while ago I read you a list of words five times and asked you to remember the words so that you could repeat them back to me. Now I'd like you to tell me as many of those words as you can remember. It doesn't matter in what order you say them."

Tick each item as and when the patient correctly recalls it.

Drum	☐	Curtain	☐	Bell	☐
Coffee	☐	School	☐	Parent	☐
Moon	☐	Garden	☐	Hat	☐
Farmer	☐	Nose	☐	Turkey	☐
Color	☐	House	☐	River	☐
				TOTAL RECALLED (0—15)	

PART 8

Instruct the patient as follows:

"A while ago I read you a list of words five times and asked you to remember the words so that you could repeat them back to me. Now I'd like you to look carefully at this list of words and tell me which words you can remember from that first list. It doesn't matter in what order you say them."

Show the laminated card containing the following word list to the patient and tick each item as the patient recognizes it.

Teacher	☐	Beet	☐	**Nose**	☐
River	☐	**Curtain**	☐	**School**	☐
Bridge	☐	Floor	☐	**Bell**	☐
Farmer	☐	Soldier	☐	Face	☐
Pen	☐	**Drum**	☐	**Garden**	☐
Forehead	☐	**Coffee**	☐	Classroom	☐
Kerchief	☐	Road	☐	**Parent**	☐
House	☐	**Hat**	☐	Children	☐
Moon	☐	**Turkey**	☐	Broomstick	☐
Color	☐	Minute	☐	Water	☐
				TOTAL CORRECTLY RECOGNIZED (BOLD ITEMS TICKED) (0-15)	
				TOTAL INCORRECTLY RECOGNIZED (NONBOLD ITEMS TICKED) (0-15)	

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