Study Title:

A prospective, controlled study of rehabilitation of anomia in aphasia

Dates of Approval:

VA R&D Approval Date: 10/30/13

University of Washington Approval 6/25/13

No statistical analysis plan required by IRB

R&D application

VAPSHCS APPLICATION FOR NEW RESEARCH PROJECT

(This form and all required attachments & endorsements must be submitted to the VA Research Office for review and approval. Information on the form must be typed. Incomplete submissions will be returned without a review). **This form and all of its attachments should be submitted to the R&D office/ S-151. Contact Robin.Boland@va.gov. for assistance with questions regarding submissions.**

MIRB # _____ (R&D completes this field)

PI Name: Jodie Haselkorn	**Degree(s):** MD, MPH	**Email:** Jodie.haselkorn@va.gov	**Phone #** (206) 277-3452	**Service:** _____ **Mail Code:** S-117-RCS
Contact name: Megan Oelke	**Email:** Megan.Oelke@va.gov	**Phone:** (206) 685-2140	**PI VA Title:** Director, MS Center of Excellence West	**PI Academic Title:** Professor
Academic Affiliation: UW Rehabilitation Medicine **School/Department:** Epidemiology	**PI VA Appointment:** ☒ VA Salaried (# 8ths 8) ☐ WOC Contract/Fee _____ Other _____			
U.S. Citizen?: ☒ Yes ☐ No **Visa Type:** _____ **Expires:** _____	**Please reference PI Eligibility Requirements Policy:** http://go.va.gov/r3e6			

Project Title *(titles on all related subcommittee applications, including IRB and ACORP, must match exactly):*
A prospective, controlled study of rehabilitation of anomia in aphasia

Funding Source
- ☐ VA BLR&D ☐ CSR&D ☐ VA HSR&D
- ☒ VA RR&D ☐ VA CSP
- ☐ NIH (list Institute): _____
- ☐ Dept of Defense
- ☐ Other Federal Funding: _____
- ☐ Industry (Name of Sponsor): _____
- ☐ UW
- ☐ SIBCR _____
- ☐ Other funding source *(specify)*: _____
- ☐ Non-Funded

Funding Administered by (select one only)
- ☒ VA ☐ SIBCR
- ☐ UW ☐ Other *(specify)* _____
- ☐ N/A (non-funded)

Sponsor's grant # 1 IO1 RX001183-01A1

Type of Project (check all that apply)	Type of Proposal	Type of Activity
☒ Grant ☐ Contract (incl Clinical Trial) ☐ Subaward/ Subcontract (Prime PI: _____ Prime #/Title_____ ☐ Fellowship or other Training (Mentor: _____) ☐ Pilot Study/Other Specify _____	☒ New ☐ Resubmission (Previous VA Prop #)_____ ☐ Competing Renewal, Current VA Project#:_____ ☐ Competing Supplement ☐ Transfer to VAPSHCS from another institution	☒ Clinical Research ☐Single site ☒Multi-site ☐ Non-clinical (Basic) Lab Research ☐ Health Services/ Epidemiology Research ☐ RR&D ☐ Core Project/Support Service

Project Information		Direct Cost Budget Amount per year
Proposed Start Date (m/d/yy)	10/01/2013	Year 1: $275,000 Year 2: $275,000 Year 3: $275,000 Year 4: $275,000
Total Direct Costs	$1,100,000.00	
Indirect Cost Rate (%)		

Human Subjects ☐ No ☒ Yes
(If yes, please submit an IRB application and the "Privacy Review for Research Projects" form)
Human Radioisotope Use ☒ No ☐ Yes
Will the study use coded private information or specimens from humans? ☐ No ☒ Yes
Human Radiation Exposure ☒ No ☐ Yes (including X-ray, if yes submit a Radiation safety application)
Invest. Device ☒ No ☐ Yes
IDE#_____
Picture or Voice recording ☐ No ☒ Yes *(if Yes, attach form 10-3203)*

Number of subjects to be recruited from VAPSHCS 30
Total Planned accrual all sites: 80
Invest. Drugs ☒ No ☐ Yes
If yes, attach VA Form 10-9012 and Pharmacy concurrence memo.
☐ VA Form 10-9012 and Pharmacy memo attached

Targeting Vulnerable Subjects ☒ No ☐ Yes
(Please note that if you are submitting an IRB application then the answer to the Human Subjects question is "Yes")

Animal Use ☒ No ☐ Yes (if yes, submit an ACORP and identify species here)
☐ Mouse ☐ Rat ☐ Rabbit ☐ Other (specify): _____

Does this study involve:	Hazardous Materials Use	☒ No	☐ Yes	
	Non-Human Radioisotope Use	☒ No	☐ Yes	Identify: ____
	Biological Hazard Use	☒ No	☐ Yes	Identify: _____(If yes, submit Biosafety application)
	Recombinant DNA technology	☒ No	☐ Yes	Identify: _____(If yes, submit rDNA application)

I. GENERAL INFORMATION ABOUT THE PROJECT

Attach a separate page with an abstract of the project using the following headings (Title; Background; Objectives; Hypothesis; Research Design; Methods). Additionally please address the following:

A. Relevance to Veterans Health Care:
Provide a brief (no more than one paragraph) explanation of the relevance of this study to the VA's mission and the facility's research program sufficient to justify performance at the VA:

The VA currently cares for approximately 15,000 new stroke cases each year with related VA costs estimated at one billion dollars annually (Department of Veterans Affairs, 1999). One third of these strokes are associated with aphasia. The World Health Organization has deemed stroke a worldwide health problem based upon its high prevalence, associated disability, and the burden it places on the individual, community and society (Janca et al, 2000). The treatment of aphasia is currently unsatisfactory. This proposal seeks to further develop an aphasia treatment that has high potential for improving the daily communicative lives of stroke patients.

B. Project Proposal:

Option 1 – Funded grants. If project is funded, attach the complete application submitted to the sponsor including administrative pages, narrative, notice of award and sponsor reviewer critiques.

THIS IS A FUNDED GRANT. COMPLETE APPLICATION ENCLOSED.

Option 2 - Non-Funded or Locally Funded projects: The investigator must submit a Scientific Summary Statement.

C. Does this study involve storing human biological samples or data for future use beyond the duration of the project? ☒ No ☐ Yes

If yes, then please complete and attach the VA Tissue Bank/Data Repository/Registry form and be sure that your consent instrument contains the required language. Storage of samples outside VAPSHCS may require approval of VA Central Office.

D. Will you be using data from a previous study? ☒ No ☐ Yes

II. PROJECT STAFF: As PI, I affirm that all of the personnel listed below have had appropriate training for their role in this project and certificates of training are on file.

Note: *Diane Kendall, PhD is PI of the VA RR&D Merit Review Grant. Dr. Kendall will be on approved Educational Leave from July 1, 2013 to December 1, 2013. Dr. Jodi Haselkorn will be acting PI of this study in Dr. Kendall's absence. A modification to re-instate Dr. Kendall as PI of this study will be submitted in December 2013 upon Dr. Kendall's return.*

Names	Role on Project	Biohazard/Radiation/Shipping/Animal – Human Subject Contact	% Effort on Project	Admin Office Only Confirmation of Training
Jodie Haselkorn, MD, MPH	PI	☐None ☐Animal ☒Human	20%	☐ No ☐ Yes
Diane Kendall, PhD	Sub-investigator	☐None ☐Animal ☒Human	40%	☐ No ☐ Yes
Megan Oelke, MS	Research SLP	☐None ☐Animal ☒Human	40%	☐ No ☐ Yes
		☐None ☐Animal ☐Human	0%	☐ No ☐ Yes

		☐None ☐Animal ☐Human	0%	☐ No ☐ Yes
☐ **Additional listing attached**				

III. Conflict of Interest Disclosures

Does PI or any members of the project staff (those who could influence the course of the research or the outcome), or members of their immediate family, have a consulting, equity or other financial or legal relationship with the funding source or other affiliated entity? *Note that for CIRB reviewed studies the Conflict of Interest form must be submitted for each study team member regardless of the answer to this question.*	☒ No ☐ Yes

If "YES" is answered to the question above, a VA Conflict of interest form be filled out and submitted with the project.

IV. SPACE/EQUIPMENT NEEDS: Identify ALL space where project will be conducted.
Study Sites (estimate %): % at Amlk Div. 0 **% at Seattle Div.** 10 **% at UW** 50 **% at Subjects' homes*** 40%
Specify Bldg(s)/Room(s) Numbers: VAMC Room 6 West, Building 100, Clinical research unit

***NOTE:** THE PURPOSE OF THIS GRANT IS TO PROVIDE INTENSIVE BEHAVIORAL SPEECH/LANGUAGE THERAPY TO INDIVIDUALS WITH APHASIA. THERAPY WILL BE CONDUCTED 2 SESSIONS/DAY, 5 DAYS/WEEK FOR 6 WEEKS. IN ORDER FOR THE PARTICIPANTS TO BE EABLE TO RECEIVE THIS LEVEL OF INTENSITY WE ARE EXPECTING THAT MOST OF THE THERAPY WILL BE CONDUCTED IN THEIR HOMES. THESE PATIENTS HAVE SUFFERED A STROKE AND TYPICALLY CANNOT DRIVE. BASED ON THE RESEARCHERS' PRIOR RESEARCH EXPERIENCE, THIS TYPE OF RESEARCH IS MOST SUCCESSFUL IF DELIVERED IN THE HOME.

Will additional (new) space be needed for this project? If yes, describe function (e.g. staff and/or labs or records storage), any special features required, and estimated square footage	☐ Yes ☒ No	Describe and justify: _____
Is there a need for any specialized equipment or supplies not already available to the PI	☐ Yes ☒ No	Describe and justify: _____
Will there be construction or alteration of facilities required (e.g., walls, electrical, plumbing, etc.)?	☐ Yes ☒ No	Describe and justify: _____

RESOURCE USES

Will other service lines be participating beyond routine patient care? ☒ No ☐ Yes (Indicate all that apply):

☐ Pharmacy ☐ Nursing ☐ Cardiology (EKGs)
☐ MAS (chart reviews) ☐ Radiology ☐ Laboratory
☐ Nuclear Medicine ☐ Others (list): _____

V. PI CLINICAL ROLE AND PRIVLEGES: Does the protocol require any clinical interventions that would require privileges at the VA? ☒ No ☐ Yes.

If **YES**, Who will perform those interventions?_____(name)
Do they currently have clinical privileges at VAPSHCS? ☐ No ☐ Yes.

VI. By my signature on this form I certify that I will be responsible for the overall conduct of the study and will comply with all compliance, reporting and administrative requirements. I have confirmed with my Service Chief that I have been awarded the appropriate credentials and privileges to conduct research at VAPSHCS.

Signature of PI: Jodie Hu

Department of Veterans Affairs — **R&D Committee Forms - Attachment C.1**

This is an Excel spreadsheet. Enter in shaded areas only.

RESEARCH AND DEVELOPMENT INFORMATION SYSTEM PROJECT DATA SHEET

Control Number (Leave Blank)

1 Health Care Facility No.: 663

2 Location (City, State): Seattle, WA

3 Principal Investigator (Last,First, MI, Degree): Haselkorn, Jodie, MD, MPH

4 Status in Project
- [ ] 01 Awardee (Recipient of Award)
- [X] 02 Not Awardee, but Responsible VA Invstigator

5 Project Number: unknown at this time

6 Type of Report: [X] Initial [ ] Progress [ ] Final

7 Project Title (Do not exceed 142 Spaces)

A prospective, controlled study of rehabilitation of anomia in aphasia

8 Has project title changed since last report?

N/A [ ] Yes [ ] No

9 Co-Principal Investigator(s) name, and degree(s).

Kendall, Diane, PhD

10 Funding and Administration [see codes on the file named "Attach C1 Codes"]

	Funding Code	Name if "Other"	Admin Code
1	9003	Merit Review (CC 103)	02
2			
3			

11 Project Uses (Each item must have a response)

Human Subjects	[X] Yes	[ ] No	Investigational Drugs	[ ] Yes	[X] No	Radioisotopes	[ ] Yes [X] No
Animal Subjects	[ ] Yes	[X] No	Investigational Devices	[ ] Yes	[X] No	Biohazards	[ ] Yes [X] No

12 Research Focus (Mark yes only if the major reason for the research project is to study the particular topic)

Agent Orange (Dioxin)	[ ] Yes	[X] No	Females	[ ] Yes	[X] No	Prisoners of War	[ ] Yes [X] No

13 Keywords

1 Aphasia
2 Anomia
3 Treatment
4 Phonology
5 Semantic
6
7
8

14 Abstract (Use word document named "Attach C.2 Abstract")

15 Signature of Principal Investigator

16 Date: 6-24-2013

VA FORM 10-1436
JUN 1989

RESEARCH PROTOCOL SAFETY EVALUATION

PRINCIPAL INVESTIGATOR (PI): Jodi Haselkorn

PROJECT TITLE: A prospective, controlled study of rehabilitation of anomia in aphasia

DATE OF SUBMISSION: 06/10/2013

LIST VA AND NON-VA LOCATIONS IN WHICH PI CONDUCTS RESEARCH:
VA Puget Sound, University of Washington

1. DOES THE RESEARCH INVOLVE THE USE OF ANY OF THE FOLLOWING?

a. Biological Hazards (Microbiological or viral agents, pathogens, toxins, select agents as defined in 42 CFR 72.6, or animals)	YES ☐	NO ☒
b. Human or non-human cell or tissue samples (including cultures, tissues, blood, other bodily fluids or cell lines)	YES ☐	NO ☒
c. Recombinant DNA	YES ☐	NO ☒
d. Chemicals:		
(1) Toxic chemicals (including heavy metals)	YES ☐	NO ☒
(2) Flammable, explosive, or corrosive chemicals	YES ☐	NO ☒
(3) Carcinogenic, mutagenic, or teratogenic chemicals	YES ☐	NO ☒
(4) Toxic compressed gases	YES ☐	NO ☒
(5) Acetylcholinesterase inhibitors or neurotoxins	YES ☐	NO ☒
e. Controlled Substances	YES ☐	NO ☒
f. Ionizing Radiation:		
(1) Radioactive materials	YES ☐	NO ☒
(2) Radiation generating equipment	YES ☐	NO ☒
g. Nonionizing Radiation:		
(1) Ultraviolet Light	YES ☐	NO ☒
(2) Lasers (class 3b or class 4)	YES ☐	NO ☒
(3) Radiofrequency or microwave sources	YES ☐	NO ☒

Complete all sections of this form that apply. A documented review by the local Subcommittee on Research Safety is required prior to submission. If the research involves the use of human subjects or human tissues, IRB review is required. ***NOTE:*** *Use of animals also requires submission of an IACUC-approved Animal Component.*

2. BIOLOGICAL HAZARDS

a. Does your research involve the use of microbiological or viral agents, pathogens, toxins, poisons or venom? YES ☐ NO ☒

If **NO**, skip to **Section 4 on Cells and Tissue Samples** (pg. 4)

If **YES**, list all Biosafety Level 2 and 3 agents or toxins used in your laboratory. It is the responsibility of each PI to:

(1) Consult either:
   (a) The National Institutes of Health (NIH)-Centers for Disease Control and Prevention (CDC) publication entitled Biosafety in Microbiological and Biomedical Laboratories or
   (b) The CDC online reference (http://www.cdc.gov)

(2) Identify the Biosafety Level (also called Risk Group) for each organism, agent, or toxin. Enter it into the table below.

Organism/Agent/Toxin	**Biosafety Level****
_____	Select One
_____	Select One
_____	Select One
_____	Select One

** **For each Biosafety Level 2 or 3 agent or toxin** listed, provide the information requested on the following page(s). (Description of Biosafety Levels 2 and 3 can be found in Appendix A.)

b. Are any of the biohazardous agents listed above classified as a "Select Agent" by the Centers for Disease Control? YES ☐ NO ☐

3. **BIOLOGICAL HAZARDS – Description of Use NOTE:** *Replicate this page as necessary.*

a. Identify the microbiological agent or toxin (name, strain, etc.):

b. If this is a Select Agent (42 CFR 72.6), provide the CDC Laboratory Registration # and the date of the CDC inspection:

c. Indicate the largest volume and/or concentration to be used:

d. Indicate whether antibiotic resistance will be expressed, and the nature of this antibiotic resistance:

e. Describe the containment equipment (protective clothing or equipment, biological safety cabinets, fume hoods, containment centrifuges, etc.) to be used in this research:

f. Described proposed methods to be employed in monitoring the health and safety of personnel involved in this research:

4. CELLS and TISSUE SAMPLES

a. Will personnel work with animal blood, human or non-human primate blood, body fluids, organs, tissues, cell lines or cell clones? YES ☐ NO ☒

If yes, specify: _____

b. Will research studies represent a potential biohazard for lab personnel? N/A ☐ YES ☐ NO ☒

If yes, specify the potential hazard and precautions employed to protect personnel in the laboratory:

_____

NOTE: *If these studies involve animals, the Animal Component of Research Protocol (ACORP) must be completed.*

c. Specify precautions employed to protect personnel working in the laboratory:

_____

5. RECOMBINANT DNA

a. Are procedures involving recombinant DNA used in your laboratory?

YES ☐ NO ☒

b. Are recombinant DNA procedures used in your laboratory limited to PCR amplification of DNA segments (i.e., no subsequent cloning of amplified DNA)?

YES ☐ NO ☒

(1) If **YES**, your recombinant DNA studies are exempt from restrictions described in the NIH Guidelines for Research Involving Recombinant DNA Molecules.

(2) If **NO**, it is the responsibility of each PI to:

(a) Consult the current NIH Guidelines for Research Involving Recombinant DNA Molecules, found online at http://www.nih.gov/oba/rac/guidelines/guidelines.htm.

(b) Identify the experimental category of their recombinant DNA research.

c. Description of recombinant DNA procedures:

(1) Identify the NIH classification (and brief description) for these recombinant DNA studies:

_____

(2) Biological source of DNA insert or gene: _____

(3) Function of the insert or gene: _____

(4) Vector(s) used or to be used for cloning (e.g., pUC18, pCR3.1):

_____

(5) Host cells and/or virus used or to be used for cloning (e.g., bacterial, yeast or viral strain, cell line): _____

6. USE OF CHEMICALS

(a) Has the use of chemicals in your laboratory been reviewed by an appropriate committee or subcommittee in the past 12 months? NA ☐ YES ☐ NO ☒

(b)Are personnel knowledgeable about the special hazards posed by:

Carcinogens?	NA ☐	YES ☐	NO ☒
Teratogens and Mutagens?	NA ☐	YES ☐	NO ☒
Toxic gases?	NA ☐	YES ☐	NO ☒
Neurotoxins?	NA ☐	YES ☐	NO ☒
Reactive and potentially explosive compounds?	NA ☐	YES ☐	NO ☒

NOTE: Submission of the laboratory chemical inventory is required for local review.

7. CONTROLLED SUBSTANCES

(a) Does your research involve the use of any substance regulated by the Drug Enforcement Agency? YES ☐ NO ☒

If yes, list controlled substance(s) to be used:

(1) _____
(2) _____
(3) _____

(c) Are all Schedule II and III drugs stored in a double-locked vault?
NA ☐ YES ☐ NO ☒

Note: The schedule of controlled substances can be found online
http://www.usdoj.gov/dea/pubs/schedule.pdf

8. RADIOACTIVE MATERIALS

Does your research involve the use of radioactive materials? YES ☐ NO ☒

If YES, provide the following:

(a) Identity of radioactive source(s): _____
(b) Radiation Safety Committee Approval (date): _____

9. PHYSICAL HAZARDS

(a) Are physical hazards addressed in the facility Occupational Safety and Health Plan?

YES ☐ NO ☒

(b) Do employees receive annual training addressing physical hazards?

YES ☐ NO ☒

SUPPLEMENTAL SITE-SPECIFIC QUESTIONS TO RESEARCH SAFETY SURVEY

RECOMBINANT DNA (check boxes below that apply or N/A ☒ for this category):
Does the protocol involve the following:

- ☐ Use of viral vectors
- ☐ DNA/RNA probes
- ☐ Creation of cDNA/genomic libraries
- ☐ Cloning and vector construction in bacteria/yeast
  - ☐ If yes, could toxic products be released from cells?
  - ☐ If yes, could a potentially infectious agent be produced/released from cells?
- ☐ Transgenic or gene-targeted animals
  - ☐ Creation of transgenics/knockouts/knockins
  - ☐ Cross breeding transgenics/knockouts/knockins

ANIMAL PROTOCOLS (check boxes below that apply or N/A ☒ for this category):
As part of the protocol, does anyone working on the project, including staff, faculty, students, residents, WOCs and IPAs have contact with:

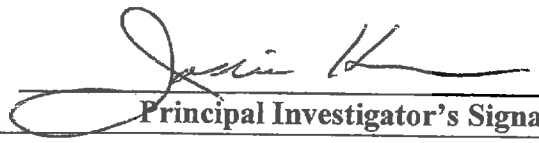
- ☐ Wild animals
- ☐ Non-human primates
- ☐ Small laboratory animals
  - ☐ SPF animals
  - ☐ Immunocompromised animals
- ☐ Large laboratory animals
- ☐ Poisonous, toxic, venomous or parasitic animals or plants
- ☐ Genetically altered animal models
- ☐ Microbiological or viral agents, pathogens, toxins/poisons

PERSONAL PROTECTIVE EQUIPMENT (check boxes below that apply or N/A ☒ for this category):
Do any procedures, chemicals or other hazards require the use of the following:

- ☐ Chemical fume hood
- ☐ Biosafety cabinet
- ☐ Respirator

Acknowledgment of Responsibility and Knowledge

I certify that my research studies will be conducted in compliance with and full knowledge of Federal, State, and local policies, regulations, and CDC/NIH Guidelines governing the use of, biohazardous materials, chemicals, radioisotopes, and physical hazards. I further certify that all technical and incidental workers involved with my research studies will be aware of potential hazards, the degree of personal risk (if any), and will receive instructions and training on the proper handling and use of biohazardous materials, chemicals, radioisotopes, and physical hazards.



Principal Investigator's Signature 6-24-2013 **Date**

Certification of Research Approval

The safety information for this application has been reviewed and is in compliance with Federal, State, and local policies, regulations, and CDC-NIH Guidelines governing the use of biohazardous materials, chemicals, radioisotopes, and physical hazards. Copies of any additional surveys used locally are available from the Research and Development (R&D) Office.

Chair, Subcommittee on Research Safety **Date**

Chair, Research & Development Committee **Date**

Radiation Safety Officer (if applicable) **Date**

Facility Safety Officer **Date**

Project Title: A prospective, controlled study of rehabilitation of anomia in aphasia
Principal Investigator: Jodi Haselkorn, PhD
Sub-Investigator: Diane Kendall, PhD

ABSTRACT: **Limit to 500 words.** The following information should be included in each abstract.

1. **Objective(s) and Hypotheses:** The objective of this study is to provide speech-language therapy to 80 individuals who have suffered a left hemisphere stroke and have aphasia (difficulty speaking). We plan to study their ability to speak before and after therapy. Specifically, this study will compare whole word (called semantic treatment) to sound based (phonological) treatment and compare the between group effects of treatment immediately post, 3 months and 1 year later.

   Hypothesis 1: Word retrieval will be improved because the previously weak and poorly differentiated phonological representations will now be strengthened and sharpened and therefore, more likely to be precisely engaged when top-down conceptual semantic processing occurs.

   Hypothesis 2: Subjects will be able to enhance residual lexical semantic knowledge on their own in a process that recapitulates normal language acquisition in children.

2. **Research Design:** A longitudinal design will be employed. The 80 subjects will be randomly assigned to one of two groups. Group A (40 subjects) will receive the phonological treatment and Group B (40 subjects) will receive the semantic treatment. Outcome measures will be administered 4 times: prior to treatment initiation, immediately upon treatment termination, and 3 months and 1 year later.

3. **Methodology:** Participants will be recruited (via flyer) through the speech pathology/audiology service at the VAMC Puget Sound, University of Washington and Portland State University Speech and Hearing Clinics, and local and regional stroke support groups. Participants will have had a single left hemisphere stroke (documented by imaging with either CT or MRI), be $\geq$ 6 months post stroke, right handed, and primary speakers of English. Therapy will consist of 60, 1-hour treatment sessions at 2 sessions/day, 5 days/week, for 6 weeks. Therapy sessions will be conducted at the most convenient site for the individual (e.g., home, VAMC, University of Washington, Portland State University). Several pen/paper measures of speech and language abilities will serve as the primary outcome measures and will be administered before and after therapy.

4. **Findings/Progress to Date:** We plan to start collecting data in January 2014.

5. **Relevance to VA Mission:** The VA currently cares for approximately 15,000 new stroke cases each year with related VA costs estimated at one billion dollars annually (Department of Veterans Affairs, 1999). One third of these strokes are associated with aphasia. The World Health Organization has deemed stroke a worldwide health problem based upon its high prevalence, associated disability, and the burden it places on the individual, community and society (Janca et al, 2000). The treatment of aphasia is currently unsatisfactory. This proposal seeks to further develop an aphasia treatment that has high potential for improving the daily communicative lives of stroke patients.

Seattle VA Puget Sound Health Care System
Research Safety Subcommittee (RSS): Project Safety & Hazard Assessment Form

	Principal Investigator	Staff/Lab Contact
Name	Jodie Haselkorn, MD, MPH	Diane Kendall, PhD, Sub-Investigator
E-mail	Jodie.haselkorn@va.gov	Megan Oelke, MS, Research SLP
Phone	(206) 277-3452	Lab: (206) 557-9877
Mail Stop	S-117-RCS	

This submission is for:	Initial Review ☒	Continuing Review ☐	Modification ☐

Complete all parts of this form.

Project Title: A prospective, controlled study of rehabilitation of anomia in aphasia

Bldg/Rm(s) where work will occur: Bldg 100, Room 6

Off Campus Site: University of Washington, Portland State University, Subjects' homes

Personnel & Training: List all personnel who will work on the project. Attach additional sheet, if necessary.

Jodie Haselkorn, MD, MPH	
Diane Kendall, PhD	
Megan Oelke, MS	

	Yes	No
All personnel listed are up-to-date for R&D annual training (either live session or video).	☒	☐
A current R&D Scope of Work is on file in the R&D Office for all listed personnel.	☐	☐

Part A

	Yes	No
1. Are chemicals used in the protocol. *If "no," skip to Part B*	☐	☒
2. The following hazardous chemicals are used in the protocol:		
Toxic chemicals (including heavy metals)? List:	☐	☐
Flammable, explosive or corrosive chemicals? List:	☐	☐
Carcinogenic, mutagenic, or teratogenic chemicals? List:	☐	☐
Toxic compressed gases? List:	☐	☐
Acetylcholinesterase inhibitors or neurotoxins? List:	☐	☐

Part B: Experimental Techniques Review

Does your project involve the use of any of the following items or hazards?	**Yes**	**No**
Cell or tissue culture? *If "Yes," attach "Application for Biohazard Approval" for Initial Review and for Modification*	☐	☒
BSL-2 items (including human tissues or fluids, viral agents)? *If "Yes," attach "Application for Biohazard Approval" for Initial Review and for Modification*	☐	☒
BSL-3 microbiological, viral agents, pathogens or toxins? *If "Yes," attach "Application for Biohazard Approval" for Initial Review and for Modification*	☐	☒
Recombinant DNA (rDNA) technology? *If "Yes," attach "Application for rDNA Approval" for Initial Review and for Modification*	☐	☒
Controlled substances? List:	☐	☒
Poisonous, toxic or venomous plants or animals? List:	☐	☒
Radioactive materials? *Enter date of Approval by Radiation Safety Committee:*	☐	☒
Physical hazards, as listed below?	☐	☒
Noise generating equipment (>75 dB)?	☐	☒
Vibration?	☐	☒
Extremes of temperature or air pressure?	☐	☒
Lasers (Class 3b or 4)?	☐	☒
Ultraviolet light?	☐	☒

Mechanical hazards?	☐	☒
Electrical hazards?	☐	☒
Additional Personal Protective Equipment? *(e.g., respirator, UV protective mask, ear protection)* List:	☐	☒

Part C: Acknowledgement of Responsibility	Yes	No
I certify that my project will be (or if closed, was) conducted in compliance with Federal, State and local policies and regulations governing the use and disposal of chemical, radioactive and biohazard materials and physical hazards.	☒	☐
I certify that all technical and incidental workers involved in this project are aware of the potential hazards and have received instructions and training on the proper handling and use of chemical, radioactive and biohazard materials and physical hazards.	☒	☐

Jamie H — 6-24-2013

Principal Investigator's Signature **Date**

Certification of Proposal Approval

The safety information in this proposal has been reviewed and found in compliance with Federal, State and local policies and regulations governing the use of chemical, physical, radioactive and biohazard materials. Resources necessary for the performance of these proposed studies are available and adequate.

Chair Subcommittee on Research Safety **Date**

Chair, Research and Development Committee **Date**

Radiation Safety Officer (if applicable) **Date**

VA PUGET SOUND HEALTH CARE SYSTEM
RESEARCH AND DEVELOPMENT

SCIENTIFIC SUMMARY OF PROPOSED RESEARCH PROJECT

All proposed research projects need to undergo a local scientific review. If a study does not have a formal protocol (i.e., unfunded or investigator initiated study) that addresses items 1-8 below, a Scientific Summary Statement is required that addresses the items.

The scientific description should be a **maximum of three pages** ***(excluding references, data security plan and data safety monitoring plan)*** and should provide sufficient detail to allow for a determination of the scientific integrity of the proposed work.

The scientific description of the proposal should be formatted as follows.

1. Name of PI and Title of Proposal
2. Hypothesis/Specific Aims
3. Background and Significance
4. Research Design and Methods
5. Analysis Plan and Power Calculations
6. Interpretation (including limitations)
7. Relevance to Veterans Health Care
8. References

1. **Name of PI and Title of Proposal**

PI of Grant: Diane L. Kendall, PhD
Acting PI while Dr. Kendall on Educational Leave (July 1, 2013 to Dec 1, 2013):
Jodi Haselkorn, PhD

2. **Hypothesis/Specific Aims**

In the context of a 2-armed randomized control trial with experimental (phonomotor) treatment versus a type of treatment that is typically delivered (lexical/semantic-based); we propose to study 80 individuals who have suffered a left hemisphere stroke and exhibit aphasia and anomia. The aims, research questions, outcome measures, time point of data collection and predictions are outlined below:

Aims	Research Question	Outcome Measure	Time point	Predictions
Primary Aim:	1. Is there a significant between group difference in word retrieval abilities following treatment?	Accuracy of confrontation naming of *untrained* nouns	3 months post treatment termination versus baseline	Based on the theoretical concept where focusing treatment at the level of phonemes and phoneme sequences intrinsically achieves generalization to all words, as well as on our preliminary data, we hypothesize that phonomotor treatment will produce a greater increase in naming accuracy of *untrained* items than will typical treatment.
Secondary Aims	2. Acquisition: Is there a significant between group difference for *trained* items immediately upon treatment completion?	Accuracy of confrontation naming of *trained* nouns	Immediately post treatment termination versus baseline	Based on the model and preliminary data, we hypothesize that both treatments will promote acquisition of *trained* items
	3. Generalization: Is there a significant between group difference for *untrained* items and contexts immediately post treatment and 3 months later?	Accuracy of confrontation naming of untrained nouns, discourse production and ecologic validity measures.	3 months post treatment termination versus baseline	Based on the conceptual model and preliminary data, we hypothesize that phonomotor will be superior to typical treatment in generalization to untrained items and discourse production.
	4. Continued growth beyond 3 months: Is there a significant difference between 3 months and 1-year post treatment termination in confrontation naming accuracy for trained and untrained nouns?	Accuracy of confrontation naming of trained and untrained items.	3 months post treatment termination versus 1 year post	We hypothesize that the phonomotor group will show continued growth from 3 months to 1 year due to the repertoire of phonological sequences that was acquired through intensive training and practiced in daily communication, while the typical treatment group will show no difference, or even a decrement, in performance over time.

3. Background and Significance

The traditional treatment approach to the rehabilitation of anomia in aphasia is to explicitly train individuals with aphasia in whole word naming (see Nickels, 2002, for extensive review) (often called lexica/semantic therapy). Controlled studies have shown that this approach may improve naming performance but generalization is typically very limited; that is, the knowledge gained by the patient tends to be limited to the words actually trained, and there is at best modest improvement in naming performance with untrained words. This generalization may be limited mainly to words that are semantically related to those in the training corpus (Kiran and Thompson, 2003; McNeil, 1997). The mechanisms underlying this generalization are not well understood. Because generalization can be limited with naming therapies, there currently exists no viable means of training patients on the full corpus of words (perhaps several thousand) they are likely to need in daily life, except in the most determined and capable of subjects (Basso, 2003).

Two approaches might be taken to solving this problem: (1) develop cost effective means for providing training on several thousand words; and (2) develop alternative training methods. We have developed an alternative method – called phonomotor therapy – and, in this project, we propose to continue development through a phase II clinical trial.

The most innovative aspect of this proposed treatment is that it explicitly targets generalization in ability to name and focuses on training a specific language mechanism that, theoretically, should enable broad generalization. Anomia is the most common and most disabling component of aphasia. An intrinsically generalizing treatment for word retrieval deficits should enable broad improvement in naming ability, not limited to trained items, and it should translate into improvement in daily communicative ability—the ultimate aim of all speech language therapy. However, in all prior attempts at treating anomia, generalization has been at best modest, hit or miss, of unknown mechanism, and never explicitly targeted in therapy. Our treatment is also highly innovative in that, by virtue of the mechanism of generalization that it engages, it should lead to continued improvement in language function after the end of treatment, rather than gradual forgetting of trained material, which is the usual course after conventional treatment. Our preliminary data provide support for the success of both innovations. Finally, while other treatments have been leveraged on (Kiran and Thompson, 2003; Plaut, 1996) or can be related to principles of neural network function captured in PDP models (Thompson and Shapiro, et al. 2003, Nadeau 2012), ours is the first to take advantage of a comprehensive PDP model to design a broadly generalizing therapy.

4. Research Design and Methods

In the context of a 2-armed randomized control trial with phonomotor treatment versus a lexical/semantic-based; we propose to study 80 individuals who have suffered a left hemisphere stroke and exhibit aphasia and anomia.

- Number: One hundred participants with chronic (duration of six or more months) aphasia following left hemisphere damage due to stroke will be recruited through the VAMC Puget Sound Speech and Hearing Clinic, the University of Washington (UW) Aphasia Registry and

Repository (Dr. Kendall is the PI of the registry), and the University of Washington Speech and Hearing Clinic.

- Selection criteria: Subjects will have had a single left hemisphere stroke (documented by imaging with either CT or MRI) and be 6 months or more post-stroke, right handed and monolingual English speaking.
- Exclusion criteria include significant apraxia of speech (see details below), depression or other psychiatric illness, degenerative neurological illnesses, chronic medical illness or a severe impairment in vision or hearing. During the screening process, bilingual participants will be interviewed with respect to the age of acquisition of English and which language they currently use most of the time. Language preference will be confirmed by an individual who has known the participant for more than one year prior to the stroke who agrees that (1) English was the preferred language and (2) English was spoken predominantly by the participant. The reason for recruiting only right-handed subjects is as follows: Because we are treating language, hypotheses are specific to the language-dominant hemisphere. Patients who are not right-handed may have different capacities in their non-dominant hemispheres to learn language, which may produce outlier effects. Individuals with dysarthria will be included as typically unilateral upper motor neuron dysarthria is the dysarthria type associated with left cortical stroke and effects on overall intelligibility are minimal.
- Inclusion criteria: Participants must (1) demonstrate word retrieval impairments for nouns as indicated by a score of <45 on the Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 2001); (2) have, at worst, mild to moderate apraxia of speech (see details below); (3) have auditory comprehension sufficient to complete the training protocol (score of >4.0 on the Western Aphasia Battery auditory comprehension subtests (WAB)(Kertesz, 1982), and (4) demonstrate a semantic impairment as evaluated by The Psycholinguistic Assessments of Language Processing in Aphasia - 53 (PALPA 53) (Kay, Lesser & Coltheart, 1992) and (5) demonstrate a phonologic impairment as evaluated by the Standardized Assessment of Phonology in Aphasia (SAPA)(Kendall et al, 2010).
- Treatment Schedule: Both treatment groups will receive a total of 60 hours of therapy (see Preliminary Studies for data justifying this dose). The phonomotor treatment will be delivered in the dosage it has been developed and studied thus far; that is, a massed practice schedule of 2 hours/day, 5 days/week for 6/weeks. Therapy sessions will be conducted at the most convenient site for the individual (e.g., VAMC, home, University of Washington, etc) to improve retention in the study program.

5. Analysis Plan and Power Calculations

- Randomization procedure: Randomization will be done from a central location, with research staff calling in to obtain the randomization assignment. A computer program written by Dr. Cain will be used to make the random assignments, while balancing on aphasia severity and aphasia type. This program uses the minimization algorithm modified to randomize subjects with a biased probability rather than assigning with certainty. It has been used in about 8 randomized trials so far.
- Statistical Analyses: Analysis will be by a mixed model analysis using measures at 3 and 12 months as outcomes and baseline measures as a covariate. The model will include as fixed factors treatment (phonomotor versus typical treatment) and time (3 and 12 months), and baseline outcome measure as covariate. Subject id will be included as a random factor. The main effect for treatment will be the primary test of difference between the two interventions.

A secondary analysis will test the interaction between treatment and time to evaluate whether the difference between the two treatment groups changed for 3 to 12 months.

- Sample Size and Power Consideration: We plan to recruit 100 participants who are greater than 6 months post stroke with chronic aphasia, with the expectation that at least 80 will provide follow-up data. In fact loss to follow-up in the pilot studies has been much lower than 20%, so this is a conservative estimate. With 40 subjects in each treatment arm, there will be 82% power for detecting a standardized effect size of 0.65 standard deviations for the main effect treatment (phonomotor versus typical treatment)(note: standardized effect size observed in the preliminary data was 0.77). This power estimate is conservative since it is based on a simple t-test. The actual analysis will use data from both follow-up time points and will control for baseline covariates, both of which should improve power relative to a t-test.

6. Interpretation (including limitations): Upon study completion, data will be interpreted as related to improvement in the ability to speak.

7. Relevance to Veterans Health Care

The World Health Organization has deemed stroke a worldwide health problem based upon its high prevalence, associated disability, and the burden it places on the individual, community and society (Janca et al, 2000). A common sequelae of left-hemisphere stroke is a language disorder called aphasia. Currently, the behavioral rehabilitation of aphasia is unsatisfactory and this proposal seeks to further develop an aphasia treatment that has high potential for improving the daily communicative lives of stroke patients.

8. References

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June 1, 2012

Director, R&D
Rehabilitation Research and Development Service Department of Veterans Affairs
810 Vermont Avenue, N.W.
Washington, D.C. 20420

Dear Members of the RR&D Review Board:

The intent of this letter is to offer full support of Dr. Kendall's R&D Merit Review Grant entitled: "A prospective, controlled study of rehabilitation of anomia in aphasia.

Dr. Kendall and her research team will be recruiting 100 individuals with acquired aphasia from stroke over the course of 5 years with the intent to offer research treatment to 80 of these individuals. In addition to other sites in the Seattle and surrounding areas, Dr. Kendall will be recruiting individuals from the VAMC Puget Sound Speech Pathology Clinical Service.

I foresee no difficulty with subject recruitment. In 2011 we received 577 adult neurogenic communication disorders referrals and currently have over 200 individuals with aphasia on our caseload.

We fully support Dr. Kendall's line of aphasia treatment research. She has successfully recruited individuals for treatment for her current VA RR&D Merit Review grant and are looking forward to supporting continued treatment research.

Sincerely,

Amy Gentzkow

Amy Gentzkow, MA, CCC-SLP
Speech Pathology Program Manager

SPEECH & HEARING SCIENCES
UNIVERSITY of WASHINGTON

June 1, 2012

Director, R&D
Rehabilitation Research and Development Service Department of Veterans Affairs
810 Vermont Avenue, N.W.
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Dr. Kendall and her research team will be recruiting 100 individuals with acquired aphasia from stroke over the course of 5 years with the intent to offer research treatment to 80 of these individuals. Dr. Kendall will be recruiting individuals from the UW Aphasia Registry and Repository, the UW Speech and Hearing Clinic, and surrounding hospitals and clinics.

It is from the perspective of Clinic Director that I write my strongest letter of support. I have held this position for 12 years and am responsible for the oversight and management of the clinical training environment of the graduate students in speech language pathology and audiology. I also supervise graduate students as they complete their rotations in adult neurologic communication disorders while enrolled in our comprehensive master's degree programs in speech-language pathology. The mission of our clinic is to serve as a center of excellence in research, education and research. As a teaching center, the clinic supports the clinical preparation of to 84 speech-language pathology graduate clinicians annually. Additionally, the clinic is a learning laboratory for over 100 undergraduate and post-baccalaureate students, as well as providing support for students in our audiology clinical doctorate and PhD degree programs. Dr. Kendall's grant proposal clearly supports the mission of this clinic in terms of clinical service (rehabilitation of aphasia) and graduate student training in research.

I foresee no difficulty with subject recruitment. We receive 100+ adult neurogenic communication disorders referrals per year and currently have over 80 individuals with aphasia on our caseload. Additionally, Dr. Kendall and I provide support to the Greater Seattle "Young Adult Stroke Survivors" Group, and interface with the Tacoma, WA Stroke Support Group where many of those individuals have a history of participating in research protocols.

Dr. Kendall will also be recruiting individuals from area hospitals, rehabilitation centers and private clinics. As a premier academic environment and research/teaching clinic, we have formal affiliations with and ready access to over 100 area hospitals, rehabilitation centers, outpatient clinics and private practices. The Department of Speech and Hearing Sciences and our teaching/research clinic are looked to as the premier education and research center in our

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community. Communications via email, mailings, workshop announcements, hosted events and community-based in-services, enables us to readily recruit for the purpose of research.

In closing, we fully support Dr. Kendall's active line of aphasia treatment research. Funded research projects are closely aligned with the overall mission of the UW Speech and Hearing Clinic. We have seen first-hand the impact of Dr. Kendall's research to date. Our patients and families have greatly benefitted from Dr. Kendall's research program in the past and we are looking forward to supporting continued treatment research.

Sincerely,

Nancy B. Alarcon, MS, CCC-SLP BC-ANCDS
Sr. Lecturer and Clinic Director

SPEECH & HEARING SCIENCES
UNIVERSITY of WASHINGTON

RICHARD C. FOLSOM, PH.D.
PROFESSOR AND CHAIR
DEPARTMENT OF SPEECH AND HEARING SCIENCES

June 1, 2012

Director, R&D
Rehabilitation Research and Development Service
Department of Veterans Affairs
810 Vermont Avenue, N.W.
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Dear Members of the RR&D Review Board,

The intent of this letter is to offer full support of Dr. Kendall's RR&D Merit Review Grant entitled: "A prospective, controlled study of rehabilitation of anomia in aphasia".

Dr. Kendall holds a 1.0 FTE position in the Department of Speech and Hearing Sciences and currently has 50% of her time protected for research, with the other 50% dedicated to teaching and service. Should this grant be funded, she will be ensured additional protected research time in terms of a course release. In terms of space, Dr. Kendall has ~650 sq ft of laboratory space adjacent to the Speech and Hearing Clinic that will easily accommodate the testing and treatment of individuals with aphasia.

Funded research projects are closely aligned with the overall mission of this Department. Dr. Kendall has forged ahead with innovative and experimental treatment studies for aphasia and continues this Phase II programmatic development of an efficacious treatment program for aphasia. Her research program clearly supports the departmental mission.

Sincerely,

Richard C. Folsom

Richard C. Folsom
Professor and Chair

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2. a. Background Significance

One of the most common and debilitating features of aphasia is an impairment in ability to retrieve words, whether it involves naming seen objects, or producing nouns, verbs and other words conveying meaning in spontaneous propositional speech (Goodglass, 1993). The traditional treatment approach to this problem is to explicitly train individuals with aphasia in whole word naming (see Nickels, 2002, for extensive review). Controlled studies have shown that this approach may improve naming performance but generalization is typically very limited; that is, the knowledge gained by the patient tends to be limited to the words actually trained, and there is at best modest improvement in naming performance with untrained words. This generalization may be limited mainly to words that are semantically related to those in the training corpus (Kiran and Thompson, 2003; McNeil, 1997). The mechanisms underlying this generalization are not well understood. Because generalization can be limited with naming therapies, there currently exists no viable means of training patients on the full corpus of words (perhaps several thousand) they are likely to need in daily life, except in the most determined and capable of subjects (Basso, 2003). Two approaches might be taken to solving this problem: (1) develop cost effective means for providing training on several thousand words; and (2) develop alternative training methods. We have developed an alternative method – called phonomotor therapy – and, in this project, we propose to continue development through a phase II clinical trial.

Through a series of phase I and phase II trials, we have shown that intensively delivered phonomotor treatment not only improves confrontation naming performance on trained words but, as predicted by the theory motivating it, achieves generalization to naming of untrained words, some aspects of discourse production, and indicators of quality of life (Kendall et al, 2008, Kendall et al 2012). The treatment program is motivated by a connectionist model of phonology (Nadeau, 2001; Nadeau, 2006, Nadeau, 2012) and by a two level interactive model of language (Dell, 1986). The theoretical foundation for the treatment is as follows: through the systematic training of phonemes (sounds) and phoneme sequences, the neural connectivity supporting phoneme sequence knowledge will be enhanced. Because these sound sequences provide the basis for the words that represent concepts, through bidirectional spread of activation among and between linguistic levels, generalization to naming of untrained words and discourse production, as well as continued improvement beyond treatment termination can be expected.

The mechanisms by which a purely phonological treatment could benefit anomia are implicit in a connectionist model of language function, discussed below.

Connectionist model of phonological function:

The Wernicke-Lichtheim (W-L) information processing model of language has played a dominant role in understanding aphasic syndromes (Lichtheim, 1885) and has stood the test of time in defining the relationship between the modular domains (acoustic, articulatory-motor, and concept representations) underlying spoken language function. Unfortunately, the W-L information processing model does not specify the characteristics of the representations within these domains and how they might be stored in the brain or how they might interact.

We have proposed a parallel distributed processing (PDP) model that uses the same general topography as the W-L model (Nadeau, 2001; Roth et al., 2006), but also specifies how representations are generated within each domain (acoustic, articulatory motor, and concepts) and how knowledge is represented in the links between these domains (Figure 1). Though not yet tested through simulations, this model is neurally plausible and provides a cogent explanation for a broad range of psycholinguistic phenomena. More generally, connectionist concepts are now deeply embedded in and receive enormous support from mainstream neuroscientific research (e.g., Rolls, 2002; Rolls, 1998).

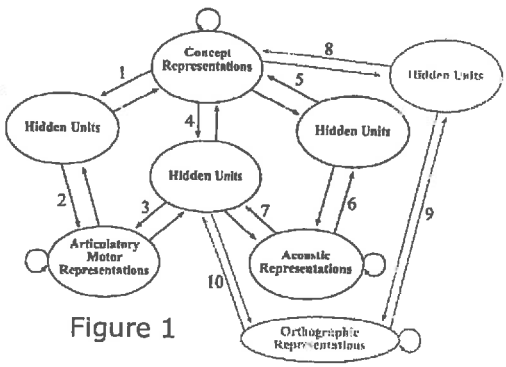

Figure 1

The PDP modification of the W-L model posits that the acoustic representations (akin to Wernicke's area) are based upon large numbers of units, located in auditory association cortices, that represent acoustic features of phonemes. The articulatory-motor representations (analogous to Broca's area) are based upon units,

located predominantly in dominant frontal operculum, that represent discrete articulatory features of speech (as opposed to continuously variable motor programs). The semantic or conceptual representations are based upon an array of units, distributed throughout association cortices that represent semantic features of concepts. Each unit within a given domain is connected to many, if not most, of the other units in that same domain (symbolized by the small looping arrow appended to each domain in Figure 1).

Knowledge within each domain is represented as patterns of connection strengths between the units. Thus, for example, semantic knowledge is represented as the pattern of connection strengths throughout the association cortices supporting this knowledge. Within any domain, a representation corresponds to a specific pattern of activity of all the units, hence the term distributed representation. Each unit within each of these domains is connected via interposed hidden units to many, if not most, of the units in the other domains. During learning of a language, the strengths of the connections between the units are gradually adjusted so that a pattern of activity involving the units in one domain elicits the correct pattern of activity in the units of another domain. The entire set of connections between any two domains forms a pattern associator network. The hidden unit regions noted in the schematic enable the association of representations in two connected domains that are arbitrarily related to one another (e.g., word sound and word meaning).

In PDP models, knowledge is stored as patterns of connectivity not only within domains but also between domains. For example, understanding the meaning of a word that is heard is achieved through the connections between the domain that contains the sound features of language and the domain that contains concept features (the acoustic-concepts representations pattern associator, Figure 1, pathway 6-5). This pattern associator network corresponds to the cognitive neuropsychological concept of a phonological input lexicon (Ellis & Young, 1988). It contains neither knowledge of acoustics nor knowledge of semantics — it serves only to translate a representation in the acoustic domain into a representation in the concepts/semantics domain (where meaning is instantiated).

The knowledge that allows a person to translate heard sound sequences into articulatory-motor sequences, and thereby mediates repetition of both real words and non-words, is contained in the network that connects the acoustic representations to the articulatory-motor representations (Figure 1, pathway 7-3). Because this network through experience has acquired knowledge of the relationships between acoustic sequences and articulatory sequences, it has learned the sound sequence regularities of the language (i.e., phonemic sequences of joint phonemes, rhymes, syllables, affixes, morphemes and words) (Nadeau, 2001); (see also Plaut et al., 1996).

The knowledge that enables a person to translate a concept into a spoken word (i.e. the phonological output lexicon; Ellis & Young, 1988) is instantiated in two different pattern associator networks that connect the concept representations domain to the articulatory motor representations domain (Figure 1, pathways 1-2 and 4-3). These two pattern associator networks, indirect and direct pathways, support different forms of knowledge. The indirect pathway (pathway 4-3) provides a robust basis for knowledge of phonological sequences. The direct pathway (pathway 1-2) on the other hand, does not contain knowledge of phonological sequences and sublexical entities because it translates patterns of activity corresponding to concepts into articulomotor sequences corresponding to articulated whole words. This translation precludes significant acquisition of phonologic sequence knowledge and makes this fundamentally a whole word pathway. Further support for the existence of direct and indirect pathways is evidenced in normal phonological slips-of-the-tongue, and in aphasic phonemic paraphasias during naming and internally generated spoken language.

Implications of the PDP model for treatment of anomia

Except for onomatopoeic words and derivational forms, the relationship between word meaning and word form is largely arbitrary. This is likely the reason that when using a whole word rehabilitation paradigm, learning to name one word provides no basis for generalization to other words (Plaut, 1996). Thus, to meaningfully alter daily communicative ability, one would have to train hundreds, if not thousands of words (as noted). If the whole word pathway, were the only pathway available to us to name concepts, then we would be bound by this constraint. However, the existence of the indirect pathway opens up another possibility. So long as there are some remnants of this indirect pathway left after a stroke (either in the damaged hemisphere or in the normal hemisphere), that is, there is some existing phonological sequence knowledge and some connections between neural networks supporting concept representations and the acoustic-articulatory motor

representations supporting phonological sequence knowledge, then it may be possible to improve word retrieval by enhancing phonological sequence knowledge. This is the fundamental hypothesis that motivates this investigation.

Support for this hypothesis comes from studies of language acquisition in young children. They first learn many of the various phonological sequence regularities of their language (Gathercole, 1995; Gathercole & Martin, 1996). Subsequently they learn to assemble these various sequences into combinations and associate these combinations with concepts (meaning), enabling both word comprehension and word production. If this principle of language development also applies to language redevelopment after brain injury, it suggests two possibilities: (1) that effective retraining in phonological sequence knowledge may generalize to all words containing the trained sequences; and (2) that once given an adequate repertoire of phonological sequence knowledge during treatment, individuals with aphasia should be able to continue after therapy to enhance existing but inadequate connections between the substrate for concept representations and the substrate for phonological sequence knowledge and steadily rebuild their working vocabularies. It is also possible that training some phonological sequences will generalize to other phonological sequences (e.g., through shared distinctive feature and motor programming sequences).

The process of developing phoneme sequence knowledge employs tasks that enhance phonemic and phonological sequence awareness. In effect, training a phoneme sequence in a way that instantiates both the phoneme sequence knowledge and phonological awareness of that sequence builds a first house to re-establish a phonemic neighborhood (Vitevitch, 1999) that could ultimately, through further learning outside of phonological therapy, be expanded to become engageable by all concept representations of words containing that sequence. Furthermore, experience with developmental phonological dyslexia suggests that given sufficient baseline impairment in the processing of phonemes with an inability to process and discriminate rapid formant transitions, phonological and phonological sequence knowledge fail to develop until explicit training in this knowledge is provided (Lindamood & Lindamood, 1998; Tallal 2004). Adults with aphasia may exhibit the same threshold phenomenon, likely because of unapparent premorbid inadequacy of phonological sequence knowledge (Goodglass 1993).

In our conceptualization of the rationale for this project, we explicitly assume extensive underactivation of phonological sequence knowledge, because of the vast reduction of synapses caused by stroke. We also assume residual lexical semantic knowledge instantiated in connections linking association cortices supporting concept representations to perisylvian cortices supporting phonological sequence knowledge.

The hypotheses being tested is that given a better repertoire of phonological sequence knowledge, 1) word retrieval will be improved because the previously weak phonological representations will now be more easily activated when top-down conceptual semantic processing occurs, and 2) subjects will be able to enhance residual lexical semantic knowledge on their own in a process that recapitulates normal language acquisition in children.

This hypothesis seems plausible because there is no evidence that brain damage of any type alters the fundamental principles of brain operation (including the way in which knowledge is acquired), which emerge from its neural network organization, and because the hypothesis is predicated upon the existence, in damaged form, of exactly the same networks that enabled these subjects to acquire language in the first place. As noted, damage to the brain produces graceful degradation, not fundamental alteration in function. Nevertheless, this hypothesis requires empirical validation.

Précis of neural network processes during treatment:

We posit the following evolving sequence of neural network processes during the course of treatment:

- Because all domains of the network pictured in Figure 1 are heavily interconnected, we assume that any input into any domain (e.g., acoustic) of the network will lead to engagement of other domains (e.g., articulatory motor). We also assume that the network consists of the damaged remnants of the left hemisphere phonologic apparatus, linked by transcallosal (and possibly anterior commissural) pathways to its

variably under-developed homologue in the right hemisphere (see Roth et al., 2006). These networks, presumably, provide the substrate for residual phonemes and phoneme sequences.

- One of the goals of treatment is to develop phoneme sequence knowledge, but one cannot hope to develop further knowledge of sequences until there is adequate neural instantiation of individual phonemes. The first phase of treatment seeks to develop the neural connections needed to establish the basis for linked distributed representations of individual phonemes in multiple functional domains. If treatment were completely successful, insertion of the acoustic form of /b/ into the acoustic domain (by saying /b/ to the subject) would instantly lead to the generation of distributed representations (patterns of neural activity) of the articulatory form of /b/, a concept of /b/, and an orthographic representation corresponding to the letter b. Eventually, sufficient neural connectivity would be developed to enable any of the individual domain-specific distributed phoneme representations to be generated and linked through the network to achieve the multi-domain distributed representation of any individual phoneme.

- The second phase of treatment consists of training in the regularities of English phonological sequences, first by inserting single syllables into the network (generating patterns of neural activity), later by inserting 2 or 3 syllable non-words into the network. Distributed representations are presumably generated in all domains and pathways of the network by this phonological sequence input.

- The ultimate goal of the treatment is to develop knowledge of phonological sequences and access to these sequences from concept representations. Because these sound sequences provide the basis for the words that represent concepts, through bidirectional spread of activation among and between linguistic levels, generalization to naming of untrained words and discourse production, as well as continued improvement beyond treatment termination can be expected.

b. Preliminary Studies

Dr. Kendall has been involved in the development and refinement of the phonomotor treatment program since 2000. The first study, a phase I proof of concept experiment, showed that by applying treatment to the level of the phoneme and phoneme sequences, reading and spoken word production improved in individuals with aphasia (Kendall et al, 2003).

The next early phase II study extended the initial findings by 1) comparing the experimental phonologic treatment to a semantic treatment, 2) by refining the experimental treatment in terms of a homogeneous patient population and 3) increasing the frequency and intensity of treatment (Kendall et al 2006, Kendall et al 2008, Nadeau et al 2006). In that study, 20 individuals with anomia due to aphasia were randomized to receive either 96 hours of phonomotor or semantic treatment delivered in a massed practice condition over 12 weeks with 3 month follow-up. Results on impairment level outcome measures showed that treatment and generalization effects in the phonomotor treatment group were superior to the semantic group. Measures of ecologic validity (ASHA-FACS) showed the phonomotor intervention had a meaningful impact on communication at home. With concerns regarding the large dosage of treatment hours delivered, a post hoc analysis revealed that treatment effects for both groups were acquired by 60 hours of treatment, and there was no significant difference on effect sizes within group between 60 and 96 hours of treatment delivered. The average individual effect size for the phonomotor group for 96 hours of treatment was ES=6.88 and for 60 hours of treatment ES=6.52 (p=.111). The average effect size for the semantic group for 96 hours was ES=4.01 and for 60 hours ES=3.79 (p=.568). ***These results support the delivery of 60 total hours to be delivered in the current proposal.***

While the results of the early Phase II study were promising, several limitations were noted:

1) Both groups received a number of treatment hours that seemed excessive given the medical re-imbursement climate, even as there was good evidence from the outcome data that gains plateaued after about 60 hours (see above).

2) There were potential opportunities for improving the efficiency of the phonomotor therapy, specifically, by limiting the training material to phonemes and phoneme sequences of low phonotactic probability and large phonological neighborhoods.

3) A sensitive and specific measure of phonology for adults with aphasia was not employed, limiting our ability to ensure that phonological mechanisms were indeed directly impacted by the treatment. To that end, the Standardized Assessment of Phonology in Aphasia (SAPA) (Kendall et al 2010) was created. All three innovations were instantiated in the treatment version currently being tested.

4) We had not yet assessed the efficacy of phonomotor therapy, however promising, by the metric of a *typically delivered* lexical/semantic-based treatment (e.g. 3 hours/week). This is the goal of the trial proposed here.

5) We have not determined the impact of distribution of treatment over time, specifically, the benefit of distributing treatment over a greater number of hours and weeks demonstrated repeatedly in the learning literature. This will be the goal of a subsequent phase III trial of phonomotor therapy.

Following the development of the SAPA (Kendall et al 2010), we continued phase II refinement of the phonomotor treatment. That trial is currently underway. It is a single arm, longitudinal study assessing phonomotor treatment, delivered in massed practice condition, on acquisition, generalization and maintenance in 30 subjects with a left hemisphere lesion and aphasia associated with impaired word retrieval abilities. The current iteration of the phonomotor treatment now includes: modified stimuli (real and non-words consisting of low phonotactic probability and high neighborhood density), reduction of the total number of treatment hours (from 96 to 60 total hours), and refinement of the primary and secondary outcome measures (addition of SAPA, new measures of discourse production and ecologic validity). At the time of this grant application, 20 individuals have completed the study protocol, 16 have returned for 3 month follow-up and 8 have returned for 1-year follow-up. Details pertaining to this active trial are as follows:

Methods:

- *Participants*: Twenty individuals with chronic aphasia following left hemisphere damage due to left cerebral hemisphere stroke participated in this study. Participants were on average 56 years of age (SD 14), had 16 years of education (SD 3) and were on average 47 months post stroke onset (SD 54). Eighteen individuals were mono-lingual English, two bilingual and English proficient, and all exhibited aphasia (Western Aphasia Battery, AQ)(Kertesz, 1982) (average AQ 79/100), word retrieval deficits (Boston Naming Test) (Kaplan et al, 1983)(average 36/60), and impaired phonologic processing (SAPA)(Kendall et al, 2010)(average 96/151). Subjects were excluded if they exhibited severe apraxia of speech as determined by perceptual assessment of rate, distorted substitutions, prosodic abnormalities and effortful groping.

- *Study Design*: The study is a single group (n=30 over 3 years) pre- and post-treatment design. In order to control for improvement in language function related to passage of time and Hawthorne effect, we randomly assigned individuals to one of 2 treatment conditions: delayed and immediate treatment. Because no significant differences between groups (delayed and immediate treatment) (p=.607) were found prior to the start of treatment, results will refer to a single treatment group only.

- *Treatment program*: All subjects received 60 hours of phonomotor treatment (1-hour treatment sessions, 2 sessions/day, and 5 days/week for 6 weeks). The treatment program description is described below.

- *Treatment stimuli*: Stimuli were comprised of phonemes in isolation, non-words, and real words consisting of phonological sequences of low phonotactic probability and high neighborhood density. Phonotactic probability was calculated using methods similar to Vitevitch and Luce (1999). All non-words were phonotactially legal in English. A web-based interface was used to calculate phonotactic probabilities for the real and non-words (Vitevitch & Luce, 2004). Neighborhood density was computed by counting the number of words in the dictionary that differed from the target by a one phoneme

addition, deletion, or substitution. Phonotactic probability and neighborhood density were computed for stimuli and were categorized as high or low based on a median split (Storkel, 2006). Real word stimuli were also controlled for frequency, imagibility, age of acquisition, syllable number, syllable complexity and semantic category. Photographic pictures representing the real word stimuli were used.

- *Outcome measure description:* The primary outcome measure was confrontation naming of *untrained* nouns at 3 months. Secondary outcome measures focused on acquisition, generalization, maintenance and quality of life. All measures were collected pre-treatment, 1-week post treatment, 3-months and 1-year later. In order to determine treatment *acquisition* effects, data were collected from repetition of trained non-word stimuli and confrontation naming of trained nouns. In order to determine any effects of treatment *generalization to phonological processing abilities*, the SAPA (Kendall et al 2010) was administered, and data were also collected on repetition of untrained non-words. In order to assess effects of treatment *generalization to lexical function*, confrontation naming of untrained nouns was probed as well as discourse production elicited by six ego centric questions. In order to determine *ecologic validity of* this treatment, data were collected on the Stroke and Aphasia Quality of Life scale (SAQOL)(Hilari & Byng, 2001) and the Functional Outcomes Questionnaire (FOQ) (Glueckauf et al, 2003). Paired t-tests were performed on pre-treatment versus 1-week, 3 months and 1 year post-treatment accuracy scores for the outcome measures.

Results: (see Table below for results summary). Acquisition data for n=20, three-month post maintenance data for n=16 and 1 year post maintenance data for n=8 have been collected and analyzed. Results are as follows:

- *Reliability*: Point-to-point reliability performed on 25% of primary outcome measures was performed. Inter-class correlations showing reliability for intra-rater .964 (non-word repetition) and .992 (confrontation naming) and inter-rater .944 (non-word repetition) and .991 (confrontation naming).

- *Primary Outcome*: A significant difference on confrontation naming of untrained nouns at 3 months (p=.033) and at 1 year (p=.033) was found.

- *Secondary Outcomes:*
  - *Treatment acquisition effects*: A significant group effect was observed for repetition of trained non-words (p=.000) and confrontation naming of trained nouns (p=.000) immediately following treatment.
  - *Generalization to phonological processing*: A significant group effect was evident for the SAPA (p=.000) and untrained non-word repetition (p=.000) immediately following treatment.
  - *Generalization to lexical function*: A significant difference for confrontation naming of untrained nouns (p=.001) immediately post treatment termination was found. Regarding discourse production, analysis thus far has been conducted on three individuals (baseline to immediately post treatment comparisons). The data showed that two of the three participants produced more verbal output and more relevant responses following therapy (Kempler et al 2012).
  - *Ecologic validity* of this treatment program was measured by pre- and post treatment performance on the SAQOL and FOQ-A. A significant difference was present immediately following treatment (p=.011 and p=.025 respectively).

- *Maintenance:*
  - *3-month* data were analyzed for n=16 individuals and were significantly improved for SAPA (p=.000), confrontation naming of trained nouns (p=.000), confrontation naming of untrained nouns (p=.033), trained non-word repetition (p=.000), untrained non-word repetition (p=.000). No significant difference was found for SALQOL (p=.182) and FOQ-A (p=.115).
  - *1-year* data for n=8 individuals were analyzed and were significantly improved for trained non-word repetition (p=.001), confrontation naming of trained nouns (p=.016), SAPA (p=.010), and confrontation naming of untrained nouns (p=.033).No significant difference was noted for untrained non-word repetition (p=.069) and SALQOL (p=.085).

	Research aim	Outcome measure	**Acquisition** *(pre- versus immediately post)* **N=20**	**3-month maintenance** *(pre- versus 3 month post)* **N=16**	**1-year maintenance** *(pre- versus 1 year post)* **N=8**
Primary Outcome	**Generalization to lexical semantics**	Untrained real word confrontation naming	P=.001 Pre 64% (SD 25) Post 70% (SD 25)	P=.033 Pre 66% (SD 25) Post 71% (SD 26)	P=.033 Pre 68% (SD 20) Post 81% (SD 19)
Secondary Outcomes	**Acquisition**	Trained non-word repetition	P=.000	P=.000	P=.001
		Trained real word confrontation naming	P=.000 Pre 64% (SD 26) Post 82% (SD 17)	P=.000 Pre 66% (SD 25) Post 79% (SD 22)	P=.016 Pre 70% (SD 18) Post 86% (SD 7)
	Generalization to phonological processes	Standardized Assessment of Phonology in Aphasia (SAPA)(151)	P= .000 Pre 97 (25) Post 106 (24)	P=.000 Pre 97 (25) Post 106 (26)	P=.010 Pre 100 (23) Post 115 (15)
		Untrained non-word repetition	P=.000 Pre 69% (SD 21) Post 82% (SD 15)	P=.000 Pre 68% (SD 22) Post 83% (SD 16)	P=.069 Pre 75% (SD 17) Post 84% (SD 14)
	Ecologic validity	Functional Outcomes Questionnaire - Aphaisa	P=.025 Pre 3.93 (SD .62) Post 4.24 (SD .54) (note: n=19)	P=.115 Pre 3.98 (SD .58) Post 4.36 (SD .83) (note: n=14)	N/A
		Stroke and Aphasia Quality of Life scale	P=.011 Pre 3.37 (SD .76) Post 3.81 (SD .85)	P=.182 Pre 3.50 (SD .77) Post 3.75 (SD .73)	P=.085 Pre 3.43 (SD .66) Post 4 (SD .66)

Conclusion: The results from the current phase II study support our hypothesis that by intensively training phonemes and phoneme sequences in real and non-word combinations, an improvement in untrained spoken word production will occur and maintained 3 months and 1 year post treatment termination as a result of increased connectivity between lexical semantics and the phonological network. Further, with regard to the continued improvement of untrained naming from 3 months to 1 year post treatment termination, we propose individuals were given an adequate repertoire of phonological sequence knowledge during treatment, that upon treatment termination previously existing lexical entities could now activate phonological processes during everyday communication resulting in larger vocabulary usage that is similar to language acquisition in young children (Gathercole, 1995; Gathercole & Martin, 1996) where children learn various phonological sequence regularities of language and they then learn to assemble sequences into combinations and associate them with concepts (meaning), enabling both word comprehension and word production.

c. Current Status of the Field

The traditional treatment approach to the rehabilitation of anomia in aphasia is to explicitly train individuals with aphasia in whole word naming (see Nickels, 2002, for extensive review) (often called lexica/semantic therapy). Controlled studies have shown that this approach may improve naming performance but generalization is typically very limited; that is, the knowledge gained by the patient tends to be limited to the words actually trained, and there is at best modest improvement in naming performance with untrained words. This generalization may be limited mainly to words that are semantically related to those in the training corpus (Kiran and Thompson, 2003; McNeil, 1997). The mechanisms underlying this generalization are not well understood. Because generalization can be limited with naming therapies, there currently exists no viable means of training patients on the full corpus of words (perhaps several thousand) they are likely to need in daily life, except in the most determined and capable of subjects (Basso, 2003).

Two approaches might be taken to solving this problem: (1) develop cost effective means for providing training on several thousand words; and (2) develop alternative training methods. We have developed an alternative method – called phonomotor therapy – and, in this project, we propose to continue development through a phase II clinical trial.

The most innovative aspect of this proposed treatment is that it explicitly targets generalization in ability to name and focuses on training a specific language mechanism that, theoretically, should enable broad generalization. Anomia is the most common and most disabling component of aphasia. An intrinsically generalizing treatment for word retrieval deficits should enable broad improvement in naming ability, not limited to trained items, and it should translate into improvement in daily communicative ability—the ultimate aim of all speech language therapy. However, in all prior attempts at treating anomia, generalization has been at best modest, hit or miss, of unknown mechanism, and never explicitly targeted in therapy. Our treatment is also highly innovative in that, by virtue of the mechanism of generalization that it engages, it should lead to continued improvement in language function after the end of treatment, rather than gradual forgetting of trained material, which is the usual course after conventional treatment. Our preliminary data provide support for the success of both innovations. Finally, while other treatments have been leveraged on (Kiran and Thompson, 2003; Plaut, 1996) or can be related to principles of neural network function captured in PDP models (Thompson and Shapiro, et al. 2003, Nadeau 2012), ours is the first to take advantage of a comprehensive PDP model to design a broadly generalizing therapy.

d. Research Design and Methods

Study Design: In the context of a 2-armed randomized control trial with experimental (phonomotor) treatment versus a type of treatment that is typically delivered (lexical/semantic-based); we propose to study 80 individuals who have suffered a left hemisphere stroke and exhibit aphasia and anomia. The aims, research questions, outcome measures, time point of data collection and predictions are outlined below:

Aims	Research Question	Outcome Measure	Time point	Predictions
Primary Aim:	1. Is there a significant between group difference in word retrieval abilities following treatment?	Accuracy of confrontation naming of *untrained* nouns	3 months post treatment termination versus baseline	Based on the theoretical concept where focusing treatment at the level of phonemes and phoneme sequences intrinsically achieves generalization to all words, as well as on our preliminary data, we hypothesize that phonomotor treatment will produce a greater increase in naming accuracy of *untrained* items than will typical treatment.
Secondary Aims	2. Acquisition: Is there a significant between group difference for *trained* items immediately upon treatment completion?	Accuracy of confrontation naming of *trained* nouns	Immediately post treatment termination versus baseline	Based on the model and preliminary data, we hypothesize that both treatments will promote acquisition of *trained* items
	3. Generalization: Is there a significant between group difference for *untrained* items and contexts immediately post treatment and 3 months later?	Accuracy of confrontation naming of untrained nouns, discourse production and ecologic validity measures.	3 months post treatment termination versus baseline	Based on the conceptual model and preliminary data, we hypothesize that phonomotor will be superior to typical treatment in generalization to untrained items and discourse production.
	4. Continued growth beyond 3 months: Is there a significant difference between 3 months and 1-year post treatment termination in confrontation naming accuracy for trained and untrained nouns?	Accuracy of confrontation naming of trained and untrained items.	3 months post treatment termination versus 1 year post	We hypothesize that the phonomotor group will show continued growth from 3 months to 1 year due to the repertoire of phonological sequences that was acquired through intensive training and practiced in daily communication, while the typical treatment group will show no difference, or even a decrement, in performance over time.

Participants:

- Number: One hundred participants with chronic (duration of six or more months) aphasia following left hemisphere damage due to stroke will be recruited through the VAMC Puget Sound Speech and Hearing Clinic, the University of Washington (UW) Aphasia Registry and Repository (Dr. Kendall is the PI of the registry), and the University of Washington Speech and Hearing Clinic. The VAMC Puget Sound speech and hearing clinic received over 500 referrals for adult neurogenic cases in 2011 and currently has 200 individuals with aphasia on caseload. The UW Aphasia Registry has over 90 individuals enrolled and approximately 3 individuals with aphasia per month are tested. The UW Speech and Hearing Clinic receives 100+ adult neurogenic communication disorders referrals per year and currently has over 80 individuals with aphasia enrolled. Additionally, individuals will be recruited from local and regional stroke support groups in Olympia, Tacoma, Bellingham and Portland, Oregon. One hundred participants total translates to 2.4 patients per month over 3.5 years. We do not anticipate any difficulty with subject recruitment as there are no other aphasia research programs in the Seattle and surrounding areas resulting in no competition for recruitment. Also, Dr. Kendall easily recruited n=30 individuals with aphasia in the current research treatment protocol in under 2 years while at the same time maintaining a waiting list qualified individuals.

- Selection criteria: Subjects will have had a single left hemisphere stroke (documented by imaging with either CT or MRI) and be 6 months or more post-stroke, right handed and monolingual English speaking.

- Exclusion criteria include significant apraxia of speech (see details below), depression or other psychiatric illness, degenerative neurological illnesses, chronic medical illness or a severe impairment in vision or hearing. During the screening process, bilingual participants will be interviewed with respect to the age of acquisition of English and which language they currently use most of the time. Language preference will be confirmed by an individual who has known the participant for more than one year prior to the stroke who agrees that (1) English was the preferred language and (2) English was spoken predominantly by the participant. The reason for recruiting only right-handed subjects is as follows: Because we are treating language, hypotheses are specific to the language-dominant hemisphere. Patients who are not right-handed may have different capacities in their non-dominant hemispheres to learn language, which may produce outlier effects. Individuals with dysarthria will be included as typically unilateral upper motor neuron dysarthria is the dysarthria type associated with left cortical stroke and effects on overall intelligibility are minimal.

- Inclusion criteria: Participants must (1) demonstrate word retrieval impairments for nouns as indicated by a score of <45 on the Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 2001); (2) have, at worst, mild to moderate apraxia of speech (see details below); (3) have auditory comprehension sufficient to complete the training protocol (score of >4.0 on the Western Aphasia Battery auditory comprehension subtests (WAB)(Kertesz, 1982), and (4) demonstrate a semantic impairment as evaluated by The Psycholinguistic Assessments of Language Processing in Aphasia - 53 (PALPA 53) (Kay, Lesser & Coltheart, 1992) and (5) demonstrate a phonologic impairment as evaluated by the Standardized Assessment of Phonology in Aphasia (SAPA)(Kendall et al, 2010).

- Characterization of included participants: In order to describe and quantify the presence and extent of aphasia, apraxia and/or cognitive involvement for the individuals who met the above inclusion and exclusion criteria, data from the following tests will be used: 1) WAB, 2) BNT, 3) SAPA, 4) PALPA-53, 4) working memory using digits forward and backwards, 5) non-verbal problem solving (Raven's Progressive Matrices)(Raven, Raven, & Court, 2003) and 6) motor speech performance (see exam below).

- Apraxia of speech: Subjects will be excluded if they demonstrate a severe apraxia of speech as determined perceptually using data gathered during the evaluation. Two speech language pathologists will evaluate speech/language behaviors to arrive at independent judgments. Video-taped data from, but not limited to, WAB picture description, spontaneous conversation, automatic speech, repetition of words of increasing length, and multiple repetition of 3-syllable words will be evaluated for the following behaviors:

slow rate, prolonged segment durations and intersegment durations (including intrusive schwa), distortions, prosodic abnormalities and effortful groping and struggling during articulation. Severe apraxia of speech is defined as a limited repertoire of speech sounds, speech limited to a few meaningful utterances, automatic speech not better than volitional speech, and inability to repeat isolated phonemes.

Outcome Measures:

- Primary outcome measure:
  - Confrontation naming of *untrained* nouns: Construction of noun stimuli is described in detail below under phonomotor and typical treatment methods (see stimuli selection).

- Secondary outcome measures:
  - Acquisition: Confrontation naming of *trained* nouns: Construction of noun stimuli is described in detail below under phonomotor and typical treatment methods (see stimuli selection).

  - Generalization: Discourse production: An interview will be used to elicit spontaneous conversation. We will use a series of open-ended questions that have proven to be effective elicitors of conversation in past studies (Altmann et al. 2001, Blonder et al. 1993, 1994; and Langer et al. 2000). Interview questions: (e.g., "Tell me about. ....") will be videotaped using digital video recording equipment and high quality digital audio recorders. All discourse samples will be transcribed and checked for accuracy and reliability by a second research assistant. The audio portion of the discourse will be transcribed and analyzed using the Systematic Analysis of Language Transcripts (SALT; Chapman & Miller, 1984, Miller and Chapman, 2002) and the Linguistic Inquiry and Word Count (LIWC; Pennebaker et al., 2001). Following the transcription, graduate students will code each transcript for a set of 12 discourse measures to gauge productivity, grammatical well-formedness, relevance, and meaningful contributory output. Each participant utterance will be coded on each parameter numerically to facilitate pre- vs. post-treatment comparison. The coding will be checked by one of the investigators and inconsistencies resolved by discussion.

  - Ecologic validity: Self-ratings of quality of communicative life (QCL; Paul et al., 2005) and caregiver ratings of communicative performance and participation on the Functional Outcomes Questionnaire (FOQ-A; Glueckauf et al., 2003).

Measure Administration: The primary and secondary outcome measures will be administered by a trained research assistant (e.g. not the therapist who will be administering treatment) on three consecutive days immediately prior to the beginning of treatment to establish baseline performance, three times on three consecutive days immediately after treatment completion, and three times on three consecutive days *three* months and 1-year post treatment cessation. Outcome measure values for each 3-day test sequence will be averaged. This is being done to reduce the effects of test-retest variability on statistical analysis of outcomes. Pictoral noun stimuli will be presented in an immediate response paradigm, which will include a visual presentation of a 250 ms, 500 Hz warning tone, 250 ms silent pause, presentation of stimulus, participant verbal response, and a 5,000 ms silent inter-stimulus interval. Instructions to respond will be as follows: "You will see a picture on the computer screen. Take your time and say the name of the picture that you see".

Scoring of outcome measures: Participant verbal responses will be digitally recorded and transcribed perceptually using broad phonetic transcription for each phoneme for subsequent analysis. Scorers will be trained research assistants who are blinded to outcome measure time point and treatment type. Accuracy of correct words produced will be calculated. Incorrect responses include phonologic and semantic substitutions, additions and deletions, neologisms and anomic responses.

Reliability of outcome measure scoring: Inter- and intra-rater reliability will be performed on all outcome measures on 25% of the data by graduate students in speech language pathology who are not involved in the research study. Inter-class correlations will be calculated on the reliability data. Scorers will be blinded to treatment phase (pre-post-maintenance) and treatment type (phonomotor or typical care).

Treatment Schedule: Both treatment groups will receive a total of 60 hours of therapy (see Preliminary Studies for data justifying this dose). The experimental phonomotor treatment will be delivered in the dosage it has been developed and studied thus far; that is, a massed practice schedule of 2 hours/day, 5 days/week for 6/weeks. Typical (lexical-semantic) treatment will be delivered in the dosage that it has been traditionally delivered; that is 1 hour/day, 3 days/week for 20 weeks. Therapy sessions will be conducted at the most convenient site for the individual (e.g., VAMC, home, University of Washington, etc) to improve retention in the study program. We realize that these treatments not only differ in linguistic mechanism (phonologic versus lexica/semantic), but also in intensity of treatment delivery (massed versus distributed); however the intent of this study is to further the development of the experimental phonomotor treatment program. In order to do so, phonomotor treatment needs to be compared to a typically delivered treatment for anomia which is a lexical/semantic-based protocol. We recognize the crucial and differential influence of massed versus distributed practice on learning and recognize the effects borne out of this trial could be a function of dosage and not linguistic mechanism. However, the important question of optimal dosage will need to be scientifically investigated in subsequent trials of the superior treatment.

Phonomotor treatment protocol:

- Stimuli: Stimuli will be comprised of phonemes in isolation, non-words, and real words comprised and will consist of low phonotactic probability and high neighborhood density. Vowel (V), consonant-vowel (CV) will be constructed in 1- and 2-syllable real and non-word combinations. The choice to use low phonotactic probability stimuli is based on the concept that training atypical exemplars of a domain will increase knowledge relevant to *both* atypical *and* typical exemplars, whereas training only typical exemplars benefits *only* typical exemplars (Kiran and Thompson, 2003 and Plaut 1996) or can be related to principles of neural network function captured in PDP models (Thompson and Shapiro, 2007; Nadeau, 2012). Storkel (2006) has provided empirical support for this concept in the domain of phonology. The choice to use stimuli with high neighborhood density has been made to maximize the number of word concepts that might engage trained phonemes and phonological sequences. Phonotactic probability will be calculated using methods similar to Vitevitch and Luce (1999). Two measures will be used to determine phonotactic probability: 1) positional segment frequency (how often a segment occurs in a position in a word) and 2) sum biphone frequency (segment-to-segment probability). All non-words will be phonotactially legal in English. A web-based interface will be used to calculate phonotactic probabilities for the real and non-words (Vitevitch & Luce, 2004). Neighborhood density will be computed by counting the number of words in the dictionary that differed from the target by a one phoneme addition, deletion, or substitution. Phonotactic probability and neighborhood density will be computed for stimuli and will be categorized as high or low based on a median split (Storkel, 2006). Real word stimuli will also be controlled for frequency, imagibility, age of acquisition, syllable number, syllable complexity and semantic category. Pictures from the Object/Action Naming Battery (Durks & Masterson, 2000) and Snodgrass & Vanderwart (Snodgrass & Vanderwart, 1980) will be used.

- Stage1 – Consonants in Isolation: The purpose of Stage One is to engage individual sounds by teaching a) motor descriptions (e.g., the tip of your tongue is behind your front teeth and taps to make the sound /t/); b) perceptual discrimination (e.g., does /t/ and /d/ sound the same or different?); c) production (e.g., repeat after me...say /t/); and d) grapheme to phoneme correspondences (e.g., letter for each sound is displayed). The length of Stage 1 is 15 hours. A mirror will be placed on the table for the participant to use for visual feedback for recognition and correction of errors. Each sound will be represented by a picture of a mouth in the corresponding posture.

- Stage 1-Task 1: Exploration of sounds: The participant is shown a mouth picture of a sound and asked to look in the mirror and repeat after the therapist to make the sound. Knowledge of results (KR) will initially be given at 100% frequency following each production then faded to 30% across trials. Following production, the therapist will ask the participant what they saw and felt when the sound was made. Socratic questioning will be used to enable the participant to "discover" the auditory, visual, articulatory and tactile/kinesthetic attributes of the sounds (e.g., "What do you feel when you make that sound?"). Through practice and repetition the participant will become adept at recognizing what they actually need to feel, see, hear and do to make the sound.

- Stage 1-Task 2: Motor description: A description of each sound will be provided. The therapist will describe what articulators are moving and how they move (e.g., for /p/ the lips come together and blow apart, the voice box is turned off, the tongue is not moving). The subject will be asked to repeat the sound and then asked to describe how the sound was made. For example, "Do your lips or tongue move to make that sound?"

- Stage 1-Task 3: Perception Task: The therapist will make a sound (e.g., /p/) and ask the participant to choose that sound from an array of pictures (e.g., /f/, /g/, /p/).. Socratic questioning will be used for correct and incorrect responses.

- Stage 1-Task 4: Production Tasks: Production of sounds will be elicited auditorily (repetition), visually (mouth picture), and via motor description (e.g., "make the sound where your lips come together and blow apart"). Socratic questioning will be used for correct and incorrect responses. For example, "you said /b/ is that the sound where your tongue taps the roof of your mouth?"

- Stage 1-Task 5: Graphemes: Graphemic tiles representing sounds will be placed on the table with the mouth pictures. The participant will be asked to select a single grapheme and place it on a picture that represents that sound. When they are finished the therapist will use Socratic questioning (e.g., "this letter says "/f/", does this picture represent /f/?"). If the production is correct, the therapist will move onto the next letter tile, if the production is incorrect the therapist will set aside the letter tile and move onto the next tile. After the subject is able to correctly match graphemes to mouth pictures, graphemes will then be used in production and perception tasks described above. Progression to Stage II will occur after 15 hours of treatment.

- Treatment Stage 2 – Syllables: The purpose of this stage is to extend skills acquired in Stage 1 to various phoneme sequences. Production, perception and graphemic tasks remain the same with the one difference that sounds will be produced in combinations rather than isolation. Training progresses hierarchically (e.g., VC, CV, CVC, CCV, VCC, CCVC, CVCC, CCVCC). Upon mastery of 1-syllable stimuli, 2-syllable stimuli will be composed using various combinations of 1-syllable stimuli. Sound combinations (both real- and non-words) consist of phonemes and phonological sequences with low phonotactic probabilities. Both real- and non-words will be trained using the same procedures detailed below. Stage II is time-based and will last 45 hours.

- Stage 2-Task 1: Perception Task: The therapist will produce a real word or non-word sound combination (e.g., VC or VCC-VC). The therapist will ask the participant to arrange pictures or graphemes to depict the target. For example, if the subject heard the VC "ip", they would select the graphemes /i/ and /p/.

- Stage 2-Task 2: Production and Graphemic Task: The therapist will show a mouth picture or grapheme tiles and ask the participant to produce the sounds within the real- or non-word individually - then blended together. For example, the participant would say "/p/ /ee/ /f/" that says /peef/. For both correct and incorrect responses, Socratic questioning will be used. In this example, the therapist would say "You said /peef/, does that match these letters?" Next, the therapist will change one sound in the word (e.g., /peef/ changed to /feef/). The participant will be cued to say the old word by touching each sound individually, then identifying the new sound and blending the new word (e.g., the old word says /p/ /ee/ /f/, /p/ will be removed and /f/ will be added, the new word says /feef/). Making one sound change will be done for a series of 5-10 non-words.

Lexical/Semantic treatment protocol:

- Stimuli: The stimuli will be comprised of black and white line drawings selected from 300 nouns distributed across ten semantic categories. The MRC Psycholinguistic Database (http://www.psy.uwa.edu.au/mrcdatabase) will be used to determine Kucera-Frances written frequencies, Thorndike-Lorge written frequencies, imageability, concreteness and age of acquisition ratings of each noun. Semantic relationships will be selected from the University of South Florida Word Association Norms (http://w3usf.edu/FreeAssociation/) and the Edinburgh Association Thesaurus (http://www.eat.rl.ac.uk/).

- Selection of stimuli for each participant: In order to determine the treatment stimuli for each participant, individuals will be asked to name all 300 pictures without cueing or feedback. Responses will be scored for correct/incorrect to determine levels of difficulty for each participant. Two hundred and twenty pictures from ten categories will be chosen (20 items for each of the 10 semantic categories for training and 20 items in one untrained control category). Within each trained category, 15 items will be administered in training, and the other five words will serve as untrained within-category generalization probes. The method for choosing stimuli will involve first determining those items that were named incorrectly and then adjusting the items in each group to balance the psycholinguistic variables known to impact on naming across the four sets.

- Procedures: The lexical/semantic treatment is designed utilizing some characteristics of traditional semantic feature analysis (Coelho et al. 2000) combined with a modified cueing hierarchy typical of semantic therapies (Linebaugh & Lehner, 1977). The treatment will focus on accessing semantic features of the stimulus item prior to naming aloud, and the cueing hierarchy will be employed to handle incorrect responses. Progression of treatment from one semantic category to the next will be criterion based. Participants much achieve 90% accuracy for 3 treatment sessions consecutively before moving on to the next semantic category.

- Treatment routine: The therapist will sit across the table from the participant. The therapist will place a picture in the center of a modified feature analysis chart (Coelho et al 2000). The chart will contain empty squares for semantic (group, use, action, property, location, association), orthographic (written word) and phonologic (number of syllables) features. The participant will be asked to name the picture. Regardless of the ability to name the picture, the participants will be guided in verbalizing the semantic, orthographic and phonologic features of each target with the aid of the chart and cues from the therapist. The therapist will write the features on the chart after they are verbalized. For example, the stimulus item is a 'hammer'. The group feature would be "tool", use feature "*used to pound nails*", action feature "*swing it*", property feature "*has a metal end and wooden handle*", location feature "*is found in the garage*", association feature "*reminds me of a mallet*", orthographic feature "*is spelled h+a+m+m+e+r*", phonologic feature "*has 2 syllables*". If the participants cannot verbalize a feature, the therapist will provide it orally and in writing. All features will be produced for all pictures, even those that were named accurately on the first trial. If the participants are still unable to name the picture after all features are written, the therapist will say the name aloud and require the participants to repeat 3 times.

- After criterion is achieved on List 1, treatment will be initiated for words in List 2, and upon meeting criterion to List 2, treatment will be applied for words in List 3, and so on. In order to determine when performance criteria are met so that the next list can be trained, probe data on the trained will be collected via confrontation naming after every 4 hours of treatment.

Therapist training: Because several research speech therapists will be administering both of the treatment protocols, systematic training prior to study initiation is planned. The purpose of this training will be to enable treatment providers to learn the protocols and procedures for informed consent. The principal investigator will train the therapists using a printed treatment handbook and actual participant video tapes created in the pilot studies. Upon conclusion of training, the therapists will be required to perform treatment tasks across hierarchical levels with a volunteer individual with aphasia. The PI will observe all therapists performing therapy to determine that the therapists demonstrate an adequate level of performance as well as equivalency to one another.

Treatment integrity: In order to know that treatment protocols were administered consistently, we will assess reliability in 10% of treatment sessions across participants and therapists. All sessions will be videotaped and a second examiner will randomly select one in 10 and will score the primary measures of picture naming. Discrepancies in scoring will be resolved with a third examiner. To determine reliability of the treatment protocols, we will construct a grid that includes each training step and tally whether each step was administered as directed for each training word. If reliability is less than 90% in early analyses, we will complete additional examiner training to improve subsequent reliability in the administration of treatment sessions.

Operational Plan:

- Year 1: Hire study staff, develop treatment protocols, and provide training to the therapists. Order equipment and supplies. Prepare experimental stimuli, forms and administration score sheets. Recruit subjects. Enter 20 participants into training anticipating 5-8 months to complete. Data and reliability analysis of enrolled subjects. Enter data into database.
- Year 2: Enter 20 participants into treatment experiment. Data and reliability analysis of enrolled subjects. Enter data into database. View videotapes of treatment protocols to evaluate reliability of treatment administration and provide feedback regarding results of reliability analyses. Prepare initial reports for dissemination at scientific meetings. End of year 2: Complete annual report.
- Year 3: Enter 20 participants into treatment. Enter data, complete reliability analyses, and perform statistical analyses as participant's complete training. End of year 3: Complete annual report.
- Year 4: Enter 20 subjects' participants into treatment. Enter data, complete reliability analyses, and perform statistical analyses as participant's complete training. Prepare additional manuscripts. Meet with collaborators. Complete annual report. Complete data entry, reliability analyses, and statistical analyses. Prepare manuscripts, abstracts for scientific meetings, and final reports.

  Note: Since the Merit Review grant mechanism is for 4 years in length, immediately post treatment data and 3 month maintenance data will occur on n=80 individuals; however at the end of 4 years we will have 1-year maintenance data on n=60 individuals only.

Randomization procedure: Randomization will be done from a central location, with research staff calling in to obtain the randomization assignment. A computer program written by Dr. Cain will be used to make the random assignments, while balancing on aphasia severity and aphasia type. This program uses the minimization algorithm modified to randomize subjects with a biased probability rather than assigning with certainty. It has been used in about 8 randomized trials so far.

Statistical Analyses: Analysis will be by a mixed model analysis using measures at 3 and 12 months as outcomes and baseline measures as a covariate. The model will include as fixed factors treatment (phonomotor versus typical treatment) and time (3 and 12 months), and baseline outcome measure as covariate. Subject id will be included as a random factor. The main effect for treatment will be the primary test of difference between the two interventions. A secondary analysis will test the interaction between treatment and time to evaluate whether the difference between the two treatment groups changed for 3 to 12 months.

Sample Size and Power Consideration: We plan to recruit 100 participants who are greater than 6 months post stroke with chronic aphasia, with the expectation that at least 80 will provide follow-up data. In fact loss to follow-up in the pilot studies has been much lower than 20%, so this is a conservative estimate. With 40 subjects in each treatment arm, there will be 82% power for detecting a standardized effect size of 0.65 standard deviations for the main effect treatment (phonomotor versus typical treatment)(note: standardized effect size observed in the preliminary data was 0.77). This power estimate is conservative since it is based on a simple t-test. The actual analysis will use data from both follow-up time points and will control for baseline covariates, both of which should improve power relative to a t-test.

Intent-To-Treat Analyses and Missing Data: Intention-to-treat procedures will be followed, meaning that every effort will be made to get follow-up data on all subjects who have been randomized; regardless of how many therapy sessions they actually received. The staff who collect outcome data will be separate from the staff involved in providing the intervention. All subjects will be analyzed according to the treatment arm to which they were assigned, regardless of adherence. Every effort will be made to minimize loss to follow-up and missing data, since any methods to deal with missing data are dependent on untestable assumptions about the randomness of missingess. This will include collecting all baseline data prior to randomization to ensure that only subjects who have demonstrated the ability to provide data will get randomized. However, there probably will be some missing data in spite of these efforts. If data are missing at random conditional on data which are available (baseline data, and partial outcome data if available) then the mixed model analysis provides unbiased estimates of treatment differences. Multiple imputation analyses will also be explored, though these are also dependent on the same missing at random assumption being true.

Department of
Veterans Affairs

Memorandum

Date: January 28, 2014

From: Jodie Haselkorn, MD, MPH

Subj: Lead Researcher (PI) Transfer

To: R&D Office

MIRB#00648 "A prospective, controlled study of rehabilitation of anomia in aphasia" is currently overseen by Lead Researcher, Jodie Haselkorn, MD, MPH. This position will be transferred to Diane Kendall, PhD, effective now, as Dr. Kendall has returned from Educational Leave (July 1, 2013 to December 1, 2013).

Jodie Haselkorn, MD, MPH

Diane Kendall, PhD

Department of Veterans Affairs

Memorandum

Date: December 19, 2013

From: Acting Associate Chief of Staff, R&D (S-151)

Subj: Initial Approval of R&D Project

To: Jodie Haselkorn, MD, MPH

1. Your project entitled "A Prospective, Controlled study of Rehabilitation of Anomia in Aphasia" has been reviewed by all relevant R&D subcommittees and has met all administrative requirements for initiation, and has been approved to begin by the R&D Committee. As of the date of this memo you may begin the project. This approval is based on VHA Handbook 1200.01, as revised June 16, 2009, and subsequent guidance from the Office of Research and Development (Central Office) dated May 1, 2009.

2. Your RDIS# is 0026. Your MIRB# is 00648.

3. The R&D Committee approval date is 12/19/13.

4. Your current IRB approval date is 10/30/13. This approval expires 10/29/14.
RSS review occurred 07/24/13.

5. You are responsible for submitting continuing renewal applications to the R&D office for each relevant subcommittee approval in a timely manner (at least 60 days prior to the relevant expiration date). The R&D office will make every effort to send you reminder notices in advance but you must not rely on these, and must track your approval dates carefully.

6. Prior to submission to a journal, you are required to send to the VA R&D office a copy of any manuscript arising from work on this project. No manuscript may be submitted to a journal without first obtaining R&D approval.

7. You must inform the R&D office immediately of any significant changes to your protocol (such as design modification, change in PI, addition or deletion of study staff, etc.). If the funding source or status of this project changes please contact the R&D office at ext. 61417.

8. If there are investigational drugs in use for this project it is the investigator's responsibility to ensure that the pharmacy receives copies of the current, approved protocol, pertinent amendments and modifications as well as copies of the currently approved consent form.

For questions or assistance, please contact Robin Boland at ext. 61417.

Murray Raskind, MD

Human Studies Subcommittee (IRB#2)
VA Puget Sound Health Care System
1660 S. Columbian Way • S-151 • Seattle, WA 98108-1597 • 206-277-1715 • Fax: 206-682-0353

IRB APPROVAL - Initial Review

Date: December 17, 2013
From: Charles Maynard, PhD, Co-Chairperson
Investigator: Jodie K. Haselkorn, M.D., M.P.H. (S-117-MSCOE)
Protocol: A Prospective, Controlled study of Rehabilitation of Anomia in Aphasia
ID: 00648 Prom#: N/A Protocol#: N/A

APPROVED VAPSHCS R&D OFFICE 12/19/13

The following items were reviewed and approved at the 10/30/2013 meeting:

- Initial Review Submission Form - IRQ (06/24/2013)
- Consent for Use of Picture and/or Voice (06/24/2013)
- Standardized Assessment of Phonology in Aphasia (06/24/2013)
- Addendum / Appendix - Appendix A: Staff (06/24/2013)
- Addendum / Appendix - Appendix C: University of Washington Aphasia Lab (06/24/2013)
- Addendum / Appendix - Appendix J: Safety Monitoring (06/24/2013)
- Addendum / Appendix - Appendix K: $300 or pro-rated (06/24/2013)
- Addendum / Appendix - Appendix O: Consent (06/24/2013)
- Request - Expedited (Minimal Risk) Review (06/24/2013)
- Request - Waiver of Consent/HIPAA to Release Medical/Health (06/24/2013)
- HIPAA Authorization Form (06/24/2013)
- Other Compliance Approval Letters/Reports - IRB approval letters re recruitment and funding (06/24/2013)
- Study Instrument - Assessing Speech Planning/Programming (Apraxia) (06/24/2013)
- Study Instrument - PALPA: Auditory Synonym Judgements (06/24/2013)
- Study Instrument - PALPA: Spoken Word-Picture Matching (06/24/2013)
- Study Instrument - PALPA: Written Synonym Judgements (06/24/2013)
- Study Instrument - PALPA: Written Word-Picture Matching (06/24/2013)
- Study Instrument - Real Word Probes and NW Probes (06/24/2013)
- Study Instrument - The Pyramids and Palm Trees Test (semantics) (06/24/2013)
- Study Instrument - Western Aphasia Battery (Part 1) Record Form (06/24/2013; Revised)
- Study Instrument - Boston Naming Test (Set 1) Record Booklet (06/24/2013; Second Edition)

The following additional items were received to address stipulations and are now approved:

- Consent Form - Study (06/20/2013; 1)
- Recruitment - Flyer (06/24/2013)
- Recruitment - Screening Questionnaire Phone Script (06/24/2013)

Conditions of Approval are attached. These conditions are further detailed in the HHS, FDA, and VA regulations, which are available in the Research Office.

The following Human Studies Subcommittee (IRB#2) members recused themselves (or were otherwise excused) from deliberations and did not vote: Jodie K. Haselkorn, MD, MPH.

Approval is granted for a period of 12 months and will expire on 10/29/2014. Your Continuing Review is scheduled for 08/27/2014, and the requirements are attached.

The protocol was determined to have the following level of risk:
Moderate (e.g. drug/device, psyc/soc/privacy risk)

The IRB received your response on 11/25/2013 to the stipulations of its 10/30/2013 contingent approval of this study. The response was reviewed and approved on 12/10/2013.

Please note:

The IRB approved this study for twelve months. The approval period is 10/30/2013 through 10/29/2014.

The IRB determined this study risk level is:
Moderate (e.g. drug/device, psyc/soc/privacy risk)

The IRB determined this study has a FAVORABLE risk/benefit ratio.

The IRB determined the study DOES NOT recruit from a vulnerable population.

The IRB noted this study DOES recruit non-Veterans. The IRB determined the rationale for recruitment of non-Veterans was acceptable (i.e., there are insufficient Veteran patients suitable for the study).

The IRB determined, pursuant to VHA Handbook 1907.01, that this study DOES NOT require the creation or update of a medical health (CPRS) record. Due to no medical health record requirement, there is no flagging requirement (VHA Handbook 1200.05, par 44).

The IRB approved the enrollment of no more than 40 subjects. The IRB reminds the researchers that any subject who signs a consent form, including screen failures, is considered to be enrolled in the study and counts towards the maximum number of subjects.

A local ad hoc scientific review was conducted. The reviewer recommended approval to the IRB. The IRB notes the review and recommendation.

The Privacy Officer stated there were no concerns with the review.

Jodie Haselkorn was not present for the discussion due to a conflict of interest and did not vote.

The IRB determined that all appropriate elements were included in the informed consent form, and are included in the informed consent process.

The IRB determined this study DOES NOT require the use of a witness signature on the consent form.

The IRB granted a Waiver of Documentation of Consent for procedures taking place during screening prior to consenting (38 CFR 16.117[c]) for this study.

The IRB has determined this study requires the study staff DOES need to maintain a master list of all subjects from whom informed consent has been obtained.
The IRB granted a Waiver of HIPAA Authorization for prescreening potential research subjects (45 CFR 164.512(i)(2)).

The IRB determined this study's Data Safety Monitoring Plan was acceptable.

Approval for study initiation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Department of Veterans Affairs

IRB Documentation of Waiver of HIPAA Authorization for Research

VA Facility Name	Puget Sound Healthcare System	**Station Number**	663
Title of Study	00648: A Prospective, Controlled study of Rehabilitation of Anomia in Aphasia		
Principal Investigator (Last, First, Middle)	Haselkorn, Jodie K., M.D., M.P.H.		

Give a brief description of the Protected Health Information (PHI), including the identifiers, for which use or access has been determined to be necessary by the IRB. Example: name, initials, medical record information, x-rays, etc.

Name
Date of birth, date of stroke
Last four SSN

FOR IRB USE ONLY BELOW THIS LINE

NOTE: For an IRB or Privacy Board to approve a waiver of HIPAA authorization for research, it must determine that the following criteria have been met as required by 45 CFR 164.512(i).

The IRB has determined that (check all that apply):

- [x] The use or disclosure of the PHI involves no more than minimum risk to the privacy of individuals, based on, at least, the presence of all the following elements:
  - [x] An adequate plan to protect the identifiers from improper use and disclosure.
  - [x] An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
  - [x] Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted by the HIPAA Privacy Rule.
- [x] The research could not practicably be conducted without the waiver or alteration.
- [x] The research could not practicably be conducted without access to and use of the PHI.

Note: *If an IRB determines that all criteria are not meet, the IRB cannot approve the waiver.*

IRB Documentation of Waiver of HIPAA Authorization for Research - Page2

This waiver of authorization is for: (Check only one of the following)

☐ Use of PHI only of recruitment of study subjects

☒ Use or disclosure for recruitment of study subjects and one or more phases or aspects of the study. List/describe the phase or aspects.

Use of a phone script to ascertain potential study subject eligibility before consent. Potential study subjects will be contacting the researchers directly and may provide protected health information in the course of this screening

☐ Use or disclosure for one or more phases or aspects of the study but not recruitment. List/ describe the phase or aspects.

This waiver has been approved by:

☒ Convened board review

☐ Expedited board review

Signature IRB Chair or Voting Member of the IRB	Date
[signature]	10/30/13

VA Puget Sound Health Care System IRB #2

Name of the IRB

Puget Sound Health Care System

Name of the IRB's sponsoring institution

Seattle, WA

Location (City, State)

Puget Sound Health Care System
American Lake & Seattle

IRB

Regulatory Checklist **Waiver of Documentation of Consent**

Date of Final Review or Determination:	10/30/2013	IRB Application Number:	00648
Researcher Name:	Jodie Haselkorn, MD	Does the IRB approve the waiver of documentation of consent?	YES ☒ NO ☐
IRB Application Title:	A Prospective, Controlled study of Rehabilitation of Anomia in Aphasia		

If denied, summarize reason/s:

(Optional) Research study procedure/population to which this waiver of informed consent applies:
Use of a phone script to ascertain potential study subject eligibility before consent. Potential study subjects will be contacting the researchers directly and may provide protected health information in the course of this screening.

IRB Reviewer Signature	Charles Maynard	Printed Name of Reviewer	CHARLES MAYNARD

FDA Regulated?

Is the research regulated by the Food and Drug Administration (FDA)?
21 CFR 50, 56, 312, 314, 812, 814 — YES ☐ NO ☒

	All of the following are true:	YES	NO
FDA criteria for waiver 56.109(c)(2)	1. The research involves no more than minimal risk to the subjects.	☐	☐
	2. The research involves no procedures for which written consent is normally required outside of the research context.	☐	☐

OHRP Regulatory Justification for Waiver (45 CFR 46)
VA Justification for Waiver (38 CFR 16; VHA Handbook 1200.05)

Indicate which regulatory justification for the waiver of consent applies to this research by checking the boxes below.

		YES	NO
EITHER 46.117(c)(1)	**All of the following are true:**		
	1. The only record linking the subject and the research would be the consent document.	☐	☐
	2. The principle risk is potential harm resulting from a breach of confidentiality.	☐	☐
	3. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.	☐	☐
OR 46.117(c)(2)	**All of the following are true:**		
	1. The research involves no more than minimal risk to the subjects.	☒	☐
	2. The research involves no procedures for which written consent is normally required outside of the research context.	☒	☐