LOW VISION INTERVENTION TRIAL II
(LOVIT II)

PROTOCOL

Version 13
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1 SPECIFIC AIMS

1.1 Problem Statement

VA estimates more than 1 million visually impaired veterans over the age of 45 in the United States (157,000 with legal blindness and 1,026,000 with low vision not severe enough to be classified as legally blind). Visual impairments often limit a person’s ability to function in everyday life, hindering performance of simple everyday tasks such as reading, social interaction, recreation and hobbies. Besides functional disability, persons with low vision have increased risks of injury, a decline of general health, lower self-esteem or depression, and many believe that the future holds little promise. Rehabilitation programs have the potential to restore independence for such people and improve their quality of life.

In January, 2007 VA Secretary Nicholson announced a $40 million dollars plus program to establish a comprehensive nationwide rehabilitation system called the “Continuum of Care for Visually Impaired Veterans,” designed to enhance inpatient services provided by the VA blind rehabilitation centers (BRCs) and expand outpatient low vision and blind rehabilitation services. Each of VA’s 23 regional networks will have low vision services including a Basic Low Vision Service, that is available at all VA eye clinics, as well as Intermediate, Advanced or VICTORS Low Vision Services at selected facilities. Outcomes research is needed to evaluate the effectiveness of the new “Continuum of Care” service delivery models.

The proposed single-masked, multicenter, randomized, controlled trial conducted at nine VA sites will determine if the low vision (LV) rehabilitation (services provided by optometrist and low vision therapist including: low vision examination, low vision therapy to improve use of remaining vision and low vision devices, structured homework to practice use of low vision devices and provision of low vision devices) is more effective in improving visual reading ability for 330 veterans with macular diseases and best corrected distance visual acuity of 20/50-20/200 than basic LV (optometrist alone providing low vision examination and provision of low vision devices with demonstration of their use and maintenance). Effectiveness will be measured with the Veterans Affairs Low Vision Visual Functioning Questionnaire (VA LV VFQ-48), a valid and reliable instrument that is administered by telephone to measure changes in patients’ self-reported difficulty reading and performing other daily living activities before and after rehabilitation. The primary outcome measure is the comparison of changes in patients’ visual reading ability on the VA LV VFQ-48 from pre-intervention baseline to 4 months after they receive low vision care from the treatment programs. The secondary outcome measures are comparisons of changes in other VA LV VFQ-48 visual ability scores (overall visual ability, mobility, visual information processing, visual motor skills) from pre-intervention baseline to 4 months later.

1.2 Hypothesis:

The improvement in visual reading ability measured with the VA LV VFQ-48 will be greater for patients who received LV rehabilitation than for patients who received basic LV.

1.3 Specific Aims:

1. Compare the mean changes in patients’ visual reading ability (estimated from patients’ difficulty ratings of reading items on the VA LV VFQ-48 before and after low vision service delivery in the LV rehabilitation and basic LV groups.

2. Compare the mean changes in visual ability estimated from patients’ difficulty ratings of other items on the VA LV VFQ-48 (overall visual ability, mobility, visual information processing, visual motor skills) before and after low vision service delivery in the LV rehabilitation and basic LV treatment groups.

3. Identify the characteristics of patients who benefit from the LV treatment programs by determining if the mean changes in VA LV VFQ-48 visual ability scores are predicted by baseline visual impairment measures, baseline visual ability and MNREAD scores, presence of central scotomas, treatment group, age, presence of visual fluctuations or history of anti-VEGF injections in the year prior to the study.

4. Conduct an economic evaluation to compare the costs and cost effectiveness of the LV treatment programs.

1.4 Timeline Corresponding to Specific Objectives

The proposed project will extend over approximately six years.
**Figure 1. Timeline Corresponding to Specific Objectives**

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*Develop protocol, data collection forms, and operations manual; hire/train staff and collaborators

*Data for patients consented and/or randomized, August-September 2010 will be included in reports for October 2010.

(Note: Red items comprise dates for additional 10-month extension of recruitment [FY14, months 1-10,: recruitment is extended by 10 months; analyses of primary and secondary objectives will begin when 4M follow-up is complete;*
2 BACKGROUND AND SIGNIFICANCE

2.1 Background: Low Vision Outcomes Studies

Previous studies have evaluated low vision outcomes using a variety of different measures. Some studies have measured reading speed and/or accuracy of surrogate tasks in the clinics (i.e., ability to use devices to perform activities, ability to read a certain print size, or visual acuity with prescribed devices) to determine the outcome of rehabilitation. However, measuring the performance of surrogate tasks may not provide an accurate estimate of the treatment’s effect in tasks that patients perform in daily life. For example, patients may successfully perform an activity in clinic when challenged to do so, but abandon the activity in daily life because it requires too much time or effort. Other studies have employed patient self-reports of functional ability or some aspect of quality of life.

Recent changes in health care have had a major influence on the choice of measurement of low vision outcomes. The Agency for Healthcare Research and Quality reports that healthcare has been evolving away from a “disease-centered model” and toward a “patient-centered model.” In the “patient-centered model,” patients receive services designed to focus on their individual needs and preferences in addition to advice and consultation with clinicians. Outcomes research evaluates the end results of care including the effects that people experience and care about, such as their ability to function. In the “patient-centered model,” rating-scale questionnaires are now commonly used to capture changes in patient’s visual function after low vision rehabilitation.

There is general consensus that low vision services are associated with increased functional status and improved quality of life for persons with vision loss. However, consistent findings from our recent meta-analysis of 7 observational studies and 4 randomized controlled trials that used outcome measures based on rating-scale questionnaires administered to patients showed that the effects achieved by outpatient low vision services were small. As shown in Fig. 2, observed effect sizes, defined as the difference in the mean changes divided by the pooled standard deviation of the changes, ranged from 0.06 to 0.43, average of 0.3 across studies of private outpatient services (red line in Fig. 2, which does not include the VA BRC or LOVIT results). In contrast to outpatient services in the private sector, the VA provides intensive inpatient services as part of comprehensive interdisciplinary BRC programs. As shown on the right side of Fig. 2, an observational study of patients admitted to one VA BRC demonstrated an effect size of 2.1 – nearly 7 times the average effect size of private out-patient low vision services. The VA Low Vision Intervention Trial (LOVIT) provided the first compelling evidence of the effectiveness of outpatient low vision rehabilitation. LOVIT evaluated an outpatient low vision program for veterans with moderate and severe vision loss due to macular diseases. The LOVIT therapy curriculum was developed to model low vision services provided by VA inpatient BRCs. As shown in Fig. 2, the observed treatment effect in the LOVIT study is comparable to that observed in the earlier study of a VA inpatient BRC program (effect size of approximately 1.8).

Potential explanations for the differences in effect size among the studies may include differences in measurement resolution of the various self-report instruments and scoring algorithms used; differences in visual impairment severity, diagnoses or other patient traits for the various samples of patients with low vision; differences between studies in treatment protocols; and differences between studies in acquisition of devices by patients and/or the types of low-vision devices dispensed. The last possibility is particularly noteworthy as all patients in the inpatient BRC or the LOVIT outpatient program were eligible to obtain prescribed assistive devices free of charge. Typically there was little or no public health care funding to provide low vision devices for patients in the earlier private sector studies; patients had to bear most if not all, of the device costs. As was observed for other discretionary health care costs in the RAND Health Care Insurance Experiment, the coverage of low vision device costs may affect the acquisition rate of prescribed devices and therefore affect treatment outcomes.

One criticism of past clinical low vision research is that comparison of the effectiveness of treatment
protocols is not possible because different measures have been used to evaluate the benefit of treatment and there is a paucity of information reported on the actual treatment provided in most of the studies. LOVIT is the only study that used a structured protocol and reported the intensity or duration of therapy sessions and assigned homework. LOVIT II will also use a structured protocol. These protocols can be adopted by clinical practices or compared in future research studies.

Most of the previous outcomes studies and randomized controlled trials (RCT) of low-vision rehabilitation tested the effectiveness of usual care or usual care plus an intervention of interest. A single center RCT conducted in England evaluated the benefits of low vision service delivery models using vision-specific quality of life as the main outcome measure. Reeves, et al., reported that the outcomes of an enhanced low vision rehabilitation model including supplementary home based low vision rehabilitation were not significantly different from conventional (basic) low vision rehabilitation provided by an optometrist in a hospital clinic. The findings of Reeves, et al., confirm the equipoise of the hypothesis we propose to test in LOVIT II. We do not know if the change in visual reading ability scores measured with the VA LV VFQ-48 will be greater for patients who receive low vision services from the Interdisciplinary Team than for patients who receive the Basic Low Vision Service.

For policymakers to evaluate VA’s new outpatient low vision service delivery models, it is important to identify the resources that are required to implement treatment as well as patients’ improvement in visual ability. A cost-effectiveness analysis is a form of economic evaluation that is often done to evaluate the costs and consequences of alternative treatments. The U.S. Public Health Service convened a Panel on Cost-Effectiveness in Health and Medicine, which published guidelines for conducting standardized cost-effectiveness analyses. The U.S. Panel recommends comparing new treatments with usual care, determining costs from the societal perspective (e.g., costs to all relevant stakeholders), and measuring effectiveness in terms of quality adjusted life years (QALYs), which combine mortality, health status, and preferences (or utilities) for health status into one measure. Appropriate methods for eliciting preferences from low vision patients to calculate QALYs are still being debated, although some investigators have estimated utilities using a time trade-off method. Patients’ willingness to trade their remaining years of life for perfect vision in each eye depends on the vision in the fellow eye and varies considerably from 11% to 60% for patients with macular degeneration and from 15% to 41% for patients with diabetes.

The use of QALYs can be justified when making comparisons across the spectrum of health care (e.g., comparing visual impairment to angina). However, low vision patients do not respond well to purely hypothetical time trade-offs (i.e., the patient’s vision cannot be restored and visual impairments are not life-threatening) and QALY estimates are not appropriate measures of rehabilitation outcomes (asking the patient to trade life years for successful rehabilitation is viewed as absurd). For these reasons visual function questionnaires are the preferred instruments for measuring outcomes by most low vision researchers. Cost-effectiveness then is measured as units of cost per units of improvement in functional ability.

LOVIT included the first economic evaluation of rehabilitation for visually impaired veterans. LOVIT compared costs and consequences of VA blind rehabilitation programs using the changes in visual ability on the VA LV VFQ-48 as a measure of consequences. LOVIT II will use the same approach to compare costs and consequences of LV rehabilitation and the basic LV programs that serve veterans with low vision that are not legally blind. We will also use the EuroQol (EQ-5D) to estimate community preference-based health utilities, which will be used to calculate quality adjusted life years (QALYs). Although developed in Europe, the EuroQol has a scoring algorithm based upon a nationally representative sample of the U.S. adult population. In exploratory analysis we will use the cost per QALY gained to compare cost-effectiveness of the two low vision programs and to compare the cost per QALY gained after low vision rehabilitation to other disease treatments.

2.2 Significance of Research

The NIH includes visual impairment, chronic visual deficiencies that impair everyday function that are not correctable by ordinary glasses, among the ten most prevalent causes of disability in America. Currently, there is no cure for age-related macular degeneration (AMD) and other chronic visual impairments that impact central vision. Even with current medical treatments designed to delay or reverse the progression of AMD, most patients will still require low vision rehabilitation. Given the association between age and vision loss, the demand for low vision services is expected to increase from the current 240,000 to over 500,000 cases by 2025 with aging of the population. There is a need to find cost-effective methods of providing low vision rehabilitation or the cost burden for providing services will increase in direct proportion to the number of patients who need low vision rehabilitation. Chronic visual impairments restrict
self-sufficiency and independence by reducing ability to perform activities of daily living and limiting travel from place to place as well as interaction with family and friends. Rehabilitation of patients with chronic conditions may restore functional abilities and lower societal costs by reducing the need for services and increasing independence and quality of life.

Unlike other interventions based on established protocols such as medical and surgical treatments of diabetic retinopathy, low vision care consists of a wide variety of devices and therapy that can be offered to patients. Services range from admission to a six-week VA blind rehabilitation program to over-the-counter purchase of magnifiers without a low vision examination by an optometrist or ophthalmologist. Evidence on the effectiveness of different service delivery models is needed to guide policy makers and develop informed clinical practice guidelines.

2.3 Relevance of the Proposed Work to the VA Patient Care Mission

VA estimates are that there are over 1 million visually impaired veterans over the age of 45 in the United States (157,000 with legal blindness and 1,026,000 with low vision not severe enough to be classified as legally blind). Diseases affecting the central retina are among the leading causes of vision loss in veterans. With new treatments for AMD and diabetic retinopathy that improve but do not restore vision, the population of patients with low vision not severe enough to be classified as legally blind will grow. By 2010, the number of older veterans is expected to more than double. For this reason alone, the numbers of veterans needing low vision services because of age-related eye diseases will more than double. The new VA “Continuum of Care for Visually Impaired Veterans” is expanding low vision outpatient services targeted to the veterans with low vision as well as to those who are legally blind. VA administrators need information on the low vision outcomes that can be achieved in the new programs and costs and cost-effectiveness of the low vision service delivery models. Visual Impairment Service Team Coordinators and eye care practitioners need evidence-based criteria to guide referrals in order to insure veterans’ access to low vision care that is timely, cost-effective and appropriate to meet their needs.

LOVIT evaluated a new outpatient low vision program for legally blind veterans with macular diseases (VA less than 20/100 and greater than 20/500) and demonstrated the effectiveness of outpatient VA low vision services. The research proposed in LOVIT II will complement LOVIT by focusing on outcomes of low vision care for veterans with macular diseases and visual acuity 20/50-20/200. LOVIT II will be the first clinical trial to evaluate low vision services for the larger population of veterans who have permanent vision loss with near normal or moderate visual acuity loss.

3 PRELIMINARY/STUDIES PROGRESS REPORT

VA Low Vision Intervention Trial (LOVIT)

Funding for LOVIT was provided from July 30, 2004 to July 30, 2007. A no-cost extension was granted from July 30, 2007 to July 30, 2009 to accommodate additional research: a 12-month observational study to follow-up on patients in the treatment and control groups that was not included in the original proposal. Submission of the renewal application for LOVIT II was delayed further pending final policy release and to accommodate the start-up time for the new “VA Continuum of Care” programs. Thus far, there are four published LOVIT papers. Dr. Stelmack and the LOVIT research team received the award for Outstanding Contributions in Research and Literature in Low Vision from the Low Vision Rehabilitation Division of the Association for Education and Rehabilitation of the Blind and Visually Impaired in July 2008.

3.1 LOVIT Overview

LOVIT was a randomized unmasked clinical trial conducted at two sites to evaluate a low vision rehabilitation program for veterans with macular diseases that was modeled after low vision services provided in the inpatient program at the Hines BRC. Subjects were 126 legally blind veterans from Hines Hospital and Heffner VAMC with macular diseases and visual acuity less than 20/100 but better than 20/500 in the better eye. After administration of baseline questionnaires veterans were randomized to treatment from a new low vision outpatient program or a usual care (waiting list) control group. Patients assigned to the treatment group received low vision services from an optometrist who specializes in low vision and from a certified low vision therapist. Low vision services at both centers followed the study protocol and consisted of low vision examination and refractive error correction, counseling and education, low vision therapy, and prescribing and dispensing low vision devices. Therapy consisted of 5 weekly 1½-2½ hour sessions at the outpatient low vision clinic, during which the therapist taught the patient strategies for more effective use of their vision and how to use their devices. One home visit to teach patients about needed environmental adaptations and how to use their new skills and devices to perform tasks in the home also was included.
The patient was assigned 5 hours of homework exercises to be completed between therapy sessions and reviewed with the therapist. Patients in the waiting list control group received empathetic and encouraging twice-monthly phone calls to keep them engaged in the study. Patients in the treatment group also received these calls after low vision therapy was completed. Upon completion of the 4-month wait, patients in the control group were referred to usual care low vision or BRC programs.

Outcomes were measured with the VA LV VFQ-48 4 months from baseline in the treatment and control groups (two months after veterans in the treatment group completed low vision therapy). The VA LV VFQ-48 was administered by telephone interview by a masked interviewer to record the difficulty patients self-report performing daily activities at home and in the community [4-7]. “Is it difficult to ….?” is asked about all 48 items. Response choices include: not difficult, slightly/moderately difficult, extremely difficult, impossible and do not do it for non-visual reasons (which is scored as missing data).

The primary outcome measure for LOVIT was the change in visual reading ability on the VA LV VFQ-48 from baseline to 4 months later in the treatment and control groups (two months after the treatment group completed low vision therapy). Secondary outcome measures were changes in the other VA LV VFQ-48 visual ability scores (mobility, visual information processing, visual motor skills and overall visual ability) in the treatment and control groups from baseline to 4 months later (2 months after the treatment group completed low vision therapy). Other measures that were administered at baseline and 4 months later in the treatment and control groups included the SF-36 and the CESD. The MNREAD was administered at the beginning and at the end of training in the treatment group only to assess changes in maximum reading rate.

**LOVIT Specific Objectives:**

1. Compare the mean changes in self-reported visual reading ability measured with the VA LV VFQ-48 from baseline to 4 months later in the treatment and control groups.
2. Compare the mean change in other self-reported visual abilities (mobility, visual information processing, visual motor skills and overall visual ability) measured with the VA LV VFQ-48 from baseline to 4 months later in the treatment and control groups.
3. Determine if the mean changes in visual ability measured with the VA LV VFQ-48 from baseline to 4 months later can be predicted by baseline measures of visual impairment, functional status and life state or explained by measures of functional status after rehabilitation.
4. Perform an economic evaluation of costs and cost-effectiveness of the low vision outpatient program by comparing the mean changes in overall visual ability and the costs associated with these changes in the clinical trial and the inpatient Hines BRC program.

**Hypothesis:** Compared to the usual care (waiting list) control group, veterans in the treatment group will self-report a reduction of 0.78 logit (31%) or more in difficulty performing daily living activities measured by the VA LV VFQ-48 reading domain scores from baseline to 4 months after randomization (two months after veterans participate in a low vision outpatient program). The 0.78 logit change is clinically significant, as this improvement corresponds to the change in visual ability that would accompany a 6-line improvement on an EDTRS visual acuity chart.

**3.2 Review of Published Papers for LOVIT:**

**Methods Paper:**


The challenges of conducting clinical trials in a rehabilitation setting, use of a waiting list (deferred treatment) control group to address ethical issues, development of the treatment protocol, estimation of sample size, development of a vision function questionnaire for patients to self-report the difficulty they experience performing daily activities, and the use of Rasch analysis to develop and estimate this outcome measure are described. This paper also contains results of a two-dimensional confirmatory factor analysis, using a maximum likelihood algorithm (principal axis factoring) that was performed on the Rasch model estimates of patients overall visual ability and each of the domains of the VA LV VFQ-48 (reading, visual information, visual motor skills, mobility). The highest correlations with the two independent sources of variability are between the reading domain and factor 1 and the mobility domain and factor 2.

**Primary Outcome Paper:** Addresses specific aims #1-3.

Patient recruitment occurred from November, 2004 - July 31, 2006. A total of 126 patients were randomized, which represents 103% of the final target of 122 patients. The four-month follow-up questionnaires were completed by 55/64 patients in the treatment group and 62/62 patients in the control group. The interviewer administering the questionnaires that were used as outcome measures was masked. Clinicians were also masked to outcomes data until the end of the study.

Statistical Analysis: The linear functional visual ability scores for each subject were estimated by Rasch analysis of responses to all 48 items and recorded as logits (log odds ratio). Rasch analysis was used to estimate linear visual ability measures for each of the 4 functional domains and the overall score. All comparisons of visual function were analyzed by intention to treat principle. The last observation carried forward method was used in analyses of primary and secondary outcomes if values were missing. Differences between primary and secondary outcomes between treatment and control groups were compared using a 2-sample t test. The differences in changes in visual reading ability were also assessed using analysis of covariance with an adjustment for baseline scores, age, and presence of vision fluctuation and age when vision problems developed. Within group changes were tested by the paired t test.

Results: The treatment group demonstrated significant improvement in all aspects of visual function compared to the control group. The difference in mean changes was 2.43 logits (95% confidence interval [CI], 2.07-2.77; p<0.001; effect size, 2.51) for visual reading ability; 0.84 logit (95% CI, 1.15-1.62; p<0.001; effect size, 2.03) for visual information processing; 1.51 logits (95% CI, 1.22-1.80; p<0.001; effect size 1.82) for visual motor skills; and 1.63 logits (95% CI, 1.40-1.86; p<0.001; effect size 2.51) for overall visual function. As compared to the control group, treated patients 80 years of age or younger exhibited greater improvement and patients who exhibited fluctuations in vision exhibited less improvement in visual function after rehabilitation. For the comparison of quality of life measures in the treatment and control groups, there was a non-significant trend toward improvement in physical role limitations (p=0.08) and mental health (p=0.07) on the SF-36. There were no significant differences in changes in CES-D scores.

Implications for clinical practice: At least 10 hours of low-vision therapy including a home visit and assigned homework to encourage practice, is justified for patients with moderate and severe vision loss from macular diseases. Because the waiting list control patients demonstrated a decline in functional ability, low vision services should be offered as early as possible.

Limitations: There are significant differences between VA and private sector programs regarding third party coverage by Medicare for glasses/low vision devices; services provided by certified low vision therapists are covered only in the states participating in the Medicare Demonstration Project. LOVIT evaluated a new low vision program. There are multiple components to the program; education and counseling, correction of refractive error, eccentric viewing training, provision of low vision assistive devices and instruction in their use, homework and home environment evaluation and modifications. We do not know which components of the program are necessary and sufficient to achieve the outcomes that are reported. These issues must be addressed in future studies.

Economic Evaluation: Addresses specific aim #4


We examined costs and consequences using veterans in LOVIT and comparable veterans in an inpatient BRC. Methods: We compared costs and consequences between treatment patients who participated in LOVIT, a two-site randomized clinical trial, and a sample of comparable patients who received treatment at a VA inpatient BRC. We measured consequences as the change in functional visual ability from baseline to follow-up (LOVIT: 4 months after randomization; BRC: 3 months after discharge) using the VA LV VFQ-48. Results: There were 55 LOVIT and 121 BRC patients for our analyses. Average costs were $38,627.3 higher for BRC patients ($5,054.4 + $404.7 SD for LOVIT vs. $43,681.7 + $8,853.6 SD for BRC p<0.001 Thus, the BRC cost $38,627.3 per patient more than the LOVIT program (95% CI: $17,414 to $273,482).

There was a greater improvement in overall visual ability, mobility and visual motor skills scores for BRC patients; however, there was no significant difference in improvement in reading ability or visual information processing scores. Conclusion: As VA increases outpatient blind rehabilitation services, LOVIT provides a model for expanding outpatient low-vision rehabilitation services for veterans at substantially lower costs than current inpatient BRC services.
Stelmack, 09042014, LOVIT II

**Therapy and Homework Protocols:** Addresses specific aim #4


The team approach and the protocols of the treatment program are described. The time therapists spent teaching skills, use of low vision devices or reviewing homework and the time patients spent completing each of the homework assignments are presented. This information will enable administrators to provide the LOVIT treatment program within an agency or clinical practice and researchers to replicate the protocols in comparative studies.

### 3.3 Work in progress from LOVIT that is not yet published

**VA Low Vision Intervention Trial (LOVIT): MNREAD Outcomes:** Addresses Specific Aim #3

Purpose: This analysis was conducted to determine if a portion of the observed main effect in the primary outcome measure in the VA LOVIT can be explained by improvements in reading speed.51

Methods: Reading speed vs. print size measures were made with MNREAD before and after low vision rehabilitation in 55 low vision subjects who were in the LOVIT treatment group. Self-perceived reading ability, before and after treatment, was estimated from the subjects’ responses to the VA LV VFQ-48 reading items.

Results: Following intervention, maximum reading rate (measured without low vision devices) increased 0.23 log units (effect size = 0.83; p=0.00015). Self-perceived reading ability increased 2.6 logits (effect size = 3.1; p<0.0001) There was no correlation between maximum log reading rate and self-perceived reading ability (the primary outcome measure) at baseline (r=0.024; p=0.44). The correlation between self-perceived reading ability and maximum log reading rate measured after rehabilitation was significant (r=0.37; p<0.005). However, there was no correlation between change scores for the two measures (r=0.014; p=0.46).

Conclusions: An increase in maximum reading rate was observed following low vision rehabilitation. This increase most likely is the result of eccentric viewing training. Although maximum log reading rate correlated with self-perceived reading ability after rehabilitation, no correlation was observed between change scores for the two measures. The effect size for self-perceived reading ability was 3.7 times larger than the effect size for maximum log reading rate, suggesting that much of the main effect can be attributed to reading variables other than maximum reading rate.

**The Veterans Affairs Low Vision Intervention Trial Follow-up: 12-Month Outcomes**

Purpose: Exploratory analysis was conducted to compare changes in VA LV VFQ-48 scores within the treatment and control groups at three time points, pre-rehabilitation, 4 months and 12 months after baseline.50

Methods: Subjects included 44 patients randomized to the treatment group (who did not receive additional low vision/blind rehabilitation after the 4-month follow-up) and 56 patients from the control group who received usual care low vision service/blind rehabilitation after the study was completed. Seven patients in the treatment group were excluded from the analyses. Of these, 5 patients received VA low vision/blind rehabilitation services and 2 patients received services at a private low vision clinic. Only one patient experienced visual acuity loss. Two patients from the control group were excluded from analyses. Neither of these received low vision/blind rehabilitation services. One patient experienced a loss of visual acuity and the other patient died. Rasch analysis was performed on the VA LV VFQ-48 scores to estimate scores (person measures) on an interval scale from the ratings to each item. Paired t-tests were used for pre and post changes. Linear
regression models (step-wise selection and all variables) were used to evaluate the predictors of changes.

Results: For the Treatment Group, after an initial large gain at 4 months (blue bar on the left of Figs. 3 & 4), treatment effects in visual reading ability, visual information processing and overall visual ability decreased a small amount over the 4 to 12 month follow-up period (blue bar on the right of Figs. 3 & 4), during which time they received no further services. Patients with higher visual reading ability at baseline had the potential for a greater loss in function. Non-significant trends were noted for decreases in vitality and mental health scores on the SF-36 from baseline to one year.

Conclusions: The small loss of the previous gains in visual ability for the treatment group at one-year supports the recommendation of yearly low vision examinations. For the Control Group, the loss of visual ability at 4 months (magenta bar on the left of Figs. 3 & 4) calls for early intervention. The magnitude of the cross-over effect in the control group after treatment (magenta bar on the right of Figs. 3 & 4) confirms the treatment effect described for the RCT.

3.4 Development and Validation of the VA LV VFQ and Low Vision Outcomes Studies: Review of Published Papers

The VA LV VFQ is the primary and secondary outcome measure for LOVIT and the research proposed for LOVIT II. There were 3 papers published on development and validation of the VA LV VFQ and its use in low vision outcomes studies since July 30, 2004. One additional paper addressed issues in measurement of low vision outcomes.

Validation and Sensitivity of the VA LV VFQ-48 to Change after Low Vision Rehabilitation

This study evaluated the sensitivity of the VA LV VFQ-48 to change in patients who undergo vision rehabilitation and evaluated vision rehabilitation outcomes. The VA LV VFQ-48 was administered by telephone before and after vision rehabilitation to subjects from 5 rehabilitation programs in the VA and private sector.

The study demonstrated that in addition to being a valid and reliable measure of visual ability, the VA LV VFQ is a sensitive measure of changes that occur in visual ability as a result of rehabilitation. The VA LV VFQ-48 can be used to compare programs that offer different levels of intervention and serve patients across the continuum of vision loss.

There appears to be a significant dose-response relationship when outcomes of vision rehabilitation are measured with the VA LV VFQ-48. The magnitude of the effect depends on the intensity of the rehabilitation program and the level of visual ability of the patient before rehabilitation. Comparison of outcomes from the inpatient BRC and the outpatient low vision rehabilitation programs suggested that rehabilitation ceiling effects exist. The magnitude of change in visual ability that can be achieved may not depend solely on the dose of rehabilitation and types of services and assistive devices that are provided. The distribution of pre-rehabilitation visual ability may also limit the magnitude of change. Patients with more visual ability (more difficulty performing daily activities before rehabilitation) may have lower rehabilitation demand (less need for rehabilitation) than patients with lower visual ability (more difficulty performing daily activities). One consequence of the rehabilitation ceiling effect is that when low-vision outcomes studies are conducted with patients having higher visual ability, (less difficulty performing tasks) larger sample sizes will be necessary for hypothesis testing. LOVIT required a sample size of 122 patients (61 for each group). For LOVIT II, a sample size of 330 patients (165 in each group) is required as the expected treatment effect is considerably smaller.

Timing and Directions for Questionnaires

This study compared pilot data from two outcomes studies using the NEI VFQ-25 to compare changes in patients’ self-reported health-related quality of life after participation in two nearly identical VA BRC programs. Investigators at the Southwestern BRC did not modify the directions for administration of the NEI VFQ-25 to consider use of low vision devices as well as glasses and contact lenses in answering questions to elicit the difficulty patients have performing daily activities. The investigators at Hines made the modification. Patients at Hines showed improvement in health related quality of life after rehabilitation whereas those at the Southwestern BRC did not show a change. This study emphasizes the importance of the directions on responding to survey questions that are given to patients. This study also looked at
administration of questionnaires at the Hines site at two time points and raises concerns that a halo effect may occur when outcomes are measured at the conclusion of an inpatient rehabilitation program before patients have the opportunity to independently use low vision devices and skills in the community.

**Outcomes of VA Blind Rehabilitation**


This prospective observational study compared changes in visual ability of patients admitted to the Hines Blind Rehabilitation Center at three time points, pre-rehabilitation, 3 months and one year post-rehabilitation. Treatment effects decreased significantly over the period from 3 months to 12 months (p<0.001). However, the group of patients whose data were analyzed was still statistically and clinically significantly better (p<0.001) at their 1-year follow up than before beginning treatment. Measures of visual acuity, health and emotional status were not available at the three time points to explain the decrease in visual ability from 3 months to one year. The 12-month observational study to follow-up on the LOVIT treatment control groups was conducted to address these issues and to compare the changes over 12 months in the inpatient BRC program and the outpatient low vision program used in LOVIT.

**Development of the VA LV VFQ-20 and Scoring Algorithms**

Stelmack JA, Massof RW. Using the VA LV VFQ-48 and the LV VFQ-20 in Low Vision Rehabilitation. Optom Vis Sci. 2007; 84(8); 706-709.

This study was conducted to demonstrate use of a simple scoring algorithm for the 48 item VA LV VFQ that approximates measures of visual ability that would be calculated with Rasch analysis and to provide a short form version of the questionnaire for clinical practice and for outcomes studies with small sample sizes where Rasch analysis is not reliable or practical. Rasch analysis is still recommended for research studies that require more accurate measurements.

**3.5 Preliminary Studies from Robert Massof’s Laboratory**

**Responsiveness of EQ-5D to Vision-Related Functional Ability Loss**


Purpose: To evaluate the responsiveness of the EuroQoL (EQ-5D) to vision-related functional ability loss in patients seen in low vision clinics.

Methods: Health state questionnaires including the EQ-5D, Geriatric Depression Scale, TICS, SF-36 and Activity Inventory were administered by telephone to 113 low vision patients across 15 clinical centers within the US. Patients ranged in age from 18-93 years, mean 74 years. Separate Rasch analyses were performed on patient responses to the Geriatric Depression Scale, SF-36 Physical, SF-36 Psychological, and Activity Inventory. EQ-5D responses were transformed to full health utilities to generate the EQ-5D US index. Raw scores were used for the TICS and the SF-36 General Health. The correlation matrix was analyzed with exploratory and then confirmatory factor analysis using a varimax rotation.

Results: From confirmatory factor analysis, four independent factors were necessary and sufficient to explain 65% of variance. We provisionally identified these four factors as psychological (F1), physical (F2), cognitive (F3), and vision (F4). F1 explained 74% of the variance in the Geriatric Depression Scale measure, 62% in the SF-36 Psychological, 16% in the SF-36 General Health, and less than 2% in the TICS and Activity Inventory. 12% of the variance in the EQ-5D is explained by F1. F2 explains 92% of the variance in the SF-36 Physical, 28% in the SF-36 General Health, 7% in the SF-Psychological, and 6% in the Geriatric Depression Scale. 2% or less of the variance in the TICS and Activity Inventory load onto F2. 33% of the variance in the EQ-5D is explained by F2. F3 explains 34% of the variance in the TICS score, 8% in the Geriatric Depression Scale and 5% in the SF-Physical. Only 1% of the variance in the SF-General Health and Activity Inventory load onto F3. None of the variance in the EQ-5D or SF-36 Psychological is explained by F3. F4 explains 97% of the variance in the Activity Inventory. Only 2% of the variance in the EQ-5D and Geriatric Depression Scale could be explained by F4. Almost no variance in the SF-36 Psychological, TICS and SF-General Health loaded on to F4. For all factors, a similar pattern of loading is seen with the EQ-5D and SF-36 General Health. Overall, only 47% of the variance in the EQ-5D can be explained by the four factors.

Conclusions: The variance in the EQ-5D does not load heavily on any one of the four factors identified for low vision patients, while most of the variance in the EQ-5D can be explained by the physical and psychological domains. With less than 2% of the variance explained by the vision factor, the EQ-5D is not an adequate measure of the functional consequences of visual impairment. The TICS appears to be a well-
aimed measure of the cognition factor but much of its variance remains unexplained. Of the four examined, only the vision factor contributes to Activity Inventory measures. Support: EY012045

3.6 Development and Pilot Testing of a Structured Therapy Curriculum for LV rehabilitation and a Dispensing Protocol for Optometrists in the basic LV.

Homework assignments and therapy procedures used in LOVIT and the optometry dispensing protocol were modified and pilot tested in the Hines Low Vision Clinic from 1/1/08-10/1/08 to ensure that the protocols are feasible. Many of these lessons in the therapy protocol were adapted from published training manuals and therapy procedures used in the outpatient low vision program at the Hines BRC and in the LOVIT study. Most patients who needed eccentric viewing therapy required three therapy sessions and patients who had central fixation most frequently required only two therapy sessions. The mean time for the dispensing visit was 30 minutes. However, the time for dispensing and therapy will vary based upon the number of devices prescribed.

4 RESEARCH DESIGN AND METHODS

4.1 Experimental Design: Overview

The study will be a single masked, randomized, controlled clinical trial conducted at nine VA medical centers. The purpose of the proposed clinical trial is to determine if the LV rehabilitation model of low vision service delivery is more effective than the basic LV model in improving visual reading ability for veterans with macular diseases and best-corrected visual acuity of 20/50-20/200. Eligible and consenting veterans will be randomly assigned to either LV rehabilitation or basic LV. The flow of patients through the trial and the experimental design timeline are included in Figure 5. Because of the nature of the experimental and control arms, masking of study subjects is not possible. Masked interviewers located in the office of the chair, who are not involved in clinical service delivery, will perform questionnaire administration. A script, approved by the Central IRB, will be read by the interviewers to explain administration of the questionnaires to each subject, that responses to the questionnaires are anonymous and confidential, and that the patient should not disclose his or her group assignment during the interview. Disclosures will be tracked: none was reported during LOVIT. Clinical service providers will not have access to questionnaire data until the conclusion of the study. The Hines Cooperative Studies Program Coordinating Center (CSPCC) will assume responsibility for masking the data. The optometrists will also be masked by postponing subjects’ randomization to the treatment and control groups until after the optometric low vision examination is completed. This procedure will ensure that the low vision devices prescribed will not be influenced by patients’ assignment to the treatment or control groups.

In LOVIT II, the post- rehabilitation questionnaires will be administered at baseline and four months from baseline.

After the formal study is completed, we will continue to observe all the patients who are enrolled in the study to describe additional services received by these patients and to measure visual ability (reading, mobility, visual motor, visual information processing, overall visual ability) 12 months from baseline. Exploratory analysis will be conducted to compare mean changes in VA LV VFQ-48 scores within the treatment from four months to 12 months after baseline. Exploratory analysis will also be conducted to compare the magnitude of the treatment effect in the subgroup of patients who are actively undergoing treatment for their ocular disease to those who are not being treated.

Treatment and Control Groups:

LV rehabilitation and basic LV are the treatments that will be evaluated in the trial. LV rehabilitation includes services provided by optometrist(s) and low vision therapists, low vision therapy to improve use of remaining vision and low vision devices, and structured homework to practice use of low vision devices. Basic LV is provided by the optometrist alone and demonstration of low vision device use and maintenance is provided without low vision therapy or homework and with less contact time. Veterans in the treatment and control groups will be provided the same low vision devices (at no expense to the veteran) consistent with VA policy. A control for the additional contact time provided for patients in LV rehabilitation group is not included as the additional contact time is an integral component of the interdisciplinary team approach. Low vision programs consist of multiple components. As in LOVIT, it is our goal to evaluate program effectiveness, not the components of the programs.26,38

The home visits that were provided for all patients in the LOVIT treatment group will not be provided for patients in LOVIT II. The new “continuum of care” low vision programs are office-based and home visits are provided for legally blind patients by the Blind Rehabilitation Outpatient Specialists. Home visits are not routinely recommended for patients with vision loss that is not severe enough to be classified as legally
blind. However, if a home visit is needed, a referral will be made to an appropriate provider after the patient has completed the 4-month follow-up telephone interviews. Patients with symptoms of depression or difficulty adjusting to vision loss will be referred to psych-social services by their optometrist. Referrals for psych-social services will not be delayed.

There is a reasonable doubt as to the effectiveness of LV rehabilitation as one clinical trial did not show significantly different outcomes for Conventional (Basic) and Enhanced Low Vision models. LV rehabilitation is provided at selected VA facilities, but the Basic Low Vision Service (Program B), basic LV is provided at every VA eye clinic by VA “Continuum of Care” policies.
Referral/Chart Review/Recruitment Letter/Clinic Visit

Baseline Screening Visit

Telephone Baseline Questionnaires
*Forms: VFQ-48, EQ-5D, SF-36*

LV Exam Visit

**RANDOMIZATION**

LV Rehabilitation

Training Sessions 1, 2, 3

Last Training Session

B-Basic Low Vision

Dispensing Visit

Four-month Telephone Follow-up
*Forms: VFQ-48, EQ-5D, SF-36*

One-year Telephone Follow-up
*Forms: VFQ-48, EQ-5D, SF-36*
4.2 Subjects

Subjects will be 330 patients from the Chicago, IL; Philadelphia, PA; Baltimore MD; Milwaukee WI; Madison WI; Dayton, Ohio; Cincinnati, Ohio; Salisbury, North Carolina, and Washington, DC areas, who are interested in obtaining low vision services at Hines VA Hospital, Philadelphia VAMC, Baltimore VAMC, Dayton VAMC, Clement J. Zablocki VAMC, William S. Middleton Memorial VA Hospital, W.G. Hefner VAMC and Washington, DC VAMC. The inclusion/exclusion criteria have been chosen to enroll patients with chronic, uncorrectable visual impairments that impact central vision who are expected to react positively to treatment focused on vision enhancement.

Inclusion Criteria: Included are veterans with primary eye diagnosis (better-seeing eye) of macular disease and best-corrected distance visual acuity in the better-seeing eye of 20/50 to 20/200 who are expected to benefit from either treatment.

Exclusion Criteria: Excluded are patients who do not have a telephone, or do not speak English, or have previously received interdisciplinary low vision services, or have English literacy less than 5th grade level; or failed Telephone Interview for Cognitive Status Screening (score of 30 or lower)\textsuperscript{52}; or are unable or unwilling to attend clinic visits required for the study; or have severe hearing impairment that interferes with participation in telephone questionnaires; or plan cataract extraction within 4 months after randomization; or who have visual fields contracted to a diameter of 20 degrees or less in their better seeing eye; or have severe hearing impairment that interferes with communication, encrypted email, a phone call using a secure landline or transmission by FAX to a designated machine that is only used by study staff. If the clinician is sending an electronic consult to the designated machine that is only used by study staff. If the clinician is sending an electronic consult to the

Recruitment of Women and Minorities

Every effort will be made to recruit and retain women and minority subjects with macular diseases from the population of VA patients that are referred to the low vision clinics for outpatient low vision rehabilitation to enroll the widest range of population groups. All staff will participate in cultural sensitivity training during the start-up meeting to facilitate interaction with minority subjects.

Recruitment Procedures

More than one means of recruitment may be employed. The research coordinator or site investigator will review the medical records of patients who have been referred to their local low vision clinic. National VA policy requires that the veteran is served and appointments made within 30 days. For this reason, the study information letter and a follow-up phone call will need to be done quickly and in relation to one another. A HIPAA waiver for screening purposes has been obtained so that each VA optometrist serving as site PI will be able to review consulted patient’s electronic medical records to screen for study eligibility and to obtain names, addresses, and telephone numbers. The local site coordinator will mail an information letter describing the study to these veterans. The letter will include a form for the veteran to indicate whether he/she does/does not want to be contacted by the study coordinator to learn more about the study. A preaddressed card/envelope will be included for the veteran to mail the completed form back to the site coordinator. On receipt of the response card/letter the coordinator will contact the veteran by telephone. If the response is not returned within two weeks, the site coordinator will contact each veteran by telephone to confirm whether he/she has received the informational materials. If the veteran has received the informational materials, the site coordinator will ask if the veteran is interested in learning more about the study or declines to participate. Veterans who express interest in learning about the study will be scheduled for a screening visit with the site coordinator. If the veteran did not receive the information letter, another letter will be mailed and the veteran will be contacted on receipt of the response.

Clinical staff may discuss the study with their patients and will have a flyer approved by the Central IRB. If patients tell their clinician that they are interested in learning more about the study, the patient will be contacted by phone to set up an appointment with the coordinator for information/screening. Clinical staff will use a secure mode of transmission of PHI for recruitment. Methods may include personal communication, encrypted email, a phone call using a secure landline or transmission by FAX to a designated machine that is only used by study staff. If the clinician is sending an electronic consult to the

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st clinic requesting low vision examination, the clinician may note on the consult that the patient is interested in being contacted by study staff.

If a potential patient is found to be enrolled in another study, but eligible for this protocol, dual enrollment will be pursued as follows: a memo will be sent from the LOVIT II local site investigator to the site investigator of the other study that will request permission to enroll the patient in LOVIT II. The Chairs of both studies will be copied. The patient will be enrolled in LOVIT II on receipt of the signed agreement memo. If the site investigator for the other study is not available, permission will be sought from the study Chair. The memo will be kept in the patient’s file in both studies and will be forwarded with the consent to the site RCO to prevent any concerns in case of an audit.

Screening Procedures

After the study is described by the site coordinator, veteran’s questions are answered and consents/HIPAA authorizations are read to the veteran and signed, habitual visual acuity OD and OS will be measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart to exclude veterans with distance visual acuity in the better-seeing eye that is better than 20/50.54 Literacy will be evaluated using the Dolch word test.53 Baseline demographic information, medical history, and history of eye treatments will also be obtained at the screening visit for veterans whose screening indicates that they may be eligible. The Telephone Interview for Cognitive Status (TICS) will also be administered at the screening visit. Patients who do not meet inclusion criteria based upon the optometrist’s measurement of best-corrected visual acuity and those who are to be excluded based on ocular health criteria will not be randomized. The number of patients screened and the number excluded for each criterion will be tracked and reported in the primary outcome paper. The site coordinator will direct the interviewer to administer the baseline questionnaires: VA LV VFQ-48, SF-36, and EQ5-D. Following completion of the questionnaires, the patient will be scheduled for a low vision examination to be conducted by a staff optometrist. Best-corrected visual acuity and a final ocular health screening to confirm eligibility for the study will be evaluated by the optometrist after refraction during the low vision examination.

Baseline Measurements: Administration of Pre-Low Vision Program Questionnaires to Treatment Groups

The interviewers will administer the baseline questionnaires, SF-36, VA LV VFQ-48, and EQ5D by telephone. Our experience is that most veterans can participate in a 45-minute phone interview. If veterans tire during the questionnaire administration, a return phone call will be made within a week to complete the interview.

Overview of Intervention: Low Vision Rehabilitation for Veterans with Central Field Loss

Patients with low vision from macular diseases frequently have disturbances in their central vision resulting in blur, distortion or blind spots. These blind spots, called scotomas, cause visual performance difficulties such as objects “jumping in or out of nowhere” or “parts of letters or words appearing to be missing or blurry.” The presence of scotomas decreases performance of many activities of daily living (reading, face recognition, visual search and space perception) and visual functions (contrast sensitivity, contrast discrimination, stereoscopic depth perception and fixation stability/precision).55-57 To compensate, patients with a central scotoma rely on a small area(s) of viable retina spared from damage or an area of retina outside of the damaged foveal/macular region called a preferred retinal locus (PRL).55-56 In this case, low vision rehabilitation forces the use of alternate areas of retina with lower resolution that are often located outside of the affected foveal/macular area. The process of aligning the image into a new retinal viewing area is referred to as eccentric viewing, and training veterans’ oculomotor skills to more effectively use their PRL(s) or a new trained retinal locus (TRL) is called eccentric viewing training.58-61 The ability to resolve fine detail decreases as the image of interest is relocated from the fovea toward the peripheral retina, The lower resulting visual acuity is compensated through optical magnification that can be provided at far or intermediate distances with telescopic devices or at near with magnifying eyeglasses, microscopes, pocket magnifiers or electronic systems that enlarge print for reading and writing. Because larger size objects or letters are easier to see, large print reading materials and use of large or bold print on clocks, cans or other common household items are often used.

New treatments for macular degeneration have resulted in more patients presenting for low vision rehabilitation with functioning foveas than 10 years ago.62 These patients may also have small paracentral scotomas that progress to horseshoe-shaped and then ring shaped scotomas around the fovea. The retina inside the ring scotoma is typically the fovea, which allows the patient to perform well on visual acuity tests but to have difficulty with other visual tasks like reading.55-56,62 Electronic systems or filters that improve
contrast or provide low levels of magnification may be more effective in improving reading performance than higher levels of magnification because larger words may not fit within the seeing area.62

Persons with low vision often have problems with contrast loss and glare. Objects blend with the background and lights are distracting or uncomfortable. Eyeglasses with filters to reduce glare and increase contrast are often helpful as is modification of the environment to control lighting, reduce glare and enhance contrast

Overview of Intervention: Low Vision Devices Prescribed for Veterans

While veterans participating in VA rehabilitation programs do not receive an unlimited number of prosthetic devices, VA has liberal issuance policies. Low vision devices most frequently prescribed in low vision clinics for patients with visual acuity from 20/50 to 20/200 will be available for prescriptions/issuance to veterans in both arms of the study. These include: pocket magnifiers for spot checking at near; stand magnifiers, portable electronic magnifiers, reading glasses, or large in-line video magnifiers that can be used for short or sustained reading activities; monocular telescopes for far/intermediate distance spot checking, teleloupes for viewing TV and spectator events; optivisor for writing or other near activities; daily wear spectacle Rx; filters to control glare; and non-optical, independent living aids (e.g., reading stands, lamps, clocks, games, household/cooking, watches, labeling, writing) and resource catalogs.

Low Vision Examination and Rehabilitation Planning

The low vision examination will be conducted by a staff optometrist according to Optometric Clinical Practice Guidelines for Care of the Patient with Visual Impairment (Low Vision Rehabilitation) published by the American Optometric Association.63 Patient history (eye, medical, visual, and social), discussion of specific goals and needs, distance and near visual acuity, eccentric viewing assessment, refraction to best-corrected visual acuity, contrast sensitivity testing, low vision device evaluation, binocular vision and ocular motility testing, ocular health assessment, and visual field testing will be performed.

Habitual visual acuities will be measured with the Early Treatment of Diabetic Retinopathy Research Study (ETDRS) distance visual acuity chart.54 Eccentric viewing will be assessed with Face Fields, a technique developed by Sunness.64 Refraction will be performed and best corrected visual acuity OD, OS, OU will be measured. Reading acuity, critical print size and maximum reading rate will be measured with the MNREAD Acuity Chart and the Lighthouse Near Visual Acuity Test. The Pelli Robson chart will be used to measure contrast sensitivity.65 Subjects will be evaluated with all the low vision devices included in the low vision outpatient program protocol. The initial magnification level for devices will be determined from reciprocal of vision formulas66 with refinement of magnification during the examination to achieve, if possible, an equivalent of 20/40 distance vision through the telescope, 0.8 M word acuity on Lighthouse Game card for pocket magnifiers, and 0.8 M continuous text with ease for stand magnifiers and or low vision reading glasses.

Kinetic confrontation fields will be performed in the better seeing eye to confirm eligibility. Visual fields with Goldmann III4e target or equivalent should be performed if kinetic confrontation visual fields indicate that the visual fields are constricted to less than 60 degrees in diameter.

Visual fields to identify scotomas will be mapped binocularly with the visual field test developed by Gislin Dagnelie. This test was chosen in lieu of more expensive equipment such as the Nidek MP-1 microperimeter that is out of the financial reach of most low vision clinics.

Ocular health will be assessed. Examination of the globe, adnexal tissue and neuro-components will include neuro-ophthalmic examination of extraocular muscle motility, pupil light and accommodative reflexes including assessment for afferent pupil defect, confrontation visual fields; external and anterior segment examination of eye lid apposition, position and symmetry, lacrimal secretion and drainage, cilia, supportive glands and palpebral conjunctiva, bulbar conjunctiva, sclera and cornea, anterior chamber, iris, lens, posterior chamber and tonometry to measure intraocular pressure; fundus examination including anterior vitreous, peripheral retina, optic disc, maculae, retinal and choroidal vasculature.

After the low vision examination and counseling, prescription of low vision devices and therapy to manage visual impairment will be incorporated into an individualized rehabilitation plan. Referral for orientation and mobility, home visits, etc., are not routinely made for patients meeting the eligibility criteria for LOVIT II. If these services are indicated, they will be included in the rehabilitation plan but delayed until after veteran completes the post treatment outcome measurements four months after randomization. However, all veterans with symptoms of depression or difficulty adjusting to vision loss will be referred for psych-social services without delay regardless of their treatment assignment.

Randomization
After the final determination on eligibility is made, the baseline questionnaires have been administered, low vision examination/treatment planning are completed, and the prescribed low vision devices are available at the site, the site coordinator will contact the data center and obtain the treatment assignment. Prior to the start of patient recruitment, the statistician will develop a randomization scheme that will be kept at the data center. Study personnel at the sites will not have access to the randomization scheme. A permuted block randomization with random block sizes will be used. Randomizations will be stratified by participating site and baseline visual acuity 20/50 or less to and including 20/63 and less than 20/63 to and including 20/200 based upon best-corrected visual acuity measured by the optometrist after refraction. The site coordinator will contact the patient to relay the treatment assignment and to set up a dispensing appointment with the optometrist or the first visit with the low vision therapist.

**Treatment Provided for Veterans Randomized to Basic Low Vision**

Veterans randomized to basic LV will receive an appointment for the staff optometrist to dispense the low vision devices and two catalogs for independent living aids for the visually impaired. During the dispensing visit the optometrist will demonstrate use of the prescribed optical or non-optical low vision devices pointing out adjustment or focusing, scanning/tracking to locate information, maintaining orientation, adjustment of lighting and proper maintenance (cleaning and changing batteries or bulbs) using the EDTRS chart, Lighthouse “Continuous Text” Card for Adults, the Lighthouse “GAME” and “Number” Cards.

The MNREAD test will be repeated at the end of the dispensing visit.

The mean time for the dispensing visit was 30 minutes during pilot testing. However, the time will vary based upon the number of devices prescribed. The dispensing visit will not exceed 1 hour, as it would not be feasible for an optometrist providing a basic LV service to spend more time dispensing devices. Prior to the start of the study, Dr. Stelmack will meet by conference call and email with the other optometrists to finalize the dispensing protocol that will be used by all of the sites. Optometrists will be certified in the protocol during the orientation and training meeting that will be held before the start of the study.

**Follow-up for Veterans Randomized to Basic Low Vision**

Veterans will be given business cards with a phone number to contact the optometrist with questions or concerns regarding the devices that are prescribed. If the low vision plan needs to be modified, the patient may pick up a stronger power device or have a new device dispensed by the optometrist. Patients may be contacted by the local site coordinator two months after randomization to keep them engaged in the study and to obtain information regarding any adverse events that they have experienced since their last low vision clinic visit. However, the period following randomization usually involves frequent contact with the patients and additional contact will not be necessary. Veterans will be offered low vision therapy and any other services included on the low vision rehabilitation plan after the post-treatment outcomes measurements are made four months from baseline. As every veteran will have the opportunity to receive LV rehabilitation patients randomized to basic LV will be less likely to withdraw from the study or to seek additional low vision services outside of the study.

**Treatment Provided for Veterans Randomized to LV Rehabilitation**

Veterans randomized to LV rehabilitation will be referred to low vision therapy for dispensing of devices and instruction to more effectively use remaining vision and prescribed devices. Low vision therapy will be administered in one to three 1½-2½ hour sessions at the outpatient low vision clinics. Based upon our pilot testing, we anticipate that patients who need eccentric viewing therapy will require three sessions and patients who have central fixation will usually require only one or two sessions. The MNREAD test will be repeated at the end of the last therapy session.

These therapy techniques are adopted from or are similar to those found in low vision therapy manuals and textbooks. Prior to the start of the study, Low Vision Therapy Subject-Matter Expert, Steve Rinne, MA, CLVT will meet by conference call and email with the low vision therapists at the sites to finalize the homework and therapy curriculum. The therapists will be certified in the therapy procedures during the orientation and training meeting. Use of a structured curriculum will help insure consistency of the treatment across sites.

For patients who do not have central fixation, the therapy plan begins with the development of eccentric viewing skills using the recommended spectacle prescription for best visual acuity. Training with the prescribed low vision devices will follow. The amount of time spent in low vision therapy will depend upon the devices prescribed and the progress of the veteran in learning the skills that are taught. Training is considered complete when the veteran has completed the lessons for eccentric viewing (if indicated) and training with each low vision aid included in the rehabilitation plan; the veteran’s visual acuity with the device(s) is as good as the visual acuity projected in the rehabilitation plan; and the veteran can
demonstrate to the therapist independent and safe use of device(s) to meet identified goals. These are the same performance criteria that were used in LOVIT. Therapists will be permitted to add additional time at each session to accommodate veterans with slower learning styles; but none of the veterans will be provided a therapy program that exceeds three visits.

As in LOVIT, each participant will be given a homework package that includes all necessary materials. Homework exercises and practice strategies are used to guide veterans’ practice with devices between weekly sessions with the low vision therapist. Five hours of homework is assigned at each lesson, turned in and reviewed at the next. Veterans also record starting and ending times. The homework review during the therapy sessions encourages veteran’s compliance with completion of their homework. The assignments are intended to enhance the participants’ efficiency and confidence, to improve the carryover skills by having the participants practice everyday tasks at home, to provide opportunities for independent decision making and problem solving, to demonstrate a large variety of potential uses for a particular low vision device, and to identify problems and develop competence so that decisions or techniques will not be burdensome to use. The homework exercises incorporate tasks important to veterans’ independent living e.g., reading product labels to determine the ingredients, calories and fat content in foods.

Follow-up for Veterans Randomized to LV Rehabilitation

The low vision therapist will consult with the optometrist to review the rehabilitation plan prior to starting therapy and to discuss any need for changes in the rehabilitation plan. Veterans will be given business cards with a phone number to contact the therapist with questions or concerns regarding the devices that were prescribed. Patients will be contacted by the local site coordinator two months after randomization to keep them engaged in the study and to report any adverse events that they have experienced since their last low vision clinic visit.

The patient incentives of $20 per visit will help defray transportation costs so that patients who are randomized to LV rehabilitation do not withdraw from the study for financial reasons. If the cost of a patient’s actual transportation costs exceeds $20 per visit, additional funds (up to $50 per visit) can be made available upon proof and in coordination with the study team. Collection of patients’ social security numbers will be necessary to process reimbursement. Transportation reimbursement exceeding $50 will require prior approval of the study Principal Investigator.

Administration of Follow-up Questionnaires to the Treatment Groups

The interviewer(s) will administer the post rehabilitation questionnaires (VA LV VFQ-48, EQ5-D, SF-36) by telephone, four months from baseline to assess primary and secondary outcomes of the study. The interviewer also will administer the post rehabilitation questionnaires 12 months from baseline for exploratory analysis of changes in visual ability from four months to 12 months after baseline. Patients will be questioned regarding any adverse events that they have experienced in the time interval between administration of the four month and 12 month questionnaires.

4.3 Measurement of Outcomes

Validation of the VA LV VFQ-48

The VA LV VFQ-48 is a valid and reliable questionnaire that is sensitive to low vision rehabilitation outcomes for veterans across the continuum of vision loss. Validation, development and sensitivity to change are documented in previously published studies. Specific aims 1 and 2

Most low vision programs target reading because reading is one of the most frequently reported goals of low vision patients. Therefore, the primary outcome measure is the comparison of the mean changes in patients’ self-reported visual reading ability (rating of difficulty performing reading activities on the VA LV VFQ-48 before and after low vision service delivery) from baseline to four months later in the LV rehabilitation and basic LV treatment groups. The VA LV VFQ reading items include: tell time, identify money, handle finances, read street/store signs, read signs, read headlines, read menus, read mail, read print on TV, keep place while reading, read newspaper/magazine articles, and read small print on package labels. Secondary outcome measures are comparison of the mean changes in other self-reported visual abilities (mobility visual processing, visual motor skills and overall visual ability) measured with the VA LV VFQ in the treatment and control groups. Independent variables are type of intervention (Basic Low Vision Service Control Group or Interdisciplinary Team Treatment Group), best corrected visual acuity measured at the optometric low vision exam (20/50-20/63 or less than 20/63-20/200) and clinical center.

Specific Aim #3 Predicting/Explaining Low Vision Program Outcomes

Identify the characteristics of patients who benefit from LV rehabilitation and basic LV by determining if the mean changes in VA LV VFQ-48 visual ability scores from baseline to four months later are predicted
Stelmack, 09042014, LOVIT II
by baseline measures of visual impairment, visual ability and MNREAD scores; presence of central scotomas, age, treatment group, presence of visual fluctuations, and history of anti-VEGF injections in the year prior to the study. The mean change in VA LV VFQ-48 visual reading ability and other visual ability scores from baseline to four months later for the treatment and control groups are the dependent variables. Independent variables are baseline measures of visual impairment, visual ability and MNREAD scores; presence of central scotoma, age, presence of visual fluctuations, treatment group, and history of anti-VEGF injections in the year prior to the study.

4.4 Statistical Issues
Sample Size

Our studies indicate that there is a rehabilitation ceiling effect. The magnitude of change in visual ability that can be achieved is dependent upon the dose of rehabilitation services and pre-rehabilitation visual ability. Figure 6 illustrates the change in visual ability after rehabilitation vs. pre-rehabilitation baseline ability for results obtained from BRC and private low vision outpatient clinic outcome studies and from LOVIT. The solid line drawn through the data is the outcome predicted by an average rehabilitation ceiling. Patients with more visual ability may have less rehabilitation demand (less need for rehabilitation) than patients with lower visual ability (more difficulty performing activities). The LOVIT treatment group demonstrated large treatment effects (ES 2.51) compared to the delayed treatment control group.

Because LOVIT II will enroll patients having greater visual ability at baseline (lower expected change score in figure 6), and all enrolled patients in both the treatment and comparison groups will receive a low vision exam and low vision devices, a smaller treatment effect, relative to that in the comparison group, is anticipated. Assuming a small treatment effect size of 0.35 (referring to difference between treatment and comparison group change score distributions), setting the alpha error at 5%, power at 85%, and using a two sided t-test for 2 independent groups, a sample size of 300, 150 for each group, is required. Assuming a 10% withdrawal rate (death, loss to follow-up, withdrawal of consent), 330 patients (165 per group) will need to be randomized. This sample size also provides 80% power to detect a treatment effect size of 0.325. We expect less than a 10% dropout rate in this study because patients enrolled in the study have been referred to the low vision clinics for rehabilitation services, all enrollees are expected to benefit from the rehabilitation provided for treatment or control groups and patients randomized to the control group will be offered low vision therapy at the conclusion of the study. Patients will also receive compensation to help defray the costs of travel to the clinic.

There is a strong linear trend between visual ability (in logits) and visual acuity (in log MAR units). Using the LOVIT SD of 0.93 logit and a difference between the means in the treatment and control groups of 0.325 logit, an Effect Size of 0.35 is equivalent to a change of 2.5 lines of visual acuity on an EDTRS chart. A 2.5 line visual acuity difference would be considered clinically significant (3-line change is often used as an endpoint in ophthalmological randomized clinical trials and epidemiological studies).
Patient Recruitment

Six sites were originally planned. Initially each site was expected to randomize two patients per month. Assuming randomization of 9 pts/month, it was anticipated that approximately 36 months would be required to reach the goal of 330 randomized patients. In LOVIT, our target was 2.65 patients per month and we were able to recruit 103% of the final target within the accrual period. We did anticipate any difficulty in recruiting subjects because the population of patients with low vision that is not severe enough to be classified as legally blind is almost 6 times larger than the population of veterans who are legally blind. Also, the new low vision “continuum of care” clinics are strategically located in areas where visually impaired veterans reside. To facilitate recruitment, each participant will receive $20 per session to help defray expenses associated with their transportation to the clinic. Table 1 describes the targeted enrollment of veterans over a thirty six month accrual period.

Table 1: Targeted/Planned Enrollment Table

<table>
<thead>
<tr>
<th></th>
<th>FY 2010</th>
<th>FY 2011</th>
<th>FY 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 sites</td>
<td>9 10 1</td>
<td>1 2 3</td>
<td>4 5 6</td>
</tr>
<tr>
<td></td>
<td>7 8 9 10</td>
<td>11 12</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Per site</td>
<td>2 4 6</td>
<td>8 10 12</td>
<td>4 6</td>
</tr>
<tr>
<td>Total</td>
<td>6 32 8</td>
<td>4 6</td>
<td>6</td>
</tr>
</tbody>
</table>

The plan for enrollment was modified. Several sites experienced delays in hiring coordinators due to VA Human Resources policies; and two sites discontinued participation in the study. The LV program at Cincinnati closed. Personnel issues at the Salisbury site resulting in this site being dropped from the study. Increased use of anti-VEGF injections also resulted in more patients with visual acuity outside the required range. Recruitment was extended through July, 2014 (a total of 48 months of recruitment) to reach the goal of 330 total patients.

Placement of the Continuum of Care Low Vision Clinics

The location of these sites within the VA System was strategically chosen. The VA system is divided into 23 networks called Veterans Integrated Services Networks (VISNs). All VISN Offices were asked to provide data for a Gap Analysis for a Visual Impairment Advisory Board appointed by VA Headquarters. The Gap Analysis examined existing locations of low vision/blind rehabilitation services and their complexity within each network area. A Continuum of Care Placement model was then developed for each VISN based upon density of patient need, with priority given to facilities with the largest Visual Impairment Services Team roster sizes in a given VISN. After concurrence with the Network Directors, memorandums of understanding regarding the timelines for operations deployment, facility placement, funding arrangements, staffing and space considerations as well as a commitment that every optometry/ophthalmology eye clinic would provide basic low vision services were signed.

Interim Reporting

Summaries of primary and secondary outcomes reported by treatment group will not be provided until after data collection is completed. The statistician will produce semiannual data summary reports including information on patient baseline characteristics, recruitment and retention, adherence to protocol and data quality. An interim analysis will be performed when 50% of the four-month outcome data have been collected to determine whether the extension of the recruitment period and changes in the eligibility criteria have resulted in the study’s being over- or under–powered.
General Statistical Analysis Issues

All analyses will be based on intention to treat principles, i.e., will include all randomized patients. We estimate that no more than 10% of patients will be excluded from the analysis because of early withdrawal from the study. All patients who discontinue treatment will be encouraged to complete the post-rehabilitation questionnaires at the conclusion of the study. All statistical tests will be two-sided using an alpha of 0.05. Patient baseline characteristics will be compared by treatment group. Characteristics of patients in each treatment group who withdraw early will be compared with those who complete the study to evaluate possible bias due to withdrawal from the study. Study quality factors, such as mis-randomizations, treatment non-compliance and protocol deviations will be reported. Monthly recruitment and comparisons with recruitment goals, withdrawals and reasons for withdrawal will be reported.

Specific Aim #1 will compare the mean change in visual reading ability (self-report of difficulty performing reading activities) for patients participating in LV rehabilitation and basic LV from pre-intervention baseline to four months later. Rasch analysis will be performed on the VA LV VFQ-48 scores to estimate scores (person measures) on an interval scale from the ratings to each item. Primary analysis will compare the mean change in VA LV VFQ-48 visual reading ability scores between treatment groups using a t test for independent groups. Exploratory analysis will evaluate longer-term changes in visual reading ability from four months to 12 months using persons’ measure scores calculated from Rasch analysis. Exploratory analysis will also be conducted to compare the magnitude of the treatment effect in the subgroup of patients who are actively undergoing treatment for their ocular disease to those who are not being treated.

Limitations: Results cannot be generalized to veterans who are not referred or who decline referral to the outpatient low vision clinics.

Specific Aim #2 will compare the mean change in other visual abilities (overall visual ability, mobility, visual information processing, visual motor skills) for patients participating in LV rehabilitation and basic LV groups from baseline to four months later. Rasch analysis will be performed on the VA LV VFQ-48 scores to estimate these scores (person measures) on an interval scale from the ratings to each item. The t tests for independent groups with correction made for multiple statistical comparisons will be used to compare the mean changes in scores of overall visual ability, mobility, visual information processing and visual motor skills between treatment and control groups. Exploratory analysis will evaluate longer-term changes in other visual abilities (mobility, visual information processing, visual motor, and overall visual ability) from 4 months to 12 months using persons measure scores calculated from Rasch analysis.

Specific Aim #3 will use regression models to determine if the mean change in VA LV VFQ-48 visual reading ability scores from baseline to 4 months later can be predicted by baseline measures of visual impairment, visual ability and MNREAD scores, presence of visual fluctuations, age, treatment group, and history of anti-VEGF injections in the year prior to the study.

Specific Aim #4 is to perform an economic evaluation of costs and cost-effectiveness for the outpatient low vision service delivery models.

Cost Analysis Overview: The cost analysis will identify the costs associated with LV rehabilitation and basic LV. We will also compare the costs and consequences (in terms of functional visual ability) between treatment group patients who participated in LV rehabilitation and those who received basic LV. We will measure direct healthcare costs of the treatment programs from the healthcare provider’s (i.e., VA’s) perspective. We will measure consequences as the change in functional visual ability from baseline to 4 months later.

Resource Identification: The resources to be identified along with the relevant perspective and source of the resource utilization are presented in Table 2. Following the resource categories enumerated by the U.S. Panel on Cost-Effectiveness, we will examine direct medical resources (low vision evaluation, outpatient low vision services [either LV rehabilitation or basic LV], and equipment repair), direct non-medical costs (transportation), and time (veteran’s time receiving treatment).

Table 2. Resources Identified

<table>
<thead>
<tr>
<th>Direct Medical Resources</th>
<th>Perspective</th>
<th>VA</th>
<th>Societal</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Vision Evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td>X</td>
<td>X</td>
<td>Direct measurement</td>
<td></td>
</tr>
<tr>
<td>Examination equipment</td>
<td>X</td>
<td>X</td>
<td>Direct measurement</td>
<td></td>
</tr>
<tr>
<td>Clinic facility and overhead</td>
<td>X</td>
<td>X</td>
<td>VA Decision Support System (DSS)</td>
<td></td>
</tr>
<tr>
<td>outpatient Low Vision Services</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examination equipment</td>
<td>X</td>
<td>X</td>
<td>Direct measurement</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation equipment and supplies</td>
<td>X</td>
<td>X</td>
<td>Direct measurement</td>
<td></td>
</tr>
</tbody>
</table>
Costing: We will estimate the direct healthcare costs of resources used for the treatment programs. We will determine direct medical costs used from the VA’s perspective. Direct medical costs include personnel costs, equipment costs, and facility overhead costs. Personnel include an optometrist, low vision therapist, secretary, and prosthetic clerk. We will estimate the personnel costs for each component of the outpatient low vision programs on the basis of the wage rate of the personnel (including fringe benefits) and the time required for each component of the program, which will be collected at the patient level on study forms or determined through interviews with relevant staff. The wage rate for the optometrist will be based on the average hourly rate for an optometrist in the VA from the VA Decision Support System (DSS), which is a relational database that contains the integrated process of care and cost information from multiple VA data sources. The wage rates of a low-vision therapist, secretary, and prosthetics clerk will be based on wage rates from the general schedule of payments for federal employees, assuming a 30% fringe benefit rate. There are multiple types of equipment: the examination equipment, the rehabilitation equipment at the outpatient clinic, and the devices dispensed at no charge to the patient. We will estimate a cost per outpatient visit for the examination and outpatient rehabilitation equipment, using information on the acquisition costs and useful life. The costs of devices for veterans will be based on acquisition costs. VA facility and overhead costs will be determined from the VA Decision Support System (DSS). The costs of the low-vision devices and other materials (e.g., pens, typoscopes, etc.) provided to patients will be based on acquisition costs.

Direct non-medical costs will consist of transportation costs. We will determine the mileage from the veteran’s home to the VA low vision outpatient rehabilitation center. To determine the costs of veteran’s transportation to the low vision outpatient rehabilitation center, we will determine the veteran’s usual mode of transportation and an appropriate reimbursement rate per trip.

Total direct medical and non-medical costs per patient will be estimated by summing the costs of the initial evaluation, the outpatient low vision services (either LV rehabilitation or basic LV), the low-vision devices and other materials, veterans’ transportation, and facility overhead costs. All costs will be adjusted for inflation using the Consumer Price Index.

As noted above, time is an important resource that is also required to receive healthcare. Time patients spend receiving care is a resource being used from the societal perspective. Our primary focus will be to measure the time that patients spend receiving low vision services. To insure accurate record keeping for time, veterans will record the starting and ending times on each homework assignment that is turned in weekly. Studies indicate that self-reported recall for encounter events is good over short time periods. Low vision therapists will record the time spent in each training session. Because there are no standardized methods for valuing time of patients, we will use alternative methods. We will estimate the value of patient’s time based on employment and earnings data for persons with disabilities from the US Census Bureau's Survey of Income and Program Participation. As a sensitivity analysis we will estimate the value of patient time based on age/gender specific wages for the U.S. Bureau of Labor Statistics.

Analysis: The main cost analysis will be to determine total costs of providing low vision services from the VA perspective. To do so, we will add the direct medical costs and the direct non-medical costs. We will perform a cost–consequences analysis to compare costs and outcomes of the LV rehabilitation with basic LV. We will compare the difference in costs between patients in LV rehabilitation and basic LV using t tests. We will calculate 95% confidence intervals using bootstrapping procedures. We will compare consequences in terms of functional visual ability between patients in LV rehabilitation versus basic LV. We will measure consequences as changes in the VA LV VFQ-48 scores between baseline and four-month follow-up for both overall visual ability and for each of the four functional domains. Differences in mean VA LV VFQ-48 scores between patients in LV rehabilitation or basic LV will be compared using t tests.

In sensitivity analyses, we will increase and decrease device costs, optometrists’ and therapists’ wages, and inpatient costs by 20% to examine the impact that cost variations would have on the average total costs of LV rehabilitation and the basic LV.
This study will use data collected as part of the LOVIT II study as well as information from national VA databases (i.e., the Medical SAS Inpatient and Outpatient Datasets, the Decision Support System National Data Extracts (DSS NDEs) (also called the Managerial Cost Accounting [MCA] NDEs), the Health Economics Center (HERC) Average Cost Datasets, the VA Vital Status Database, Fee Basis Files, and the Corporate Data Warehouse data. We will identify patients in the national VA databases who participated in the LOVIT II study, using scrambled Social Security Number (SSN). We will use patients’ real SSNs, collected from study participants, to obtain the scrambled SSNs in the national VA databases. We will obtain data from national VA databases for patients in the LOVIT II study from fiscal years 2011 through 2015. We will compare the healthcare utilization and costs during the 12 months following randomization between patients in the intervention and control arms of the study. We will obtain healthcare utilization information (e.g., number and type of outpatient visits, inpatient days) from the Medical SAS Inpatient and Outpatient Datasets, the DSS NDEs, the Fee Basis files, and the Corporate Data Warehouse data. Costs will be obtained from the HERC Average Cost Datasets, the DSS NDEs, and the Fee Basis files. The VA Vital Status files will be used to ascertain whether any differences in healthcare utilization or costs between the intervention and control groups were related to mortality. We will calculate differences in healthcare utilization (e.g., number of outpatient visits, inpatient days) and healthcare costs between patients randomized to the treatment groups. We will calculate 95% confidence intervals around these differences using bootstrapping approaches.

**Limitations:** The economic component of this study is mainly a cost analysis to identify the costs of the low vision outpatient rehabilitation treatments. Because some of the patients who receive basic LV may go on to the LV rehabilitation treatment, a more complete economic evaluation would examine costs and health related quality of life between patients who had both basic LV and LV rehabilitation treatment versus patients who had basic LV only or LV rehabilitation only. However, such a comparison is beyond the scope of the current study.

**Exploratory analysis:** The responses to the 5 items on the EQ5D will be transformed into utilities and life expectancy will be estimated for each participant from actuarial tables based upon age, gender and chronic disease diagnoses. QALYs will be calculated (multiplying the utility index times the life expectancy and adjusting by recommended annual discount rates). The QALYs gained from pre-rehabilitation to 4 months post rehabilitation will be compared for basic LV and LV rehabilitation. The cost per QALYs gained will be used to compare the cost-effectiveness of the two programs and to compare the cost per QALY gained to other disease treatments.

4.5 Data Collection and Management

The Data Coordinating Center will have primary responsibility for data collection and management. Its staff will collect, edit, store, and analyze data generated by the clinical centers. It will also provide key assistance in designing the data collection system and be responsible for developing and monitoring quality control. The Data Coordinating Center, in accordance with CSP policy, will maintain a copy of the informed consent for each patient enrolled in the study. Additional responsibilities of the Data Coordinating Center include: (1) schedule meetings and conference calls (2) preparing, in collaboration with the Principal Investigator, the protocol, forms, and the Manual of Study Operations; (3) developing the experimental statistical design and the randomization procedure for the study; (4) working with the investigators in the development and pre-testing of forms and procedures, and assuming responsibility for the reproduction and distribution of forms to be used in the study; (5) training data coordinators and other clinical center personnel, and to monitor clinic performance; (6) managing quality control aspects associated with the collection and management of study data; (7) summarizing clinical center performance at approximately six-month intervals, for the Principal Investigator; (8) providing detailed reports regarding participant recruitment, data collection activities, and interim results, if required, to the Sponsor’s Data and Safety Monitoring Committee; and (9) preparing, in collaboration with the principal investigator, various manuscripts of the study results.

After a patient has consented to participation in the study, the site coordinator will create a patient file to hold copies of the consent form, contact information, all completed case report forms, source documents needed to verify case report form entries, and other information that may be useful to monitor health status and progress during the patient’s participation in the study. Documents containing patient identifiers will be kept physically separate from documents containing PHI. These files are separate from any others within the site’s institution that may contain information on the patient. To minimize risks, the local site will maintain files that contain patient’s identifiable data in a locked cabinet. De-identified data will be shared only with study personnel within the VA system.
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The interviewer(s) administering the outcomes assessment are located in the Office of the Chair. They will require the patients’ names, initials, phone numbers, addresses, and DOB’s to conduct the telephone questionnaires. This information will be transmitted to a designated fax in the office of the interviewer. This identifiable patient information will be kept in a locked cabinet in the research office Bldg. 113, Room B218 at Hines. The information will only be used by the study interviewer to contact the participants for the administration of the questionnaires. The interviewer(s) and the Principal Investigator (for emergency purposes) will be the only persons to have access to this information.

Each patient will be assigned a unique study number. The link to the study number will be kept by the local site in a locked cabinet or on a password protected VA server. Access will be limited to the study staff at the local site. The study number will be used on all of the data collection forms. The forms will not contain any personal identifiers. All communications and data presentation will be by patient number and no information that would personally identify the patient will be used. Direct patient contact will only be through the appropriate participating clinic and the centralized interviewers. The Data Coordinating Center will not directly contact any patient. All data entry will be by the unique patient number. Paper study records will be kept in locked file cabinets and access to electronic files will be password protected and limited to the data coordinating center. Files, paper or electronic, that contain identifiable information, will be stored in a separate, locked, cabinet, or separate computer location, from forms containing patient health information.

Completed case report forms will be reviewed by the site coordinator and either entered directly into the EDC (Electronic Data Capture) system or faxed to a secure fax machine at the Data Coordinating Center twice a month. Upon receipt, the forms will be logged in and undergo a visual inspection for completeness and legibility. Data will undergo key entry with verification. Alternatively, sites will be able to enter data electronically through “SharePoint” software developed for the VA Cooperative Studies Program. Once entered electronically or by centralized data entry the data will be checked for potential problems by a computer program, which produces a query report. The query report will be electronically returned to the site coordinator to be addressed via SharePoint.

Built into the computer program will be an audit trail mechanism that will track and retain records of all errors detected and changes made to the master file. Error analysis of the audit trail file will be conducted to monitor unusually high error rates for a particular data item or at a particular hospital. Based on these analyses, the Data Coordinating Center will notify the hospitals as needed to address any data quality problems.

Adherence to Protocol

The Data Coordinating Center will manually review paper data forms and incorporate computerized edits into the SharePoint system to check for any discrepancies or evidence that the protocol is not being followed. The Principal Investigator will be notified of any protocol adherence problems. The Data Coordinating Center will periodically select a random sample of completed study forms and request de-identified source documentation from the study site to substantiate what has been entered into the forms. The Principal Investigator and Low Vision Therapy Subject-Matter Expert will advise the Data Coordinating Center staff as to how to read the source documentation and verify adherence to protocol and accuracy of the information contained on case report forms. The Principal Investigator or the Low Vision Therapy Subject-Matter Expert will make a study site visit to resolve problems if there is an indication from the centralized coordination of the study that one of the sites is having a problem.

Data Monitoring Committee (DMC)

The DMC for this study has been selected and approved by VA CSP Central Office. The DMC comprises four members, three of whom served as members of the original LOVIT DMC. The DMC will provide interim, independent and unbiased reviews of the study’s ongoing progress. The committee is composed of members who are independent from the planning and conduct of the study. The Principal Investigator, Study Biostatistician and Director of the Data Coordinating Center are ex officio (liaison, non-voting members of the board). The DMC will convene prior to the start of the study and every 12 months to monitor the study and the safety of participants. The DMC will review the progress of the study and to recommend to the Director, Rehabilitation Research and Development Service whether or not the study should continue. To help them make their assessment, the Study Chair and Study Biostatistician will furnish the DMC with appropriate monitoring data at least three weeks before each meeting.

Training and Certification of Study Personnel

Toward the end of the 6-month start-up period, training and certification of study personnel will take place during a 2-day orientation and training meeting in Chicago. All participating investigators, site coordinators, low vision therapists and coordinating center personnel will attend. Prior to the meeting, case
report forms will be finalized and a detailed Manual of Study Operations will be written and circulated. This manual will serve as the training manual for the meeting and as a reference document following the meeting. The Principal Investigator and the Data Coordinating Center staff will provide the training. Included will be training on the study intervention, patient screening, and consent, baseline evaluation and follow-up procedures, and proper entry and maintenance of data. The Data Coordinating Center will assist in all aspects of these training sessions.

A questionnaire will be completed by all study personnel after the initial meeting to assess the knowledge of the purpose and design of the trial. The Principal Investigator will provide additional orientation for staff if needed based upon these assessments. Training provided during the orientation and training meeting will be reinforced during monthly conference calls with site coordinators, therapists and site investigators. The study group will meet yearly during the accrual period to review progress in meeting the goals and objectives of the study and to reinforce training.

5 COLLABORATION:

The collaborators were carefully chosen based upon their expertise and their willingness to work together to achieve the goals of LOVIT II. The following represents the list of collaborators: Principal Investigator, Joan Stelmack OD, MPH, Chief Optometry, Blind Rehabilitation Service, Edward Hines Jr. VA Hospital, Hines, IL, Associate Professor, Illinois College of Optometry, Clinical Associate Professor Department of Ophthalmology and Visual Science, University of Illinois College of Medicine; Co-Investigator, Robert W. Massof, PhD, Director, Lions Rehabilitation Research Center and Professor, Wilmer Eye Institute, Johns Hopkins School of Medicine; Co-Investigator, Domenic Reda, PhD, Director, Hines CSPC; Co-Investigator, Charlene Tang, MD, PhD, MPH, Biostatistician, Hines CSPCC; Co-Investigator, Kevin Stroupe, PhD, Health Economist, Hines CSPCC; Project Manager, Dan Lippe, MS, Hines CSPCC; Yongliang Wei, MS, Statistical Programmer, Hines CSPCC, Kelly Tir, BA, Data Management Programmer, Hines CSPCC, Maria Rachelle, In-House Monitor/Site Contact (Data Coordinator), National Study Coordinator, Scott Sayers, PhD, and Nancy Ellis, MS*, Office of the Chair, Hines Edward Hines, Jr. VA Hospital. Low Vision Therapy Subject Matter Expert, Steve Rinne, MA, CLVT; Hines Edward Hines, Jr. VA Hospital. Consultants: Donald Fletcher MD, California Pacific Medical Center, San Francisco, Janet Sunness MD, Greater Baltimore Medical Center, Gislin Dagnelie PhD, Wilmer Eye Institute, Johns Hopkins University School of Medicine.

The collaboration of PI Joan Stelmack, a low vision clinician, and Robert Massof, PhD, a Research Scientist, builds upon successful working relationships established during the early 1990s, Low Vision Outcomes (#2086R) and Tools and Methods to Study Eccentric Viewing (#C2707I) and VA Low Vision Intervention Trial (#C3457) all funded by VA Rehabilitation Research and Development Service. Drs. Massof and Stelmack are also collaborating on a NEI Clinical Trial Planning Grant, Low Vision Devices and Rehabilitation Services, to evaluate outcomes of different Medicare low vision coverage options in the private sector, which does not overlap administratively with this project. Dr. Stelmack and Dr. Massof communicate regularly by telephone e-mail, conference call and face-to-face meetings. Dr. Massof has taken an active role in validation of the VA LV VFQ-48 and development of the scoring system for the instrument. In the role of co-investigator, he has actively participated in study design. The Hines Cooperative Studies Data Coordinating Center, the data coordinating center for LOVIT, has been actively involved in the design and planning of LOVIT II. Biostatistician, Charlene Tang, Health Economist, Kevin Stroupe, and National Coordinator, Nancy Ellis, all worked together on LOVIT. Rex Ballinger and Joan Stelmack have collaborated previously in the evaluation of the Low Vision Enhancement System developed by Robert Massof that was funded by VA Rehabilitation Research and Development Service.

Participating Clinical Sites:

Baltimore VAMC-Maryland Health Care System: Rex Ballinger OD, Site Investigator, Low-Vision Optometrist, Olga Whitman OD, Assistant Site Investigator, Site Coordinator, Low-Vision Optometrist, Chana Hurvitz MA, Low-Vision Therapist, Sheila Davis MA*, Low-Vision Therapist.

Cincinnati VAMC: Timothy Morand OD, Site Investigator, Low-Vision Optometrist, Mary Colleen Rogge RN, BSN, Site Coordinator, Brittany Swedelius MA*, Low-Vision Therapist.

Dayton VAMC: Timothy Morand OD, Site Investigator, Low-Vision Optometrist, Cynthia Thompson, Site Coordinator, Brian Joos MS, Low-Vision Therapist.

Edward Hines, Jr. VA Hospital: Joan Stelmack OD, MPH, Site Investigator, Low-Vision Optometrist, Stephen Rinne MA, Site Coordinator, Timothy Korwin BS, Site Coordinator, Jack Houston MSEd, MBA, Low-Vision Therapist.
William S. Middleton Memorial Veterans Hospital: Karen Brahm OD, Site Investigator, Low-Vision Optometrist, David LaCrosse BS, Site Coordinator, Amy Wurf MSEd, Low-Vision Therapist.

Clement J. Zablocki Veterans Affairs Medical Center: Kenneth Rose OD, Site Investigator, Low-Vision Optometrist, Joseph Berman PT, MHS, Site Coordinator, Nancy Ellis MS*, Site Coordinator, Claire Seefeldt OTR, Low-Vision Therapist.

Philadelphia VAMC: Denise Wilcox OD, PhD, Site Investigator, Low-Vision Optometrist, Connie Chronister OD, Assistant Site Investigator, Low-Vision Optometrist, Rajkaran Sachdej BS, Site Coordinator, Janet Meyers MS, OTR, Low-Vision Therapist.

Washington, DC VAMC: Ellen Kwon OD, Site Investigator, Low-Vision Optometrist, Andrew Pierce BS*, Site Coordinator, LaShandra Holmes-Russell MS, Low-Vision Therapist.


*Former participants

Data Monitoring Committee:
Thomas W. Raasch OD, PhD, Chair DMC, The Ohio State University, Mae O. Gordon PhD, Biostatistician, Washington University School of Medicine, Leslie G. Hyman PhD, Head, Division of Epidemiology, Stony Brook University Medical Center, Patti S. Wimbs-Fuhr OD, PhD, Low Vision Optometrist, Birmingham VA Medical Center.

Letters of Collaboration and Support:
Letters of support from John Townsend, OD Director Optometry Service VA Headquarters; James Orcutt, MD, PhD, National Program Director Ophthalmology; Dr. Tom Margrain, Cardiff University; Lori Grover OD, Chair, Low Vision Section, American Optometric Association and Mary Lou Jackson, MD, Chair Low Vision, American Academy of Ophthalmology; letters of Collaboration from Hines Cooperative Studies Clinical Coordinating Center, Co-Investigators Domenic Reda PhD, Charlene Tang, MD, PhD, Kevin Stroupe, PhD and Co-Investigator Robert Massof, PhD, Consultants Janet Sunness, MD and Donald Fletcher, MD and the participating clinical sites are included in the Support Documents Attachment.

6 ORGANIZATIONAL STRUCTURE AND PERSONNEL RESPONSIBILITIES

Principal Investigator (Study Chair):
The Chair's Office at the Edward Hines, Jr. VA Hospital, Hines, Ill. is responsible for the overall conduct of the study, including its day-to-day scientific and administrative coordination. This includes the development and interpretation of the study protocol, operations manual, and case report forms; ensuring the appropriate support of the participating sites; answering questions about the protocol; conducting site visits; and publication of newsletters. Dr. Stelmack will work with the optometrists to finalize the optometric dispensing protocol and with the research team on preparation of presentations and manuscripts.

National Coordinator: Nancy Ellis, MS* and Scott Sayers, PhD will assist Dr. Stelmack in the day-day operation of the trial. They will the main liaison between the site personnel and the Chair's office; will coordinate study-wide conference calls; and serve as the primary interface with the central IRB.

Co-investigator Robert Massof, PhD is responsible for consultation on Rasch analysis, collaboration with the Study Chair and Data Coordinating Center on development and interpretation of the study protocol and working with the other members of the Study Group to provide scientific leadership and management of the study.

Site investigators will be responsible for the day-to-day administration and coordination of the study at their sites including: hiring and supervising a site coordinator, supervising low vision therapy, protocol adherence, patient recruitment, IRB and HIPAA compliance, and reporting/ transmission of data to the Data Coordinating Center for their site. The site investigators will work with the Study Chair and the Data Coordinating Center to finalize protocols, procedures and Manual of Operations, pre-test forms, and review study progress. The site investigators will collaborate with the research team on papers and presentations.

Low Vision Optometrists will be responsible for conducting the low vision exam, prescription of low vision devices and therapy, dispensing low vision devices for the control group and completing data forms for the services they have provided. Low vision optometrists will work with the study chair to finalize optometric examination and dispensing protocols. The low vision optometrists will collaborate with the research team on papers and presentations.
Low Vision Therapists will be responsible for providing low vision therapy, dispensing low vision devices to patients in the treatment group and completing data forms for the services that they have provided. Low vision therapists will work with the Study Chair to finalize low vision therapy and homework protocols. The low vision therapists will collaborate with the research team on papers and presentations.

Site Coordinators are responsible for coordinating activities at their site, participation in conference calls, scheduling patients, patient recruitment, obtaining consent/HIPPA authorizations, collecting/reviewing study data from their site and transmitting it to the Data Coordinating Center, working with the investigators and Data Coordinating Center to finalize protocols, procedures, Manual of Operations, pre-test forms and review study progress.

Masked Interviewer(s) with experience in administering telephone questionnaires in research studies will administer the questionnaires by telephone using a telephone script approved by the VA Central IRB.

Subject-Matter Expert in Low Vision Therapy: Steve Rinne MA, a certified low vision therapist collaborated with Dr. Stelmack to develop the therapy and homework protocols that are planned for LOVIT II. He will work with the low vision therapists at the sites to finalize the protocols for low vision therapy and homework and with the Data Coordinating Center to create the data collection forms. He will also be available to provide consultation to the other therapists during monthly conference calls and by email if any problems arise during therapy sessions.

Consultants will assist in the development of materials to be used in training sessions to teach and certify the optometrists and other personnel in the study procedures during the kick-off-meeting. Janet Sunness, MD will assist in development of training materials/protocol for Face Fields, a technique for determining eccentric viewing that she developed. Donald Fletcher, MD will assist in development of training materials/study protocol. Gislin Dagnelie, PhD will assist with the protocol for the electronic visual fields test he developed.

Data Coordinating Center: Domenic Reda, PhD (Center Director), Charlene Tang, MD, PhD (Biostatistician) and Kevin Stroupe, PhD (Health Economist are employees of the Hines Cooperative Studies Program Coordinating Center (CSPCC) at the VA Hospital, Hines, IL. The data coordinating center will assist the Chair’s Office in the day-to-day scientific coordination of the study. The data coordinating center will have primary responsibility for data collection and management. Its staff will collect, edit, store, and analyze data generated by the clinical centers. It will also provide key assistance in designing the data collection system and be responsible for developing and monitoring quality control.

The Steering Committee will provide scientific leadership and management of the study. The Steering Committee will consider any protocol changes that are needed (before they go to the DMC for consideration), write the primary paper, manage the manuscript process for other papers and review the performance of the study sites addressing problems at these sites including decisions to place sites on probation and possibly to replace them if they do not perform adequately. The Steering Committee will include the Study Chair, Biostatistician, Co-investigator, National Study Coordinator, and a Site Investigator. The Study Chair, will chair the Steering Committee. All of members have experience conducting clinical trials. The Director of the Coordinating Center will serve as an ex-officio member.
Literature References:

64. Sunness JS. Face fields and microperimetry for estimating the location of fixation in eyes with macular disease. In press J Vis Impair Blind.
67. California Low Vision Test, Personal Communication from Test Developer, Donald Fletcher, MD.
71. Personal communication, Mike Williams, PhD, Blind Rehabilitation Service VACO.