Title: Visual Restoration for Hemianopia

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Purpose: This project will collect data to quantify the effect of visual training on visual defects resulting from damage to the primary visual cortex. Subjects will be recruited, undergo baseline visual testing, undergo visual training designed to reduce their visual deficit, and perform post-training visual tests. This research is designed to determine if different visual training treatments are capable of reducing visual defects in a large population of adult subjects with cortical blindness in a double blind clinical trial.

Background and Motivation for the study: When brain damage is incurred in adulthood, through stroke, trauma, or other neurodegenerative conditions, functional deficits result depending on the brain region that was affected. As roughly half of the human cerebral cortex is devoted to visual processing, many people who suffer brain damage experience consequent impairments in vision. When damage affects the primary visual cortex (V1), the visual deficits are severe and are described as cortical blindness (CB), or hemianopia/quadrantanopia, depending on the size of the defect. CB dramatically impacts the lives of those affected, decreasing quality of life (Gall et al., 2008; Gall et al., 2009; Gall et al., 2010). CB subjects often lose the ability to drive (de Jong and Warmink, 2003; Papageorgiou et al., 2007), reducing their independence, while others who continue to drive pose a potential danger to themselves and others (Bowers et al., 2009, 2010; Bowers et al., 2014). Those suffering from CB also have other types of impaired daily functioning (Ramrattan et al., 2001), and reduced independence (Jongbloed, 1986).

Currently, there is no accepted treatment for cortical blindness. Some spontaneous recovery of vision was reported in a portion of subjects during the first 2-3 months following a stroke (Zhang et al., 2006). However, after this period the visual deficit is believed to become stable and permanent (Horton, 2005; Pollock et al., 2011). As such, in the rare instances when subjects are prescribed rehabilitation, it is essentially limited to substitution (Rossi et al., 1990; Peli, 2000) or compensation therapies (Weinberg et al., 1977; Kerkhoff, 1999, 2000; Spitzyna et al., 2007). In the limited number of subjects who benefit from these therapies, quality of life and daily functioning are improved (Weinberg et al., 1977; Spitzyna et al., 2007). However, neither therapy is able to restore any of the lost vision; instead, they are designed to teach subjects how to make use of what vision they have left more effectively (Lane et al., 2010).

In order to restore lost vision, subjects need to undergo restitution therapy. Multiple research studies have shown visual training to recover particular functions within chronic CB fields (See Melnick et al., 2016 for review). These studies have shown that in addition to improving performance on the trained tasks, such training can also recover untrained aspects of vision, such as those measured by standard, clinical visual perimetry (Cavanaugh and Huxlin, 2017). However, none of these studies were unbiased (i.e., subjects were not randomized and no blinding was used). To fill this important gap in the field, we have designed the present double blind clinical trial to assess whether visual restitution training using visual discrimination tasks presented in the blind field are clinically relevant and obtainable in a larger patient population. The trial will involve recruiting CB patients, measuring their baseline visual performance, randomizing them to one of two treatment groups, training them with one of two types of visual discrimination training therapy and bringing them back for a repeat of all baseline visual measurements. The results of this study will be submitted for publication to scientifically and clinically relevant journals, and they will be submitted to the Food and Drug Administration for approval.

Criteria for subject selection

1. Number of subjects: 20 subjects will be recruited at each of three study sites, leading to a total of 60 subjects. The subjects will be divided randomly into two training cohorts, with 30 subjects receiving one form of visual discrimination training therapy, while the other 30 will receive another form of visual discrimination training.

2. Gender and age range: Subject gender is intended to have an even distribution. Women and men are both susceptible to the conditions that would qualify participation as study subjects in the proposed research. All subjects who have sustained vision losses as a result of brain damage, that are able to give informed consent and are willing and able to undergo testing and training will be eligible for inclusion in this study, subject to the limitations described in the following paragraph. Since vision losses as a result of brain damage do occur in women, we will aim to recruit equal numbers of men and women in the proposed study.

Since the goals of the proposed research are to examine the effects of visual retraining on visual performance following adult-onset visual cortical damage, children will not be recruited as subjects. Only adults ranging in age between 21 and 75 years of age will be recruited. The upper limit of 75 years of age is included to ensure that subjects are able to properly fixate during the course of training. Children under the age of 21 will be excluded from enrollment as they rarely develop brain injury affecting the visual system. Very young children (<10 years of age) may also not be able to understand the study components/requirements or maintain the discipline necessary to participate correctly in daily visual training. Moreover, on the rare occasion that children develop V1 damage, because their brain is more plastic than that of adults, and because long range connections are still forming in their visual system, they are sometimes able to recover from their hemianopic deficit (see work by Tinelli et al., 2013). This may occur because after such damage, children can more easily develop abnormal connectivity between visual areas within and between their two brain hemispheres (Bridge et al., 2008), endowing their residual vision with properties that are not seen in subjects who sustain V1 damage in adulthood. As such, children do not form a suitable population for the proposed study. Finally, teenagers and younger children have not been subjects in our preliminary studies, so it is unknown whether their perceptual learning after cortical damage is comparable to that in adults. Whether and what kind of visual retraining may be beneficial to children and teenagers requires completely separate and novel scientific investigations, which are outside the scope of the proposed application.

References

Bowers A, Mandel A, Goldstein R, Peli E (2009) Driving with hemianopia: I. Detection performance in a driving simulator. Invest Ophthalmol Vis Sci 50:5137-5147.

Bowers A, Mandel A, Goldstein R, Peli E (2010) Driving with hemianopia: II. Lane position and steering in a driving simulator. Invest Ophthalmol Vis Sci 51:6605-6613.

Bowers A, Ananyev E, Mandel A, Goldstein R, Peli E (2014) Driving with hemianopia: IV. Head Scanning and detection at intersections in a simulator. Invest Ophthalmol Vis Sci 55:1540-1548.

Bridge H, Thomas O, Jbabdi S, Cowey A (2008) Changes in connectivity after visual cortical brain damage underlie altered visual function. Brain 131:1433-1444.

Cavanaugh M, Huxlin K (2017) Visual discrimination training improves Humphrey perimetry in chronic cortically induced blindness. Neurology 88:1856 - 1864.

de Jong P, Warmink H (2003) Homonymous hemianopia and driving. Eye 17:545.

Gall C, Franke G, Sabel B (2010) Vision-related quality of life in first stroke patients with homonymous visual field defects. Health and Quality of Life Outcomes 8.

Gall C, Lucklum J, Sabel B, Franke G (2009) Vision- and health- related quality of life in subjects with visual field loss after postchiasmatic lesions. Invest Ophthalmol Vis Sci 50:2765-2776.

Gall C, Mueller I, Kaufmann C, Franke G, Sabel B (2008) Visual field defects after cerebral lesions from the subject's perspective: Health- and vision-related quality of life assessed by SF-36 and NEI-VFQ. Nervenarzt 79:185-194.

Horton J (2005) Disappointing results from Nova Vision's visual restortation therapy. Br J

Ophthalmol 89:1-2.
Jongbloed L (1986) Prediction of Function After Stroke: A Critical Review. Stroke 17:765-776.
Kerkhoff G (1999) Restorative and compensatory therapy approaches in cerebral blindness - a review. Restorative Neurology and Neuroscience 15:255-271.
Kerkhoff G (2000) Neurovisual rehabiliation: recent developments and future directions. Journal of Neurology, Neurosurgery and Psychiatry 68:691 - 706.
Lane A, Smith D, Ellison A, Schenk T (2010) Visual exploration training is no better than attention training for treating hemianopia. Brain 133:1717-1728.
Melnick M, Tadin D, Huxlin K (2016) Relearning to see in cortical blindness. The Neuroscientist 22:199-212.
Papageorgiou E, Hardiess G, Schaeffel F, Wiethoel H, Karnath H, Mallot H, Schoenfisch B, Schiefer U (2007) Assessment of vision-related quality of life in subjects with homonymous visual field defects. Graefes Arch Clin Exp Ophthalmol 245:1749-1758.
Peli E (2000) Field expansion for homonymous hemianopia by optically induced peripheral exotropia. Optom Vis Sci 77:453-464.
Pollock A, Hazelton C, Henderson C, Angilley J, Dhillon B, Langhorne P, others. a (2011) Interventions for visual field defects in patients with stroke. The Cochrane Library:1-83.
Ramrattan R, Wolfs R, Panda-Jonas S, Jonas J, Bakker D, Pols H, Hofman A, de Jong P (2001) Prevalence and causes of visual field loss in the elderly and associations with impairment in daily functioning: the Rotterdam Study. Arch Ophthalmol 119:1788-1794.
Rossi P, Khefyets S, Reding M (1990) Fresnel prisms improve visual perception in stroke patients with homonymous hemianopia or unilateral visual neglect. Neurology 40:1597-1599.
Spitzyna G, Wise R, McDonald S, Plant G, Kidd D, Crewes H, Leff A (2007) Optokinetic therapy improves test reading in patients with hemianopic alexia. Neurology 68:1922-1930.
Tinelli F, Cicchini GM, Arrighi R, Tosetti M, Gioni G, Morrone MC (2013) Blindsight in children with congenital and acquired cerebral lesions. Cortex 49:1636 - 1647.
Weinberg J, Diller L, Gordo W, Gerstman L, Lieberman A, Lakin P, Hodges G, Ezrachi O (1977) Visual scanning training effect on reading-related tasks in acquired right brain damage. Archives of Physical Medicine and Rehabilitation 58.
Zhang X, Kedar S, Lynn M, Newman N, Biousse V (2006) Natural history of homonymous hemianopia. Neurology 66:901-905.

3. Racial and ethnic distribution: Subjects will be included in the study regardless of race or ethnic origin. All minorities are susceptible to the conditions that would qualify participation as either study or as control subjects. The Universities of Rochester, Miami and Pittsburg are all in metropolitan areas with some degree of ethnic diversity; therefore recruitment of minorities is likely and anticipated.

	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	Female	Male	Female	Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	1	2	1	1	5

Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	6	2	2	15
White	12	14	3	4	33
More than One Race	1	2	2	2	7
Total	19	24	8	18	60

4. Inclusion and exclusion criteria

Inclusion Criteria at Screening Visit

1. Ages 21-75 years old
2. Ability and willingness to sign informed consent
3. Willingness to participate in both the training and evaluation sessions
4. MRI or CT scan demonstrating lesion in the occipital lobe of the brain and/or affecting white matter tracts that provide visual input to the occipital lobe of the brain.
5. Brain injury due to ischemic or hemorrhagic causes that occurs after age 18 and at least 90 days prior to the screening visit.
6. At least two reliable HVF's demonstrating good fixation and a stable homonymous incomplete (e.g., quadrantanopia or relative defect) or complete hemianopia
7. Reliable HVFs with repeat HVFs if randomization takes place more than 4 weeks after screening visit
8. A homonymous, contiguous visual deficit measured by the 24-2 HVF to be a minimum of two testing locations high and two testing locations wide, where impaired locations are any that measure a threshold of less than 15 dB
9. Demonstration of good fixation on visual training task – able to fixate the small targets presented as fixation letters reliably for 1000ms with jitter over less than 1 degree of visual angle in any direction away from target edge

Exclusion Criteria at Screening Visit

1. Physical, neurological or mental disability that would interfere with study intervention
2. Concurrent participation in "vision therapy" other than standard occupational or physical therapy
3. Unreliable visual fields on prior testing, indicated by greater than 20% fixation losses, false positives, or false negatives.
4. Inability to discontinue medications judged to affect training and/or assessment (e.g., Ritalin, amphetamines, dopamines, or chemotherapeutic agents)

5. Physical condition likely to preclude completion of the clinical trial (e.g. end-stage or uncontrolled cancer, uncontrolled epilepsy, or end-stage heart disease)
6. Ocular or neurological condition that would interfere with training or assessment (e.g. damage to the optic nerves or lateral geniculate nucleus, any degenerative ocular condition)
7. Best corrected vision worse than 20/40 in either eye
8. Impaired foveal Humphrey sensitivity as indicated by the HVF tests.
9. Presence of vision loss resulting from ocular disease or disorder
10. Presence of bilateral visual acuity loss from any source

Additional Exclusion Criteria at Randomization Visit

1. Inability to demonstrate fixation stability on eye movement monitored testing
2. Inability to follow training instructions

Concomitant Medications

1. No medication is required for participation in the study
2. Allowed Concomitant Medications: Any medications that do not affect learning or motor performance are allowed. All concomitant medications must be used according to the prescriber's instructions.
3. Disallowed Medications: Ritalin, amphetamines, dopamines, or chemotherapeutic agents are specifically disallowed. Other medications may be disallowed based upon subject's individual side-effects (e.g. severe drowsiness, tardive dyskinesia, etc.). The site PI should contact the enrollment center to discuss findings and appropriate action in the event use of any disallowed medication is discovered. In all cases, the use of any disallowed medication should be documented along with any applicable instructions to the subject.

Discussion of Eligibility Criteria

Adults were chosen because the incidence of stroke-induced hemianopia is most frequent in adults, and because reliability and persistence are required for following the training regime. Older adults (65-75 years) were not excluded as they performed equally well in pilot perceptual training compared to younger adults. However, adults older than 75 years old are excluded from enrollment because they present with a greater incidence of ocular, physical, and/or mental conditions that can interfere with their ability to train effectively. In addition, our preliminary studies over the last 10 years show that hemianopic subjects older than 75 years have increased problems with concentration and maintaining steady fixation, both of which are absolutely necessary for successful training in the present trial.

Methods and procedures

<u>1 - Screening Visit (Visit SC)</u>

Informed consent: At the screening visit, a signed informed consent document will be completed. This consent form describes the interventions and enumerates the risks and benefits of participation. It will include consent for screening evaluation as well as consent for randomization if subject is found to be eligible. Potential subjects will have the opportunity to ask questions and receive answers prior to signing the consent.

Eye examination: A complete medical history, eye history, and eye examination will be performed in order to determine eligibility for the study. A comprehensive, routine dilated eye exam that includes slit lamp examination and retinal optical coherence tomography (OCT), will be performed on each patient by a qualified ophthalmologist or neuro-ophthalmologist at each site to verify ocular health. OCT should have a signal strength of at least 6, otherwise the test should be repeated. If any problems or signs of ongoing, developing or progressing eye disease are observed, this will constitute grounds for exclusion from the study. The eye examination will include Snellen best corrected acuity, intraocular pressure measurement, exophthalmometry, motility, external examination, slit lamp examination, dilated fundus examination and OCT imaging of the retina.

Visual field testing: Certified technicians will perform 24-2 Humphrey visual fields on each subject. Fixation and pupil monitoring will be "on" for each test. The examination will be performed twice with a 30-minute rest period after each test. Examinations need to be done twice at baseline, with the second test used for future analysis, to ensure that patients are proficient in performing the tests at baseline, so that we can rule out practice on the test as a reason for post-training improvements. During Humphrey perimetry, the eye tracker will be engaged at all times. Tests will be repeated if the patient fails to generate acceptable test reliability (in terms of rate of fixation breaks, false positives and false negatives). If repeated perimetry tests fail to yield acceptable reliability measures (as per device specifications), this will constitute grounds for excluding the subject from the study. Our research to date shows that accurate fixation is critical both to generate reliable perimetry results (our primary outcome measure) and to elicit training-induced improvements in the blind field. All excluded subjects will be replaced with a new enrollment.

Determination of eligibility: Sites having potential subjects for inclusion into the study will collect the required documentation at the Screening visit and forward relevant medical history, two sets of Visual Fields and an MRI or CT scan of the brain. The medical history will be sent to the Principal Study PI who will, jointly with the Site PIs, review the records for eligibility criteria. The visual fields will be sent to the Visual Field Reading Center for confirmation of visual field defect and reliability/stability of testing. The reading center will forward its information to the Principal Study PI who will jointly determine with the Site PIs whether the subject should appear for a Baseline Visit.

<u>2 - Baseline Visit (Visit BL; 2-4 weeks post SC)</u>

Eye examination: The history and eye examination as described in Visit SC will only be repeated if more than four weeks has elapsed between the Visit SC and Visit BL.

Visual field testing: Humphrey visual field testing as described above will only be repeated if more than four weeks has elapsed between Visit SC and Visit BL.

Eye fixation testing and restoration protocol training: Each subject will undergo MAIA perimetry in order to assess fixation quality and patterns. MAIA testing is a fundus-controlled form of perimetry, and as such, is the most precise way of performing gaze-contingent stimulus presentation. The test output includes a detailed mapping of each patient's fixation locations during stimulus presentation, allowing us to quantify the spread of their eye movements around the fixation spot.

In addition to performing the MAIA, we will assess the ability to visually process complex visual stimuli in the normal and abnormal portions of the visual field in each subject, using

computerized tests developed at the University of Rochester. These tests present visual stimuli consisting of drifting random dots. The subject is required to indicate (by pressing the corresponding keys on the computer's keyboard) the global direction of motion in the stimulus. While simple visual perception can be assessed during routine visual testing in the clinic, complex aspects of visual processing cannot. This is a significant shortcoming of the field right now and one that we will address in the present study. When sequentially measuring global direction discrimination performance at different locations across the intact field, and into the blind field, the blind field location where the patient's direction discrimination performance falls to chance (~50% correct) in a 100 trial block will be designated as the first training location. The potential subject will sit comfortably and be instructed on how to correctly position him/her self in the head/chin rest. The subject's laptop computer (or one provided for the subject) will be set up in front of the subject. After an explanation by the technician, eye movement fixation monitor will be adjusted. A full explanation of the task, including need for steady fixation, response to fixation "catch trials", alternative test stimuli and appropriate responses will be given. The subject will then be asked to perform both training tasks at fixation and then at peripheral locations in their blind field selected for training based on the Humphrey visual field test results. Feedback will be provided by the technician during training until independence is achieved.

The National Eye Institute Visual Functioning Questionnaire – 25 (VFQ-25) version 2000: This questionnaire will be completed online in the self-administered format by the subject, in the presence of qualified site personnel. The subject may ask for assistance from site personnel as needed. A fully validated neuro-ophthalmologic disease supplement of 10 items, also on line, will be used in addition to the standard VFQ-25.

Randomization: Eligible subjects will receive their randomization assignment. All subjects will be double masked. Treatment locations and training cohort will be pre-assigned for all subject ID numbers and given to each subject at the end of visit BL. The site will then call the DCBC to obtain the subject ID to be used for each randomized subject and enter this number into the training software, which includes the randomized stimulus sequence.

<u>3 – Post training visit (28 week visit +/- 2 weeks)</u>

Eye fixation testing and restoration protocol testing: The eye fixation testing and protocol testing will be repeated as described for visit BL.

The National Eye Institute Visual Functioning Questionnaire – 25 (VFQ-25) version 2000 and supplement will be repeated, as described for Visit BL.

<u>4 – Post training clinic visit (29 week visit +/-2 weeks)</u>

Eye examination: The history and eye examination will be repeated as described for Visit SC.

Visual field testing: Visual field testing will be repeated as described for Visit SC.

Assessment Schedule

Visit Number	**1 (screening)**	**2 (2-4 weeks post screening)**	**3 (28 weeks +/- 2weeks)**	**4 (29 weeks +/-2 weeks)**
Informed Consent	Y			
Inclusion/Exclusion Criteria	Y			
Demographics	Y			
Medical History	X			X
Concomitant Medications	X			X
Slit-lamp exam	X			X
Retinal Optical Coherence Tomography	X			X
24-2 Humphrey	X			X
24-2 Humphrey repeated	X			X
MRI/CT	Z			
Comprehensive routine dilated eye exam*	X			X
Visual Functioning Questionnaire		Y	Y	
VFQ supplement		Y	Y	
MAIA perimetry		Y	Y	
Eye fixation testing and restoration protocol		Y	Y	

X Performed by clinician
Y Performed by study personnel
Z From patient chart
*dilated fundus exam, Snellen best corrected acuity, intraocular pressure, exopthalmometry, motility, external exam

Unscheduled telephone contacts: These contacts may be initiated by the sites in response to contact from the TC indicating compliance (e.g. missed training sessions) or performance issues (e.g. fixation losses). These contacts may be initiated by the subject for any reason, including equipment failure, motivational issues, or notification of inter-current events that may affect training. The date and reason for the unscheduled telephone contact will be recorded in the source documentation.

Unscheduled visits: These visits may be initiated by the sites in response to contact from the TC indicating compliance (e.g. missed training sessions) or performance issues (e.g. fixation losses).

These visits may be initiated by the subject for any reason, including equipment failure, motivational issues, or notification of inter-current events that may affect training. The date and reason for the unscheduled visit will be recorded in the source documentation, along with whatever portions of the visit protocol were conducted.

Premature withdrawal: Subjects have the right to withdraw from the study at any time without prejudice. The Site Investigator may withdraw training from a subject in the study in the event of inter-current illness, adverse events, or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation, non-compliance, protocol violation or other administrative reasons. In the event of premature withdrawal from the study, the Premature Withdrawal (PW) Visit procedures and evaluations should be completed whether or not the withdrawal is determined at a regularly scheduled study visit or at an unscheduled visit. In instances where the subject refuses to return for a PW visit, the Steering Committee may recommend an attempt to obtain outcome data by a visit to a non-participating ophthalmologist. Reasons for withdrawal of the subject prior to completion of the study must be stated in the case report form and in the site source documentation for all study subjects who were enrolled in the study. The DCBC must be informed within 24 hours of all study subjects who are withdrawn due to an adverse event.

Early Discontinuation of Study Training: In the instance that subjects refuse to continue specified training but choose to remain in the study, then scheduled visits should by designated as a NOTRAIN visit and all regular visit activities will be completed.

Re-Entry Visits: In the instance that subjects who opted for Early Discontinuation of Study Training or Premature withdrawal decide to re-enter the study, then a Re-Entry visit with a protocol identical to a Baseline Visit (BV) will be performed, except that the subject's original randomization schedule will be utilized.

Adverse events: An adverse event is any symptom, sign, illness, or experience which develops or worsens during the course of the study, whether or not the event is considered related to the study intervention. A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

At each subject visit the site study staff will assess adverse events by recording all voluntary complaints of the subject and by assessment of clinical and laboratory features. At each study visit, the subject should be questioned directly regarding the occurrence of any adverse experience since his/her last visit.

All adverse events, whether observed by the Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience, the date of onset, the date of resolution, the duration and type of experience, the

severity, the relationship to investigational product, contributing factors, and any action taken with respect to the study device. All adverse events occurring between the time of consenting and subject completion or withdrawal from the study will be recorded. Follow up will continue until the adverse event is resolved, including those unresolved at the time of subject concluding study participation.

Data analysis and data monitoring: HVF test results will be analyzed using a custom program in Matlab. Changes in HVF over time will be mapped across the visual field and the area of the visual field that increases or decreases in sensitivity by >6dB will be quantified. Subject age, lesion age, visual deficit size, and type of precipitating neurologic event will be analyzed using linear regression and ANOVA to determine if any of these factors are correlated with change; when appropriate, post-hoc analyses will be conducted using Tukey's HSD and a family-wise Type I error rate of 0.05.

Data storage and confidentiality

a. Data will be stored on a secure, encrypted server hosted on the URMC private network. Only study personnel directly involved in raw data processing and analysis will have access to data files containing protected health information.
b. A separate key will be created linking the subject identifiers with a unique study ID number to avoid any direct identifiers stored with the collected data.
c. Data collected will be used for future research studies.

Risks/benefit assessment

a. Risk Category: Minimal risk
b. Potential Risks: There are no known risks of the visual tests and examinations used in this study. There are also no known risks of the visual training to be used. Subjects may become tired during the course of testing and/or training. There is a risk that subject confidentiality will be breached. In addition, as the visual training used in this study is experimental, there may be unknown risks.
c. Protection against risks: If a subject becomes tired during the course of testing or training, they will be allowed to rest until they feel ready to continue. Subject confidentiality will be protected as well as possible through the use of de-identified ID numbers and secure data transmission.
d. Benefits: We cannot promise any benefits of taking part in this research. However, possible benefits include an expansion of the subjects' visual fields through the reduction of the cortically blind deficit, and improved visual functioning in portions of the visual field.
e. Alternatives to participation: Alternatives may include visual training programs or other research studies.

Subject identification, recruitment, and consent/assent

1. Method of subject identification and recruitment: Subjects will be recruited for this study from the clinical practices of the three sites, as well as from waiting lists of subjects who have previously contacted the study sites. If additional subjects are required, we will widen the search to include the clinical practices in the immediate areas near each study site. Examples of the expanded recruitment pool include online hospital recruitment databases such as Iconnect and other forms of digital recruitment. Candidate subjects will then be randomly selected for screening by our inclusion/exclusion criteria. If a subject fails the screening process they will be replaced with a new subject randomly selected from the waiting pool.

2. Process of consent: This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50. In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks will be read and/or explained to each subject. Each subject will sign such an informed consent form. In this consent, the study will be adequately described in addition to all procedures subjects will need to do, how their confidentiality will be maintained. The subject will be assured of the freedom to withdraw from participation in the study at any time. The consent process for each subject who signs informed consent will be documented in the subject's source (e.g., research file, research progress note) and will include the title of the study, that the consent was discussed with an opportunity for questions and answers, how the subject demonstrated comprehension, that the consent was signed prior to the first study procedure, and that the subject received a signed copy of the consent.
3. Subject capacity: Subjects will only be considered for this study if they are capable of understanding the study, its burdens and risks, their responsibilities, and giving informed consent. Subject capacity will be determined at the time of consent by the person obtaining consent.
4. *Costs to the subject:* There is no cost to participate in this research study except that subjects will be expected to provide their own transportation and/or accommodation to and from the study site for study visits.

Payment for participation: Subjects will receive $30.00 for each completed study visit. There will be a total of four paid visits. Payment will be received at the end of each visit. This payment may be in the form of a pre-paid debit card, gift card or check at our discretion. Subjects will not be paid for visits that they do not complete. Each subject will be paid up to a total of $120.00.