Early Melodic Intonation Therapy for Post-Stroke Aphasia: A Randomized Controlled Trial

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EARLY MELODIC INTONATION THERAPY FOR POST-STROKE APHASIA:

A RANDOMIZED CONTROLLED TRIAL

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

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TABLE OF CONTENTS

TABLE OF CONTENTS ........................................................................................................ II
LIST OF TABLES ............................................................................................................... IV
LIST OF FIGURES ............................................................................................................ V
ABSTRACT ....................................................................................................................... VI

CHAPTER 1: INTRODUCTION............................................................................................ 1
  1.1 BACKGROUND ........................................................................................................ 1
    A. Epidemiology of Stroke and Aphasia........................................................................ 1
    B. Consequences of Post-Stroke Aphasia...................................................................... 3
    C. Neural Basis of Speaking, Aphasia, and Recovery................................................ 3
    D. Treatment for Post-Stroke Aphasia........................................................................ 5
  1.2 STATEMENT OF THE PROBLEM.......................................................................... 6
  1.3 STUDY GOALS AND OBJECTIVES........................................................................ 8
  1.4 HYPOTHESIS......................................................................................................... 9
  1.5 DEFINITIONS.......................................................................................................... 9
REFERENCES.................................................................................................................. 10

CHAPTER 2: REVIEW OF THE LITERATURE.................................................................... 14
  2.1 LITERATURE SEARCH CRITERIA....................................................................... 14
  2.2 CLINICAL IMPACT OF THERAPY FOR PERSONS WITH APHASIA: REVIEW OF RELEVANT TRAILS......................................................................................... 14
    A. Efficacy of Therapy.............................................................................................. 14
    B. Type of Therapy.................................................................................................. 17
    C. MIT..................................................................................................................... 19
    D. Timing of Therapy.............................................................................................. 24
    E. Very Early Therapy............................................................................................. 26
    F. Intensity of Therapy............................................................................................ 27
  2.3. REVIEW OF RELEVANT METHODS .................................................................. 28
    A. Study Design....................................................................................................... 28
    B. Patient Selection................................................................................................. 28
    C. Clinical Management.......................................................................................... 30
    D. Intervention........................................................................................................ 30
    E. Control................................................................................................................ 32
    F. Primary Outcome............................................................................................... 32
    G. Secondary Outcomes.......................................................................................... 34
    H. Sample Size....................................................................................................... 34
    I. Estimated Recruitment Sites............................................................................... 35
    J. Confounding......................................................................................................... 36
    K. Conclusion.......................................................................................................... 37
REFERENCES.................................................................................................................. 38

CHAPTER 3: STUDY METHODS ...................................................................................... 46
  3.1 STUDY DESIGN..................................................................................................... 46
  3.2 STUDY POPULATION AND SAMPLING.............................................................. 46
  3.3 PROCEDURES AND RECRUITMENT................................................................... 47
  3.4 SUBJECT PROTECTION AND CONFIDENTIALITY............................................. 47
LIST OF TABLES

Table 1 Eligibility.................................................................46
Table 2 Other Descriptive Measures........................................49
Table 3 Schedule of Assessment.............................................51
Table 4 Estimated patients available for study recruitment and analysis at largest Veterans Administration Medical Center Primary Stroke Centers ..........77
LIST OF FIGURES

Figure 1 CONSORT Flow diagram of early Modified Melodic Intonation Therapy trial .................................................................55
ABSTRACT

Stroke patients who lose the ability to produce language (aphasia) often remain able to sing. This observation has stimulated interest in a structured music therapy, Melodic Intonation Therapy, for post-stroke aphasia. While existing studies find positive outcomes with Melodic Intonation Therapy, its efficacy has yet to be substantiated by adequately powered, randomized, controlled trials. Focusing on acute stroke patients, we aim to determine the impact of melodic intonation therapy versus usual care on aphasia recovery. The study will be a single blind, randomized controlled trial with modified melodic intonation therapy and usual care groups. Aphasia severity will be scored at baseline and 3 weeks, and the mean difference from baseline will be compared across groups. Post-stroke aphasia has high morbidity and mortality and profoundly impedes daily living. Its rehabilitation is imperative. In the absence of standard of care, my results may inform early treatment options that can enhance recovery.
CHAPTER 1: INTRODUCTION

1.1 Background

A. Epidemiology of Stroke and Aphasia

Each year, approximately 795,000 Americans experience stroke, with an overall adult stroke prevalence of 2.7%, projected to increase by 20.5% to 2030.\textsuperscript{1-3} Stroke is now the 5\textsuperscript{th} leading cause of death in the U.S., however, stroke mortality has been declining, with a 33.7% decline in the age-adjusted stroke death rate over 2003 – 2013.\textsuperscript{1-3} While the decline in stroke mortality is good news, morbidity remains high; an increasing number of stroke patients survive, with but with moderate to severe disability (15-30%) or moderate functional impairment (40%).\textsuperscript{4}

A common and particularly devastating impairment that results from stroke is aphasia. Estimates of post-stroke aphasia vary with selection of the study population and assessment timing and instrument. Most incidence evidence comes from Europe. In a prospective community based study of consecutive acute-stroke patients (N = 881) in a pre-specified catchment area, incidence of aphasia on admission was found to be 38%.\textsuperscript{5} A large series (N = 11,572) of unselected randomly sampled hospitalized acute-stroke patients found aphasia incidence of 28%.\textsuperscript{6} In a 1-year, prospective, population based study of a pre-specified catchment area with 188,015 inhabitants, 30% of first ever stroke patients had aphasia.\textsuperscript{7} In a prospective sample (N = 106) of every 4\textsuperscript{th} acute stroke patient admitted to a Swedish hospital, 33% were found to be aphasic.\textsuperscript{8} Finally, 34.8% of consecutive patients (N = 2,389) from a dedicated cognitive stroke registry of an
American tertiary care facility were found to have aphasia when assessed within 1 month of stroke onset.\textsuperscript{9}

The natural history of aphasia is variable and poorly understood. Study of spontaneous recovery is complicated because baseline assessment should be conducted early to precede early cortical re-organization\textsuperscript{10} but may be difficult to accomplish in unstable patients.\textsuperscript{8} Additionally, transient perfusion-related defects may resolve without developing into full aphasia syndromes.\textsuperscript{11} Inter- and intra-study variability in assessment timing introduces spurious variation in aphasia scores, and the different aphasia assessment instruments have varied and imperfect ability to classify aphasia syndromes.\textsuperscript{12}

Studies of spontaneous aphasia recovery find that most improvement occurs within the first 3 months after stroke onset, with improvement attenuating subsequently until it plateaus, typically within 1 year.\textsuperscript{5,11,13-17} In a longitudinal study of 24 patients from a Veterans Administration Medical Center (VAMC) followed for 2-years with language assessment at 1, 2, 6, 12, 18, and 24 months, paired t-tests revealed significant aphasia reduction ($p < .01$) in all but the final 6 months, with greatest recovery in the first followed by the next 6 months, although 22 of these patients underwent unquantified treatment that may confound results.\textsuperscript{15} In a 1-year prospective study of 106 consecutive first time ischemic stroke patients presenting to a single center, 2/3 of patients diagnosed with aphasia remained aphasic at 12 months.\textsuperscript{17} In an unselected sample of N = 119 post-stroke aphasic patients who underwent serial language assessment, at 18 months, 24% had recovered completely, 21% had died, and 43% still had significant aphasia.\textsuperscript{8}
B. Consequences of Post-Stroke Aphasia

Post-stroke aphasia is costly, disabling, and deadly, in both the short and the longer term. In a cohort (N = 3200) of Medicare patients from North Carolina with ischemic stroke, at one year, attributable costs (Medicare payments) of aphasia were estimated to be $1703 using multi-variate analysis, 8.5% higher than general stroke care attributable costs in the absence of aphasia. During the acute period after stroke, persons with aphasia (PWA) have longer hospital stays, more inpatient complications, and higher inpatient mortality rates than persons without aphasia.

In the longer term, among survivors of stroke, PWA have greater rates of depression (33% compared with 11% at 12 months, p=.033) and other morbidity. In 11,572 unselected hospitalized acute stroke patients, at 2 years, PWA had greater disability (odds ratio [OR] 1.74, 95% confidence interval [CI]: 1.55–1.96) and less frequently lived at home (OR 1.39, 95% CI: 1.17–1.65) than those without aphasia, and in a 10 year prospective cohort study of 2,297 hospitalized stroke patients, moderate/severe aphasia independently predicted dependence after controlling for initial stroke severity and medical complications.

Finally, PWA have significantly higher rates of mortality than stroke survivors without aphasia at 2 years (OR 2.09, 95% CI 1.89–2.32), and at 10 years (hazard ratio 1.50, 95% CI 1.24–1.84).

C. Neural Basis of Speaking, Aphasia, and Recovery

Language maps to regions in the perisylvian cortex and the tracts that connect them. Wernicke’s territory, located in the posterior superior temporal gyrus, receives input from the auditory cortex and assigns word meanings. The arcuate fasciculus
connects Wernicke’s territory to Broca’s territory in the posterior inferior frontal gyrus, which in turn innervates motor neurons that control facial muscles to produce speech. Additionally, recent imaging has shown that Geschwind’s territory (the angular and supramarginal gyri) connect to both Broca’s and Wernicke’s territories by large tracts providing a second, parallel pathway for language. Productive language is typically left-oriented, while receptive language is often bilateral. However, functional imaging has revealed a spectrum of left-right lateralization in the general population, and using transient focal virtual lesions in healthy subjects, individual heterogeneity in degree and side of lateralization as well as degree of bi-laterality has been shown to affect language disruption.

Stroke disrupts blood supply, resulting in infarction with ultimate necrosis of tissue, hypo-perfusion of the surrounding ischemic penumbra, and diaschisis, disruption of distant and structurally normal structures due to disruption of the axonal pathway to those structures. If the infarction occurs in the left perisylvian regions discussed above, aphasia results.

From clinical observation and neural imaging studies, it is known that the brain undergoes profound reorganization of structure and function after stroke. The neurologic mechanism underlying spontaneous post-stroke aphasia recovery has been attributed to activation of preserved left peri-lesional regions, activation of right homotopic regions, or both. These disparate patterns in lateralization of recovery can now been understood as different cortical activation patterns over time post-stroke, identified in a landmark study with serial functional magnetic resonance imaging (fMRI) for one year after stroke. Right hemispheric activation increases, with acutely decreased left
hemispheric activity, in the initial 2 days to 2 weeks post stroke, and correlates \((r = .92)\) better than any other dynamic activation pattern with improving language function. However, in the chronic phase (mean 321 days post-stroke), there is re-normalization with a return of activation to the left hemisphere.\(^10\) This has important implications for post-stroke aphasia care: there is scope for therapy at all stages of recovery, but ideally, it would be specifically tailored to harness activation of cortical structure most implicated at each stage of recovery.

**D. Treatment for Post-Stroke Aphasia**

Aphasia is not a single uniform disorder: fluency, comprehension, repetition, naming, and/or information content may be impaired. Different patterns of impairment (typically reflecting lesion location and size) have been used to classify aphasia taxonomically (e.g. global, Broca’s, Wernicke’s), beyond the gross distinction between non-fluent (expressive) and fluent (receptive) aphasia.\(^33\) Different aphasia types have been observed to have heterogenous susceptibility to spontaneous and thus presumably therapy mediated recovery.\(^8,34-36\)

Historically, aphasia was thought to be irreparable, with any functional improvement over time resulting from spontaneous recovery, leaving no role for therapeutic intervention.\(^37,38\) However, in the last few decades, neuroplasticity, is widely accepted to occur on the basis of animal models and imaging studies.\(^39,40\) It is now believed that rehabilitative therapy can augment spontaneous recovery, especially if well-timed and well-aligned with a hypothesized “critical period” of neural plasticity.\(^39\) Additionally, while adequately powered randomized controlled trials (RCTs) have been scarce, a large body of experimental research, program evaluation data, and case studies
have found positive effects of therapeutic intervention delivered by speech language pathologists (SLPs), such that it is now considered to be unethical to withhold therapy from PWA, and this is reflected in current clinical guidelines.\textsuperscript{4,37,41}

The most common practice is for an SLP to formally assess the PWA to then design and manage individualized therapy, specific to the patient’s particular deficits, comorbidities, and psychosocial situation, drawing on a large and diverse set of established therapeutic approaches to optimize functional improvement\textsuperscript{42,43}

In this paper, we focus on one of the oldest and most formalized therapeutic approaches: Melodic Intonation Therapy (MIT).\textsuperscript{44,45} MIT was developed in response to the longstanding clinical observation that patients with severe expressive aphasia who are unable to speak, are often able to sing familiar songs.\textsuperscript{46} It was thought that through structured use of melody and rhythm, which are processed in the right hemisphere, patients could overcome left hemispheric infarcts and learn a new and permanent way to speak.\textsuperscript{47}

1.2 Statement of the Problem

Aphasia is a common and devastating impairment resulting from stroke and from a pathophysiologic perspective, rehabilitative therapy has the potential to interact with neuroplasticity to augment spontaneous recovery, however, there are no clear guidelines on when to initiate what type of therapy. The American Heart Association/American Stroke Association (AHA/ASA) states that “For individuals with stroke-induced aphasia, speech and language therapy is recommended (Level A Recommendation, Class I Evidence).” However, they do not specify timing, format, intensity, frequency, or duration of treatment: “A variety of different treatment approaches for aphasia may be
useful, but their relative effectiveness is not known. (Level B recommendation, Class IIb Evidence).” Synthesis of the evidence from randomized controlled trials (RCTs) provides no additional guidance: a Cochrane review of 38 trials with pooled N = 1242 found insufficient evidence to establish the effectiveness of one therapeutic approach over another. When to initiate what kind of therapy remains an open question.

As one of the first structured aphasia programs with enduring use worldwide today, MIT is a therapeutic approach that has accumulated positive case series evidence, however, such study designs are inherently limited by their inability to control for patient selection, confounding individual heterogeneity, spontaneous recovery, and Hawthorne effects, and cannot link MIT with aphasia recovery causally. Moreover, the MIT case literature has studied predominantly chronic patients, whereas the neural mechanisms underlying recovery are dynamic and likely to favor earlier treatment, and practically, chronic patients are unlikely to receive treatment, at least in the United States, where insurance reimbursement poses a binding constraint. MIT has not been studied where it might have the greatest clinical impact.

Evidence from 3 small, recent RCTs is encouraging, but incomplete. In a waiting-list controlled crossover trial with a sub-acute study population, communication improved more in the group treated with MIT than in the group receiving alternative speech language therapy (SLT) (p < .05), and after cross-over, and communication improvement was greater when MIT was delivered earlier than when it was deferred (p = .001). Using the same study design with a chronic study population, the same authors found no difference between groups. Taken together, these results suggest relative efficacy of MIT (compared with SLT) if initiated sooner rather than later in sub-acute
patients, however they must be interpreted with caution. In both studies, subject withdrawal resulted in inadequate power, with visibly large standard errors that may have led to an inflated estimate of effect size in the sub-acute population where findings were significant, and/or may have led to an undetectable effect in the chronic population. Nonetheless, these studies underscore a need for an adequately powered RCT with earlier initiation of MIT to establish its efficacy. An RCT protocol undertook precisely this task in another underpowered, study and found greater reduction (p=.02) in aphasia severity in the Modified MIT (MMIT) group than the no therapy control group after just one 15-minute session. While it is difficult to infer a treatment effect from a single successful session and the persistence of benefit was unstudied, the finding of an effect of early MIT even at such a low therapeutic dose, demonstrates the feasibility of early MIT stroke and further impels its study in an adequately powered RCT with an acute study population.

There is no standard of care regarding what type of aphasia treatment to begin at what time, yet neuroimaging studies suggest that the “critical period” of enhanced neuroplasticity occurs early, at a time when PWA typically receive no formal therapy. In light of promising evidence of positive outcomes from early MIT, a well-designed RCT comparing MIT with usual care in the first days to weeks after stroke, would establish whether this long-standing and widely used therapy is efficacious and might serve as a cornerstone of early post-stroke aphasia treatment.

1.3 Study Goals and Objectives

This study aims to determine if a short course of MMIT enhances aphasia recovery (reduces aphasia severity) more than usual care, when initiated in patients with non-fluent aphasia 3 days post-stroke. Because on this timeline, usual care consists of
assessment but no formal therapy, treatment effect estimates from this comparison correspond to efficacy of MMIT for this population. If MMIT is associated with a clinically significant reduction in aphasia severity, it could be incorporated into early post-stroke care.

The objectives of the study are to: 1) enroll a sufficient number of patients who meet inclusion criteria and do not meet exclusion criteria and randomize them into two comparable groups: Modified MIT or usual care; 2) test whether MMIT is associated with a greater decrease from baseline aphasia severity (as measured by the Western Aphasia battery Aphasia Quotient) than usual care after the 3 week experimental period, and; 3) determine whether at 6 month follow-up following the 3 week experimental period and an additional 5 months of usual sub-acute care offered to both groups and delivered outside of experimental conditions, difference in aphasia from baseline differs across the 2 groups.

1.4 Hypothesis

We hypothesize that in non-fluent aphasia patients in the acute period following stroke, the mean difference from baseline aphasia severity will be at least 15.10 (standard error [SE] 17.71) points at 3 weeks in patients randomized to receive MMIT compared with those who receive usual care.

1.5 Definitions

**Acute period:** Treatment with MMIT or usual care will begin 3 days post-stroke.

**Aphasia severity:** Aphasia severity will be measured by the Western Aphasia Battery Aphasia Quotient (WAB-AQ), scale of 0 – 100, from most to least severe.

**MMIT:** Modified Melodic Intonation Therapy (MMIT) delivered by an SLP.
Usual Care: A swallow evaluation, and an SLP administered comprehensive communication assessment.

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Literature Search Criteria

A thorough literature search was conducted between July 2017 and July 2018 using Pubmed and Ovid MEDLINE. Keywords used initially to identify relevant (English language) articles included combinations of *aphasia, stroke, music, therapy, rehabilitation, melodic, singing*. All RCTs, controlled studies, and systematic reviews were retained for thorough review. High quality case series, and prospective and retrospective cohort studies were also included when topical. Full text was acquired for articles deemed to be relevant on abstract screening. This process culminated in close, annotated reading of 211 peer-reviewed articles.

2.2 Clinical Impact of Therapy for Persons with Aphasia: Review of Relevant Trials

A. Efficacy of Therapy

To evaluate efficacy of speech language therapy (SLT) with an RCT, the control group must receive no formal therapy; a comparison between 2 therapeutic approaches can only demonstrate that one is more efficacious than the other. Few RCTs have done this because regardless of efficacy, it has been common practice to offer SLT in the sub-acute phase following stroke and withholding it has been considered to be unethical in recent times. Although AHA/ASA guidelines recommend SLT, evidence of its efficacy is equivocal, with RCTs that find SLT versus no SLT to be effective,\(^1\)\(^-\)\(^5\) and others that find no difference in outcomes comparing SLT with no SLT.\(^6\)-\(^10\) The major difficulty in inferring efficacy of SLT from studies with positive findings is that results do not generalize beyond the particular therapeutic approach, timing, and intensity under study.
In the largest positive, a crossover designed allowed comparison of SLT with no SLT in the first period. 121 sub-acute subjects (2-24 weeks post stroke) were randomized to therapist administered SLT, volunteer administered SLT, or deferred (i.e. no initial) SLT. With repeated measures ANOVA, aphasia improved significantly (p<.05) in the two arms receiving SLT relative to the no SLT arm at the first endpoint of 12 weeks, and the magnitude of the treatment effect was clinically significant with a 40% increase in the Porch Index of Communicative Ability (PICA). However, 23% of subjects did not complete the study (although reassuringly completion rates did not differ across arms) and analysis was per protocol with high risk of resulting attrition bias.

Another 3-arm trial randomized N = 63 chronic subjects (1-22 years post-stroke) to computer SLT, computer stimulation, or no SLT. After 26 weeks, the computer SLT group had greater improvement on the PICA and WABAQ than the group receiving no SLT (p<.001). However, analysis was again per protocol. Additionally, while promising, the results do not generalize to other treatment approaches or stages post-stroke, and at 22 years post-stroke, clinical relevance of any therapy is limited.

The other positive trials used acute study populations, but were underpowered, and again, results are specific to their therapeutic interventions. In N = 59 subjects who were mean 3.19 (SE 2.2) days post stroke, randomized to intensive SLT with box, mapping, and lexical-semantic approaches or usual care (no SLT), the SLT group was found to have improved aphasia severity relative to the control (p=.010). Limitations include failure to meet pre-specified power and differences across groups at baseline, with higher modified Rankin Scores (p=.008) in the usual care group. In an RCT pilot with N = 12 patients randomized to “intensive SLT” initiated 2 days after stroke or no
SLT, the treated group improved more on naming (p=.01) and written language (p=.02) than the control group, and this improvement corresponded to a different pattern of cortical activation on event-related fMRI.\(^5\) Besides the small sample size, one limitation of this study is that in order to be capable of performing a task while undergoing fMRI, subjects could have at most moderately severe aphasia, and since initial aphasia severity is known to predict recovery, \(^8,12-18\) it may be that the skewed aphasia profile of subjects influenced outcomes more than the treatment they received. Finally, in an underpowered (N = 30) RCT pilot studying sub-acute subjects, MMIT group had greater improvement in repetition and responsiveness tests than the untreated control (p=.02),\(^5\) but this was after a single session of treatment with no longer term follow-up, so it is unknown if a similar effect would be seen with more regular therapy or persist over time.

Two\(^9,10\) of the studies finding no significant effect of SLT used small samples (N = 24) of chronic subjects (\(>\) 1 year\(^9\) or \(>\) median 30 months\(^10\) post-stroke) and a Constraint Induced Aphasia Therapy (CIAT) intervention that is a structured and very intensive (3h/day for 10 days) group therapy with no generalizability to other therapeutic approaches. The three larger trials finding no improvement in outcomes attributable to SLT have significant methodological limitations. In (N = 191) sub-acute subjects randomized to SLT for 2 hours/week or no SLT, more than 2/3 of SLT patients received significantly less than 2 hours of SLT per week,\(^19\) and even 2 hours per week is likely an insufficient dose to see a response.\(^19-21\) Additionally, patients with prior strokes were included in the study, obscuring aphasia diagnosis and assessment of recovery. Finally, despite randomization at the outset, analysis was per protocol and substantial attrition
was handled by essentially selecting a case-control sample to analyze, eliminating the benefit of initial randomization.

The remaining 2 RCTs\textsuperscript{7,22} that find no effect of SLT are large and adequately powered (N = 123 and 152 respectively), but suffer from other limitations. They include all aphasia types, relative to most other study populations, global aphasia and Wernicke’s aphasia relative were overrepresented, and these aphasia types are known to have significantly reduced propensity for recovery.\textsuperscript{8,12,14} Also both studies used a local (country-specific) therapeutic approach for intervention with no external validity, and measured outcomes with the Amsterdam-Nijmegen Everyday Language Test (ANELT-A) “understandability” assessment\textsuperscript{23}, a measure that has been used rarely,\textsuperscript{7,22,24,25} perhaps because it has limited construct validity with variable sub-construct correlation across aphasia types (range of r = .27-.66),\textsuperscript{23} and has been criticized as being “highly subjective.”\textsuperscript{26}

B. Type of Therapy

A number of RCTs have compared different types of service delivery and theoretical approaches to SLT. Service delivery comparisons of group therapy,\textsuperscript{27} volunteer-facilitated therapy in a home setting,\textsuperscript{2} and computer-based therapy\textsuperscript{1,28,29} interventions with “standard” SLP-facilitated therapy controls, have generally identified no significant differences in communication outcomes across groups. However, with small sample sizes (N = 24 to N = 121 randomized to 3 arms), it may be that differences between groups exist but are not statistically detectable. Additionally, these comparisons have been undertaken in anywhere from one to a small number of trials using heterogeneous
communication assessment instruments, outcomes, and elapsed time post-stroke onset; the evidence behind any one comparison is sparse.

Comparisons of other theoretical approaches to SLT have included local approaches with no broader geographic applicability. Two RCTs compared Cognitive Linguistic Therapy with, alternatively, Communicative Therapy or no SLT and found no significant difference between communication outcomes across groups. In trials studying specific therapeutic approaches, Constraint Induced Aphasia Therapy (CIAT) and MIT have been most studied.

CIAT is an intensive approach that makes use of groups and mass-practice and restricts use of compensatory (e.g. nonverbal) communication tactics. Generalizing across trials, it has not been found to be efficacious.

Finally, MIT is a hierarchically structured approach that uses intonation (singing) at two pitches that correspond to syllabic emphasis patterns in normal spoken language to guide non-fluent PWA through 3 levels of increasing phrase length and decreasing therapist support. Three trials with positive findings now add to case series and controlled study evidence. Briefly, while the trials were underpowered (with N = 17, 27, and 30 respectively), MIT-treated groups were found to have greater improvement in communication compared with SLT, or with no therapy in sub-acute populations, and this improvement was greater when MIT was initiated earlier rather than later. We discuss these trials in greater detail below.
C. MIT

a. Proposed Mechanism of Action

In 1836, Béhir first described a patient who was able to sing la Marseillaise while he could speak only the monosyllable “tan,” and reports of this clinical phenomenon have been common since. In an observational study of 24 patients with Broca’s aphasia and underlying left hemispheric lesions, 87.5% had at least some preserved singing ability.46

Singing maps to bilateral cortical structures that largely overlap the structures that underlie speaking, but with greater right lateralized activation of the superior temporal gyrus, inferior central operculum, and inferior frontal gyrus in singing than in speaking.47 Melody is processed predominantly in the right hemisphere,48,49 and this may account for stroke patients’ ability to sing the text of a song which they are unable to speak.47

MIT was proposed by its originators to use melody to engage the right hemisphere to promote speech.50,51 Several functional imaging studies support this hypothesis. In a functional magnetic resonance imaging study, 2 subjects matched on lesion size, location, and baseline aphasia severity received MIT or a control therapy identical to MIT but without intonation or hand tapping, and underwent communication assessment and fMRI before and after treatment. The MIT subject was found to have greater communication improvement relative to the control, with changes in the right-hemispheric premotor, inferior frontal, and temporal lobes, while the control-treated subject had changes in the left-hemispheric inferior pre- and post-central gyrus and the superior temporal gyrus.43 In a Diffusor Tensor Imaging (DTI) study of 6 subjects who underwent DTI and behavioral assessments before and after treatment with MIT, a significant increase in right hemisphere arcuate fasciculus fibers and volume was found.
to in parallel improvement on behavioral testing. Another larger (N = 20) DTI study used a controlled but non-randomized design and found right hemispheric white matter changes in the MIT group, but not the control (p < .05), as well as within group improvement in behavioral testing only in the MIT group (p < .001). However, mirroring the broader debate about lateralization in spontaneous recovery, one study of 7 patients previously treated with thérapie mélodique et rhythmée (TMR, the French version of MIT) who underwent positron emission topography (PET) scan while performing MIT and control tasks found the opposite pattern: left hemispheric cerebral blood flow (CBF) increased on MIT tasks, and right hemispheric CBF increased on control tasks. This study has some major limitations and should be interpreted with caution: 5 of the 7 patients had global or Wernicke’s aphasia and thus poor candidates for MIT, the facilitation techniques used and hypothesized mechanism of action behind TMR do not implicate the right hemisphere, and most importantly, the imaging is only post-treatment: it is hard to know whether the task-related CBF changes correspond to residual deficits or recovery.

Other imaging studies have tried to isolate the aspect of MIT that might underlie efficacy, with a focus on melody versus rhythm. These studies yield equivocal results, finding that rhythm alone is associated with improved “articulatory quality,” or alternatively that “speech informativeness” improved only after treatment with both melodic and rhythmic components of MIT.

Imaging studies in general suffer from the limitation that the particular task used in functional imaging can spuriously impact the lateralization observed. For example, formulaic language and spontaneous language lateralize distinctly. Given that even in
healthy patients there is a spectrum of lateralization,\textsuperscript{57} and that hemispheric activation varies in spontaneous recovery,\textsuperscript{58} it is not surprising that there are contradictory findings in studies of brain remodeling associated with MIT. Inter-subject variability in time since stroke, lesion size and location, and environmental and genetic factors, may also confound findings, and case studies cannot control for patient selection. Moreover, the imaging studies employ chronic patients who have previously received SLT to which they have been refractory, and without comparing randomized treatment and control groups, it is difficult to know whether communication performance and imaging findings issue from MIT, spontaneous recovery, or some other source.

b. Efficacy

The American Academy of Neurology has rated MIT as “promising” for Broca’s aphasia, with support from class III (expert opinion and case based) evidence.\textsuperscript{59} To our knowledge, no completed trial to date has established efficacy of MIT, however results from existing MIT trials are promising, with significantly positive outcomes in MIT-treated groups relative to groups receiving control treatment.

In the first period of an RCT using a crossover design (further discussed in the section 2.2(D) on timing of therapy below), 27 sub-acute (2-3 months post stroke) subjects were randomized to receive 6 weeks of MIT for 5 hours/week or an equivalent volume of SLT focused on non-oral communication and were assessed at baseline and 6 weeks with the Aaschen Aphasia Test (AAT) repetition and naming sub-tests\textsuperscript{60}, ANELT\textsuperscript{23}, and Sabadel story retelling task and an MIT repetition. In ITT analysis, the MIT treated group improved more than the SLT treated on the MIT trained repetition task (beta = 18.3, p < .01) and AAT repetition sub-section (beta = 17.2 p < .05). The two
groups were comparable at baseline, except for gender ($\chi^2 = 4.03$, $p=.045$), but gender has been found elsewhere to have no independent association with aphasia recovery elsewhere,\textsuperscript{8,12,13,15-17} and gender and initial aphasia severity were both included in regression analysis, eliminating concern for confounding. Further support for MIT comes from within group improvement ($p<.01$) in the MIT group on all but the Sabadel, with no corresponding within group improvement seen in the control group. Adherence, measured by intensity of actually received therapy did not differ across groups ($p=.49$) and exceeded pre-specified minimums.\textsuperscript{37} One limitation of this study is the lack of longer term follow-up to establish the persistence of response to treatment. Additionally, the study used the original MIT protocol,\textsuperscript{50,51} but the study authors question whether a modified version might have had greater effect.\textsuperscript{37} The main limitation of this study, however, is that it was powered to find an effect on the Sabadel, non-standard test, that may be poorly suited to the non-fluent study population.\textsuperscript{37} Four patients withdrew from MIT within 2 weeks, resulting in inadequate power. Looking at standard errors, we can see high variance in the sampling distribution of between group communication changes, and this may have inflated the estimated effect size. Regardless of power, this trial cannot establish MIT efficacy because the control consists of SLT, rather than no treatment. However, the control treatment approach deliberately avoids spoken elements, so it comes closer to approximating no SLT than many other alternate therapeutic approaches when compared with MIT. Despite inadequate power, the positive finding and its robustness in a second period after crossover (see section 2.3(C) below), strongly motivates additional RCTs to establish efficacy of MIT.
The same authors use the same study design in an RCT pilot, but with a chronic population (mean 33.1 [MIT] to 42.6 [control] months since stroke, difference not significant, \( p = .54 \)), and with a control of no SLT, reflecting common practice in such chronic patients. In principle this control would allow identification of efficacy, however, recruitment was limited by difficulty in finding subjects able to agree to the logistics of treatment, and at \( N = 17 \), the study was underpowered, with no significant differences between groups found on any outcome measures.\(^{36}\) The lack of effect may reflect the high variance in this small sample (standard errors are more than 1/2 the means and within group differences in means show some a mix of expected and counter-intuitive patterns), or alternatively, it may be that MIT indeed has no efficacy so long after stroke. This study in no way reduces motivation to establish efficacy of MIT in an acute population since this study population is so far outside the time window in which patients would ever receive treatment. If anything, juxtaposed with the authors’ positive findings in a sub-acute population, this study lends further support to exploration of initiation of MIT as early as practicable after stroke.

Finally, an RCT pilot\(^4\) compared a MMIT intervention with a no SLT control in the first weeks after stroke, and while with \( N = 30 \), it too is underpowered, it found an immediate benefit to MMIT after one brief session, further underscoring the need for an adequately powered RCT to study the efficacy of a longer regimen of MIT during the acute stage post-stroke. The study setting was an inpatient stroke unit, and 90% and the study population was sub-acute with 90% of patients within 13 days of stroke at the time of intervention. Five sessions of MMIT (intervention) or SLP visit with no SLT (control), with a responsiveness and repetition assessment designed for the study by neurologists
and SLPs administered immediately following sessions. Comparing MMIT with control, the MMIT group improved more after the first session (p=.02), and also showed within group improvement (p=.02), while the control did not (p=.73). The two groups were comparable at baseline, and post-hoc analysis ruled-out any training effects. The major limitation of this study is that due to scheduling difficulties in the stroke unit, no subjects completed the planned 5 sessions, and only 17 of 30 completed the 2nd session assessment. As a result, degrees of freedom were insufficient to compare outcomes beyond the first session. While the control of no SLT provides the right comparator to establish efficacy, it seems highly unlikely to do so based on a single successful session, particularly as patients had no longer term follow-up so it is unknown if the treatment effect persisted beyond the immediate term. Another significant drawback of this study is the use of an unvalidated, custom-designed aphasia assessment instrument. Nonetheless, these findings suggest a need for a larger RCT to compare early MIT with no SLT using a longer and more intensive MMIT intervention that spans inpatient and outpatient settings, and where aphasia severity is assessed with a validated instrument.

D. Timing of Therapy

Given that spontaneous recovery occurs at an attenuating rate over time and is associated with patterns of cortical re-organization, the timing of SLT likely affects its efficacy. In principle, therapy initiated earlier that coincides with a period of enhanced neuroplasticity could provide synergy and result in greater recovery than would be feasible relative to spontaneous recovery alone, or the same therapy initiated later time when cortical re-organization is minimal. Nonetheless, the optimal timing of SLT for post-stroke aphasia remains an open question. While RCTs have initiated interventions as
early as 2 days and as late as 29 years post-stroke, only two have directly compared earlier with later initiation of therapy. A meta-analysis of 55 studies found a greater treatment effect (Cohen’s d = .61) when therapy was initiated within 3 months of stroke, than when it was initiated later (Cohen’s d = .31). However, the majority of RCTs have been conducted in chronic populations, often one to many year post-stroke, a time period when insurance reimbursement has been exhausted and is therefore not clinically relevant. A growing body of RCTs has initiated interventions in sub-acute or acute study populations, but without directly comparing early and deferred therapy, it is impossible to infer causality between early treatment and better outcomes because the observed association may reflect selection bias if patients who can tolerate earlier treatment also recover better.

Two RCTs have directly compared earlier with later initiation of therapy and obtained orthogonal results, which must be interpreted conditionally on their interventions. One of the comparisons in a 3-arm RCT with total N = 121 sub-acute subjects is between 12 weeks of SLT for 8-10 hours/week and the same SLT initiated 12 weeks later. At 12 weeks, aphasia (as measured with PICA) improved more in the group receiving SLT than the deferred SLT group (P<.05), but at 24 there was no difference (p>.05) between groups, suggesting no disadvantage to deferring SLT. However, per protocol analysis was based on 94 subjects who completed the. Additionally, it may have been difficult to detect a difference from deferring SLT in this study because the interval of deferral was short enough that both groups began and completed therapy during the sub-acute stage when spontaneous recovery pervasive and less variable. The other trial (discussed at length in section 2.2(C) above) directly
comparing earlier and later treatment used a double crossover design with MIT and SLT interventions in sub-acute patients subjects. In ITT analysis with repeated measures ANOVA, the group receiving MIT in the first 6 weeks improved more on a repetition task than the group receiving MIT in the second 6 weeks (F = 8.89, p=.001).\textsuperscript{37}

Additionally, in a secondary analysis, time post-stroke was one of the only significant predictors of communication improvement (p< .05 on ATT repetition\textsuperscript{60}, ANELT\textsuperscript{23}, and MIT repetition), with greater communication improvement associated with shorter time since stroke. While attrition led to inadequate power, these findings suggest that at least in the case of MIT, earlier initiation of therapy may be more beneficial.

Finally, as there are some parallels between patterns of spontaneous recovery in speech and motor function,\textsuperscript{15} it is worth noting that an RCT comparing earlier (3-9 months post-stroke) and later (15-21 months post stroke) motor therapy found greater improvement in the group starting therapy earlier.\textsuperscript{61}

\textbf{E. Very Early Therapy}

While the optimal timing of therapy remains an open question whose answer may depend on therapeutic approach, recent trials have established the feasibility of starting therapy as soon as 2 days post-stroke. One of the largest (N = 123) trials in the SLT literature initiated its “Language Enrichment Therapy” intervention or no SLT at 3 days post-stroke. While there was no difference between groups on communication assessments at 3 weeks or 6 months, this may be due to limitations including the idiosyncratic intervention, a sample with overrepresentation of unresponsive aphasia types, and use of assessment instruments with weak psychometric properties. Regardless of findings, this study met pre-specified power thresholds with 93\% of subjects
completing the primary endpoint, and 80% of subjects completing follow-up, in both experimental and control groups, and all subjects in the SLT group tolerated the planned volume of SLT, showing the feasibility of recruiting a large sample and starting an intensive SLT intervention 3 days after stroke. Two smaller RCT pilots that initiated therapy within 3 days of stroke did find significant communication improvement in the groups receiving intensive SLT compared with the controls receiving no SLT. While the efficacy of therapy initiated within days of stroke remains to be established, its practicality and feasibility is clear.

F. Intensity of Therapy

While intensity of therapy has been studied, there is no universal definition of what constitutes intense treatment. RCTs have evaluated “Intense” interventions consisting of 5-7 days/week of SLT in 45 minute, 60 minute or 2 hour sessions. Two meta-analyses older trials provide benchmarks that are often cited: interventions with at least 2 hours/week of SLT resulted in a doubling of Cohen’s d, while a minimum of 8.8 hours/week of SLT was needed to obtain significant improvement in PICA scores. Intensity has also been studied indirectly by using an inherently intense structured treatment like MIT or CIAT, but findings do not generalize beyond these therapeutic approaches.

RCTs explicitly comparing higher and lower intensity treatment have yielded mixed results that vary across timing post-stroke (in an acute and chronic population, greater intensity was found to be beneficial, while in sub-acute populations it was not) and therapeutic approach (e.g. CIAT, multi-modal stimulation, computer therapy). Even without considering threats to internal validity, their results are specific
to the parameters of their interventions and do not generalize. Compared with other SLT trials, intensity trials have more often found differences between groups at baseline\textsuperscript{3,24,29} and high drop-out rates.\textsuperscript{3,30} Additionally, in a trial finding no difference between intense and standard (5 vs 2 hours/week) SLT,\textsuperscript{65} adherence was a problem, so the differential between intensities of SLT \textit{actually received} was narrow, and making it harder to find a significant effect. However, in this trial, comparing outcomes with a third group receiving standard SLT delivered by the National Health Service (NHS), the NHS group (mean) .57 hours/week SLT improved less than the non-NHS standard SLT group (mean) 1.6 hours/week SLT suggesting that some minimal dose threshold may be needed to see any treatment effect.

\section*{2.3. Review of Relevant Methods}

\textbf{A. Study Design}

The proposed study will be a multi-center\textsuperscript{22,24,36,37} randomized, controlled trial to compare aphasia recovery across patients receiving MMIT\textsuperscript{4} or usual care during a 3-week period that begins 3 days post-stroke. Randomization will be centrally accomplished using computer generated random number sequences and sealed envelopes.\textsuperscript{7,22,24,30,33,36,37} Permutated blocks\textsuperscript{24,29} will be used to maximize power via balanced (1:1) allocation of subjects to intervention and control groups.\textsuperscript{67} Block sizes will be randomly distributed across even numbers between 2 and 6 to further ensure that researchers are blinded to subject assignments.\textsuperscript{67-69}

\textbf{B. Patient Selection}

Inclusion and exclusion criteria vary considerably across SLT trials. Within the bounds of what is well-supported by multiple prior studies, our general approach will be
to keep inclusion criteria broad and exclusion criteria minimal to rapidly meet and exceed our pre-specified sample size and power.  

Eligible patients must be admitted to one of our participating VA Primary Stroke Centers (PSCs) with radiologically confirmed diagnosis of acute stroke, conforming to the World Health Organization definition on CT or MRI. Both ischemic and hemorrhagic strokes will be included. Beyond requiring that subjects be ≥18 years of age, we will impose no upper age limit on our sample. Given the difficulty in interpreting disorders of higher cerebral function when there has been prior stroke, we will include only patients with first-ever stroke. Participants must be able to react to verbal commands, but need not be fully alert (consistent with a Glasgow Coma Scale (GCS) score > 10). Patients who are unstable and require transfer to ICU, with concurrent ACS or acute heart failure, or who require hospice care will be excluded. We will also exclude patients with prior neurological or communication disorders, severe dementia, severe depression, significant hearing/sensory deficit or who are unable to consent or undergo treatment. Patients must be native or primary English speakers.

We will employ a few inclusion criteria targeted at recruiting good candidates for our MIT intervention, since different aphasia and lesion types have different propensity to respond to this therapy. In the original MIT protocol, ideal candidates were described as patients with unilateral left-sided lesions, and non-fluent aphasia with poor repetition and articulated speech but relatively well-preserved comprehension, and an early CT lesion study (N = 8) found that successful MIT patients had frontotemporal lesions extending into less than half of Wernicke’s region or the subcortical temporal isthmus.
Accordingly, we will include patients with left-sided lesions\textsuperscript{2,4,10,27,28,30,33,36,37,75} and we will exclude those with right sided or bi-hemispheric lesions.\textsuperscript{36,37}

Patients with Broca’s aphasia are considered the most ideal candidates for MIT, while patients with Wernicke’s or global aphasia are considered the least ideal aphasia types for this therapy.\textsuperscript{59} Given our acute study population and short timeline, it is not practical to formally classify aphasia type prior to enrollment, but VA/DoD acute stroke treatment algorithms\textsuperscript{77} require that acute stroke patients be screened within 24 hours using the National Institutes of Health Stroke Scale (NIHSS),\textsuperscript{78} the most commonly used global disability assessment in the U.S. with excellent psychometric peroperties\textsuperscript{78-80} We will include patients with an NIHSS language score of 1 or 2, thereby effectively excluding those with global aphasia or no impairment.\textsuperscript{4}

C. Clinical Management

From hospital admission until the sooner of hospital discharge or the end of the 3 week experimental period, the primary team responsible for the patient will provide supportive care and monitor for stroke complications according to ASA guidelines.\textsuperscript{81} Following discharge, there will be no need for incremental monitoring beyond what is determined by the primary team. The American Academy of Neurology considers MIT to be safe and without risk.\textsuperscript{59}

D. Intervention

Several case and imaging studies\textsuperscript{35,42-45} as well as the RCTs comparing MIT with SLT in sub-acute and chronic populations\textsuperscript{36,37} adhered strictly to the original MIT protocol\textsuperscript{51} in designing their intervention. However, the authors of the RCTs cite this as a
limitation and speculate that adaptation of the original MIT could yield better outcomes.\textsuperscript{36,37}

In addition to being very structured and hierarchical, the original MIT protocol\textsuperscript{51} is very intensive, with an expected 75 – 90 sessions delivered over a limited period of (ideally) 3-6 weeks,\textsuperscript{59} making it impractical in some patients and settings.\textsuperscript{4,34} The originators of MIT\textsuperscript{51} have thus endorsed MIT's adaptation to meet individual patient needs or insurance constraints and this has become common in clinical practice. The adaptation of MIT has also extended into the scientific literature, with several formally described variations including “Modified MIT,”\textsuperscript{82,83} TMR,\textsuperscript{41,53} and “Palliative MIT”.\textsuperscript{53}

In our study, we will use the MMIT\textsuperscript{83} described in Conklyn et al. 2012,\textsuperscript{4} the MIT pilot RCT whose study setting and population most closely resembles ours. In this intervention, SLP has autonomy to advance the patient through the phases of MIT faster than dictated in the original protocol, and therapy is delivered in 15 minute increments.\textsuperscript{4} As is the norm in scientific study and clinical practice, the precise content of intervention sessions will be determined by the SLP according to individual patient profile on an individually appropriate basis.\textsuperscript{2,6,21,64,84} Generalizing, an SLP will begin by teaching the patient a single melodic phrase assisted by rhythmic tapping with the left hand. Over the course of subsequent sessions, the SLP will use patient success to guide timing of progression to additional and progressively longer melodic phrases, with an ultimate transition to using less intonation to closer approximate speaking. Following the literature on very early SLT,\textsuperscript{3,5,7} the dose of our MMIT intervention will be a total of 45 minutes per day, 5 days per week, over the 3-week experimental period, and the 45 minutes per day may be accomplished through three time-spaced sessions.\textsuperscript{7,22}
While MIT is considered to be safe,\textsuperscript{59} it is worth noting that a phase II trial comparing “higher dose” of early (within 24 hours of stroke) mobilization with usual care, found no difference in mortality across groups (p=.20), and as very early mobilization has higher risk than early MIT, this reassures us that our intervention will be safe.\textsuperscript{74}

E. Control

Our control consists of “usual care” in the first 3 weeks following stroke: a swallow screening,\textsuperscript{81,85,86} a formal speech assessment by an SLP that makes use of a standardized instrument,\textsuperscript{87} and if appropriate, referral for subsequent outpatient therapy.\textsuperscript{88,89} Formal SLT is not a part of usual care during this period.

F. Primary Outcome

The majority of SLT trials have looked for differences in overall aphasia severity across groups, using language batteries to quantify receptive and expressive language. The oldest trials\textsuperscript{2,6,27} used the PICA,\textsuperscript{11} whose validity has not withstood empirical interrogation.\textsuperscript{90,91} The many SLT trials undertaken in non-English speaking countries have often used assessments designed in their local language, although translated and validated versions of at least the WAB do exist.\textsuperscript{12,39} Trials in German speaking countries have overwhelmingly used the “standard” German assessment, the AAT,\textsuperscript{5,31-33,36,37,62,63} while a few Nordic trials\textsuperscript{7,22,24,25} have used the ANELT\textsuperscript{23}, which as we noted above, has limited construct validity,\textsuperscript{23} has been criticized as being “highly subjective”,\textsuperscript{26} and does not measure aphasia severity.
The most commonly used assessment in RCTs conducted in English-speaking countries is the Western Aphasia Battery (WAB),\textsuperscript{1,3,4,28,29,39,65,72,92} which has also dominated the case and observational literature on aphasia.\textsuperscript{12,14-16,39,92-96}

As we will recruit sites from VAMCs, we adhere to the VA/DoD recommendation\textsuperscript{77} to use one of the Agency for Health Care Policy and Research (AHCPR) preferred instruments: PICA\textsuperscript{11}, Boston Diagnostic Aphasia Exam (BDAE)\textsuperscript{97}, or WAB\textsuperscript{98}.

In our RCT, we will use the WAB to assess aphasia severity because it is used extensively in clinical practice, and almost to the exclusion of all other instruments in English-language SLT trials. According to a survey of clinicians treating aphasia in English speaking countries, the WAB is the second most employed assessment.\textsuperscript{64} The WAB has rigorously tested psychometric properties. It is superior at classifying aphasia types,\textsuperscript{99} and it has high internal consistency, test re-test reliability, inter-rater reliability, content and construct validity, and discriminant validity.\textsuperscript{94,100-103} In a small sample (N = 10), depending on the cut-off employed, the sensitivity of the WAB ranged from 60 – 80\% while the specificity ranged from 100 – 80\%.\textsuperscript{102} As importantly, the WAB correlates with functional outcomes.\textsuperscript{73,95} Specifically, we will use the Aphasia Quotient (AQ) score,\textsuperscript{98} a weighted average of all spoken language subtests (spontaneous speech, auditory verbal, naming, and repetition) that has been used elsewhere\textsuperscript{1,3,28,29,65} to measure aphasia severity (see Appendix E).\textsuperscript{98}

Our primary outcome will be the mean difference from baseline across MMIT and usual care groups in change in aphasia severity as measured by the WAB-AQ after 3 weeks.
G. Secondary Outcomes

The effects of MIT have found to be stable for a 3 month period after completion of therapy.\textsuperscript{104} As we want to know if any treatment effect of MIT endures, we will continue to follow patients after the 3-week experimental period, with final WAB-AQ assessment at 6 months post-stroke. This corresponds to the follow-up period commonly used in other trials\textsuperscript{1,3,5-7,22,24,65} and also encompasses the period during which spontaneous recovery is known to be maximal.\textsuperscript{13,16,17,66,93,105,106} Our secondary outcome will be the mean difference across MMIT and usual care groups in change in aphasia severity as measured by the WAB-AQ after 3 weeks.

H. Sample Size

Our study will be powered to detect a statistically and clinically significant difference in primary outcomes across our intervention and control groups, and ex ante power calculation will determine our sample size. To establish the target effect size, we reviewed RCTs,\textsuperscript{3,4,28,30,37,65} a controlled study,\textsuperscript{39} and an outcomes study\textsuperscript{95} that used an MIT intervention, the WAB assessment, or both. As aphasia recovery varies over time\textsuperscript{13,16,17,66,93,105,106} and treatment effects may vary with dose,\textsuperscript{19-21} we will adopt the effect size of Godecke et al. 2012,\textsuperscript{3} who finds a WAB-AQ difference of (mean) 15.1 points (p=.010) in SLT versus usual care groups. While this SLT intervention differs from our MMIT intervention, the acuity of our study population and the timing and dose of intervention are closely approximated. Since no single therapeutic approach has been shown to be superior to any other,\textsuperscript{21} and MIT has more positive evidence\textsuperscript{4,36,37,34,35,40-44,50,51,107} behind it than most other approaches, if anything, the 15.1 point effect should be a lower bound for us. Moreover, 15.1 was the effect size identified after controlling for
initial aphasia severity with Generalized Estimating Equations (GEE), and while we will control for initial aphasia severity with multivariate regression in our secondary analysis, our primary outcome is a simple difference in difference, again suggesting that 15.1 is the lower bound on the treatment effect we should seek to detect. Using a lower bound on effect size to parameterize our sample size calculation is desirable, since effect size and sample size vary inversely.

However, as Godecke et al. 2012\(^3\) did not report their standard deviation, we obtain our standard deviation parameter value from Bakheit et al. 2007.\(^6\) In this study, assessment with the WAB-AQ occurred at regular 4 week intervals, so we compute the standard deviation of the between group difference after 4 weeks of intervention using the within group values in table 7 (see Appendix F for details on this computation). This yields a standard deviation of 17.71, which we will use with the effect size of 15.1 to determine the sample size needed to achieve 80% power and .05 significance with a two-sided hypothesis.

I. Estimated Recruitment Sites

We will recruit sites from the self-designated\(^10\) Primary Stroke Centers (PSCs) of the Veteran’s Administration Medical Centers (VAMCs). In 2016, there were a total of 7,616 acute stroke hospitalizations across VAMCs.\(^10\) The VAMCs constitute the largest healthcare system under single management structure in the United States,\(^6,10\) and offer consistent care, service delivery, and treatment coverage to their beneficiaries. Moreover, algorithms issued in the VA/DoD evidence-based stroke rehabilitation guidelines\(^7\) enhance consistency in treatment approach across VAMC providers and staff. Perhaps for
these reasons, the VAMCs have been the dominant sites of scientific study of SLT for post-stroke aphasia in the United States.\textsuperscript{2,27,66,103,110}

Based on the midpoint of findings in the epidemiological literature, we expect that 31\% of acute stroke patients will be aphasic on initial screening and thus eligible for our study.\textsuperscript{8,13,14,93,111-115} Additionally, averaging completion rates of 76.5\% (Godecke et al. 2012) and 44.7\% in (Bakheit et al. 2007), the studies from which we derive effect size and standard deviation, we estimate that 61\% of patients identified as eligible by the primary team will complete the study to primary endpoint.\textsuperscript{3,65}

We will use the aphasia rate and study completion rate to scale our estimate of the number of sites needed to obtain our sample size.

\textbf{J. Confounding}

The randomization process should yield MMIT and usual care groups that are comparable at baseline,\textsuperscript{67} and thus decrease the risk of confounding of the relationship between MIT and aphasia recovery. We will collect data on patient and stroke characteristics whose influence on recovery has been studied to assess the comparability of our groups, and we will include these in a multivariate regression as part of our secondary analysis as an extra safeguard against potential confounding.

Among the unmodifiable characteristics that have been studied, initial aphasia severity has consistently\textsuperscript{8,12-18} been found to predict subsequent aphasia recovery, with greater initial severity associated with lesser subsequent recovery, and moreover, initial severity has a great deal of predictive power: 81\% of the variance in aphasia difference from baseline after 3 months was explained by initial severity in a multivariate regression.
of N = 21 patients with mild to moderate aphasia, and this relationship persisted for patients who did (R^2=0.76, P=0.005) and did not (R^2=0.90, P=0.001) receive SLT.\textsuperscript{15}

There is some evidence that aphasia recovery can vary with aphasia type, with global aphasia and anomic aphasia having lower rates of recovery.\textsuperscript{14,96,105} On the other hand, most evidence finds no gender\textsuperscript{8,12,13,15-17} age difference\textsuperscript{13,15-17,96,116} or educational attainment\textsuperscript{16} in aphasia recovery, although one study found that younger patients showed greater recovery over 18 months.\textsuperscript{8} Lesion size and location are established clinical predictors of aphasia type,\textsuperscript{12,13,110,115,117,118} however, in multivariate analysis, lesion size did not predict aphasia recovery after controlling for initial aphasia severity.\textsuperscript{16} While left-handed patients may have greater right-sided lateralization, handedness did not show an independent association with degree or likelihood of aphasia recovery.\textsuperscript{13,117}

K. Conclusion

The efficacy of SLT generally and any specific therapeutic approach remains to be established, and its study has been constrained by ethical considerations that preclude use of a control with no therapy in the sub-acute and chronic study populations that have dominated the literature. MIT is well supported by case, imaging, and pilot RCT evidence, but its efficacy has yet to be established in an adequately powered RCT. Recent studies have explored starting MIT earlier than has been done in older studies, and have concluded that this is both beneficial and feasible.

Neuroimaging data tell us that the greatest potential for aphasia recovery occurs during the first days to months following stroke during which right hemisphere cortical structures are recruited to promote speech while affected homologous left hemispheric structures recover. MIT is hypothesized to work by using melody, processed in the right
hemisphere, to promote speech in non-fluent PWA, and this has some support in neuroimaging data. From a pathophysiological perspective, very early therapy could perhaps harness cortical activation patterns that are already observed in spontaneous recovery to induce greater therapeutic response, and this is particularly true in MIT with its proposed patterns of lateralization.

While the acute, inpatient population has historically been understudied, several trials including one of the largest SLT trials, have now established the feasibility of initiating therapy, including MMIT, as early as 3 days post-stroke. There are strong reasons to target this population in future RCTs with an MMIT intervention.

In addition to pathophysiologic motivation to study an early intervention, studying an acute patient population would allow ethical comparison of therapy with usual care involving no formal therapy, since this population does not typically receive therapy, the comparison we need to establish efficacy.

For these reasons, we propose an RCT to compare MMIT with usual care, initiated at 3 days post-stroke.

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CHAPTER 3: STUDY METHODS

3.1 Study Design

The proposed study will be a multi-center two arm prospective, randomized, parallel group, open-label, blinded endpoint assessment (PROBE) trial.

3.2 Study Population and Sampling

The population will consist of men and women ages 18 and older with a diagnosis of acute stroke and communication impairment (NIHSS score of 1 or 2) within 24 hours of presentation to a participating VAMC PSC. Eligible subjects who meet inclusion criteria but no exclusion criteria (Table 1) and have given consent, confirmed by a physician or midlevel provider, will be enrolled consecutively as they present. Sampling will occur over 18 months to commence on the start date of the study.

<table>
<thead>
<tr>
<th>Table 1: Eligibility Criteria</th>
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<td><strong>Inclusion</strong></td>
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<td>Age &gt;= 18</td>
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<td>First ever acute stroke, radiologically confirmed (CT or MRI)</td>
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<td>Left sided lesion</td>
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<td>NIHSS language score of 1 or 2 within 24 hours of admission</td>
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<tr>
<td>Able to react to verbal commands (need not be fully alert)</td>
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<td>Native/ primary English speaker</td>
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<td>Able to consent/ undergo treatment</td>
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<td><strong>Exclusion</strong></td>
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<tr>
<td>Requiring ICU transfer or hospice care</td>
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<td>Concurrent ACS or decompensated heart failure</td>
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<tr>
<td>Right sided or bi-hemispheric lesion</td>
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<tr>
<td>Prior stroke, lesions, neurological or communication disorders, severe dementia, severe depression</td>
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<tr>
<td>Uncorrectable hearing deficit</td>
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<tr>
<td>Prior exposure to MIT</td>
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<td>Unable to consent/ undergo treatment</td>
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3.3 Procedures and Recruitment

Eligible VAMC PSCs will be approached in order of their stroke volume ranked from greatest to lowest to satisfy the required sample size estimated below. A letter (Appendix B) with a description of the study will be sent to service chiefs in appropriate clinical service lines (e.g., Neurology) and union leadership for permission to approach VAMC employees to discuss the project. The Medical Director of participating VAMC PSCs will be contacted by letter to inform them of the study. Participating providers will be asked for their help in enrolling eligible patients in this study. We will follow-up to answer questions by phone.

Each site that agrees to participate will be assigned a research assistant who will provide information to participating clinicians and subjects, assist with identification and enrollment of patients who meet study inclusion and exclusion criteria. Research assistants will also obtain in person subject consent and communicate with the central study coordination center about subject group assignments.

3.4 Subject Protection and Confidentiality

Prior to the start date of the study, we will obtain VA Central Institutional Review Board (IRB) as well as the IRB or Human Subjects Subcommittee (HSS) at each participating VA site, as well as the IRB and Human Investigation Committee at Yale University. All subjects who will participate in the study will give written informed consent (Appendix C). The informed consent form includes a description of the study, the duration of participation, potential risks and benefits of the study, alternative options for treatment. The form explains that participation in the study is voluntary. Since we will only be enrolling English speaking patients in the study, we will only use an English
language version of the consent form. If the patient cannot read the form, an oral presentation can be given explaining informed consent. A third-party must be present to ensure that no information is withheld if the consent form is read to the patient. Given that study participants may not have the capacity to comprehend consent or may be unable to communicate understanding of consent due to the extent of their injuries, a legally authorized representative can consent on the behalf of the individual. We will make every attempt to enroll patients that can provide their own consent. The patient or representative will be given time to read over and ask questions about the consent form prior to signing. The consent form will also authorize the research team to access the individual’s protected health information (PHI) and will explain the intended uses of the PHI and length of time in which the PHI is needed.

In order to maintain confidentiality, the study protocol will be in accordance with the Health Insurance Portability and Accountability Act (HIPAA). Only pertinent health information will be collected and all patient information used during the study will be considered strictly confidential. Only authorized individuals will have access to PHI and all members of the research team must complete a privacy-training course prior to handling PHI. Each study participant will be assigned a unique ID number and all data related to the patient will be labeled with this ID number in order to de-identify the patient. All extracted data from patient charts, and assessments will be logged into a VA Research Electronic Data Capture (REDCap) database. This REDCap database will only store the unique identifiers that are not based on personally identifiable information. A separate Cross-walk Excel file will be kept by the research assistant containing the unique identifier and personally identifiable information. This Excel file will be password
protected and will be saved behind the VA firewall. All paper files related to the study will be stored in a secure location in a locked file cabinet accessible only to study personnel who must access these files. All PHI will be kept for the duration of the study and then will be disposed of in a secure manner.

3.5 Study Variables and Measures

*Dependent Variable:* The dependent variable is the change in aphasia severity at 3 weeks, measured by the WAB-AQ.

*Independent Variable:* The independent variable is the treatment arm to which the patient is assigned: MMIT or usual care.

*Other Descriptive Measures:* Additional variables (Table 2) will be used to assess the quality of randomization by comparing intervention and control groups at baseline, during the 3-week experimental period, and during the extended follow-up period. Baseline characteristics that are known to be independently associated with the dependent variable, as well as any variables that are found to vary systematically across groups, will be used as controls in secondary analysis. Treatment course and follow-up variables will be used to analyze secondary outcomes.

<table>
<thead>
<tr>
<th>Table 2: Other Descriptive Measures</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
</tr>
<tr>
<td>age, education (last grade completed), gender, handedness, active comorbidities, date of death (if applicable)</td>
</tr>
<tr>
<td><strong>Stroke Characteristics</strong></td>
</tr>
<tr>
<td>date of admission, stroke type (ischemic v hemorrhagic), thrombolysis, initial stroke severity (NIHSS score), lesion site, lesion size, baseline aphasia severity (WAB-AQ) at initiation of intervention, length of hospital stay</td>
</tr>
<tr>
<td><strong>Therapy Characteristics for 3-week experimental phase and post-experimental follow-up phase</strong></td>
</tr>
<tr>
<td>date of initial and final therapy sessions, hours of therapy completed, number of sessions, hours of homework completed, hours of other (non-speech) rehabilitation</td>
</tr>
</tbody>
</table>
3.6 Methodological Considerations

A. Description of Intervention, Control, and Follow-up

MMIT rehabilitation will be delivered to patients in the intervention group by a set of board certified designated SLPs engaged for this study who have agreed to delivering therapy according to the specific study protocol only to patients to whom they are assigned. Patients will undergo WAB assessment by an independent, blinded assessor just prior to starting MMIT. Patients will receive a total of 45 minutes of therapy per day, 5 days per week, for 3 weeks to start 3 days post-stroke after baseline communication assessment that day. The therapy may be delivered in 15-minute increments that need not be continuous. Content of MMIT will follow the procedure outlined in Conklyn et al. 2012: Patients and SLTs will sing short phrases together while tapping rhythm with the left hand. The first phrase will be short and used commonly in daily-life (“I need coffee”). The therapist will decide at what points to introduce additional phrases, which will become longer, more complex, and less frequently used in daily life. Patients will undergo repeat WAB assessment by an independent, blinded assessor at the completion of the 3-week period.

Usual care, to be received by all patients, will consist of 1) a swallow screening conducted by the primary team within 24 hours of admission and prior to starting oral intake; 2) formal communication evaluation conducted by an SLP prior to discharge to include communication impairment assessment with the WAB and assessment of environment and impact of speech impairment on activity and participation; 3) patient and family education conducted by SLP; 4) Referral to and scheduling of SLT
(depending on individual patient needs and capabilities) to begin after the 3-week experimental phase in standard VAMC venues.

In the follow-up period, all patients may elect to receive SLT with standard but individually adapted parameters. SLPs who treat patients during this period will be asked to log time spent in formal sessions and homework. The duration of SLT will vary, but all patients will receive follow-up WAB assessment by an independent, blinded outcome assessor at 6 months post-stroke. Table 3 summarizes the intervention and assessment schedule.

<table>
<thead>
<tr>
<th>Table 3: Schedule of Assessment</th>
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<tbody>
<tr>
<td><strong>acute stroke -</strong></td>
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<tr>
<td><strong>24h post-stroke</strong></td>
</tr>
<tr>
<td>NIHSS + other screening/eligibility</td>
</tr>
<tr>
<td>Consent</td>
</tr>
<tr>
<td>Randomization</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Swallow screening</td>
</tr>
<tr>
<td>WAB assessment</td>
</tr>
<tr>
<td>MMIT starts and recording of therapy</td>
</tr>
<tr>
<td>Patient diary provided</td>
</tr>
<tr>
<td>SLT starts and recording of therapy</td>
</tr>
</tbody>
</table>

X1 = primary team; X2 = research assistant; X3 = trial designated blinded assessor; X4 = trial designated SLP; X5 = VA SLP

(a) secondary outcome
B. Randomization Procedure and Assignment of Intervention

Randomization will be centralized. At each site, as patients are enrolled, a site-specific research assistant will contact the study coordination center with patient numerical IDs. A centralized independent research assistant, not involved in any participating site or other aspects of the study, will use a computer-generated randomization sequence to assign patient numerical IDs 1:1 to MMIT versus usual care groups using permuted blocks of (random) size 2, 4, or 6. Results will be placed in consecutively numbered sealed envelopes. The central research assistant will communicate patients’ randomization arms to the local IRBs. Site-specific research assistants will ensure that the patient is randomized to her assigned group.

At each site, VA administrative staff who will not be involved in treatment will ensure scheduling of MMIT therapy sessions in hospital and outpatient settings and ensure that each patient is treated by a single SLP regardless of setting. Staff will also schedule communication assessments with independent assessors who have no therapeutic role, at 3 days post-stroke, the conclusion of the 3-week experimental period, and 6 months post-stroke.

C. Blinding

While it is impossible to blind patients or SLPs to their treatment, their allocation will have been concealed and performed by an independent research assistant as described above. Over the course of their 3 weeks, patients in the MMIT group will be treated by a single dedicated SLP chosen from a pool of SLPs with comparable experience. Outcome assessment will be performed by separate independent assessors who are blinded to the patient’s group, baseline characteristics, stroke characteristics, and
previous assessment scores. Each site will have 3 independent blinded assessors engaged for this purpose. Patients will be asked not to communicate the details of their treatment to outcome assessors. Finally, statistical analysis will be conducted at the study coordination center by an independent central researcher who is blinded to patient group assignments.

D. Adherence

Clinicians participating in the study will be encouraged to adhere to protocol in regular check-ins with site specific research assistants. Patients will receive reminder phone calls prior to each treatment or assessment session at their primary contact number.

Patient adherence to assigned treatment will be monitored during the experimental phase: SLPs who administer MMIT will log date, duration, and clinical notes for each session using the Veterans Health Information System and Technology Architecture (VistA) Electronic Health Record (in use since 1981). During this phase, therapy will be limited to in-person SLP-administered sessions. After the 3-week experimental phase and until follow-up communication assessment at 6 months post-stroke, patients will receive variable, individually tailored SLT, and the treating SLPs will be asked to log dates, duration, and clinical notes in VistA for each session. During this time period, patients may be given homework assignments, and they/their family will be given a diary and asked to log dates and time spent on homework.

3.7 Data Collection

Data collection will be completed within 2 years of the study start date, including 18 months for recruitment and 6 months for treatment and final assessment of the last recruited subjects. Baseline patient characteristics, stroke characteristics, and relevant
hospitalization and therapy dates are available in VistA. As described above, members of the multi-disciplinary primary team will log NIHSS scores in VistA prior to patient enrollment. Specialized, dedicated communication outcome assessors will conduct the WAB (Appendix E) and log scores in VistA. SLPs administering MMIT or subsequent individualized SLT will log their clinical notes in VistA. An independent research assistant who is not involved in other aspects of the study will transfer relevant data from VistA into a (CSV format) spreadsheet, and this will be used for statistical analysis.

3.8 Sample Size Calculation and Site Recruitment

Sample size was computed using the statistical software package R (Version 3.2.0 on Mac OS). Based on prior studies, we expect the between groups mean difference from baseline in WAB-AQ to be at least 15.1 at the 3-week assessment, with standard deviation of 17.71. Using these values with power of 0.80 and alpha of 0.05, we determine a total of N = 46 subjects must complete the primary study endpoint and be usable in analysis, in order to detect an effect. (Appendix F).

Averaging completion rates in the same prior studies, we would expect 61% of patients with aphasia on initial NIHSS screening will complete the primary endpoint of the study, so we scale recruiting up to a total of N = 76, with 38 patients per arm.

Based on historical volumes of stroke patients at each VAMC PSC, we will need to run the trial at two VA Stroke Centers, as long as the largest two centers are willing to participate (see Appendix G with the details on stroke volume per VAMC).

The following CONSORT Diagram summarizes the sample size requirements and key assessment points.
3.9 Statistical Analysis

Baseline patient and stroke characteristics (see Table 2 above) will be compared across MMIT and usual care groups using $\chi^2$ tests for proportions computed from categorical variables and 2-sample t-tests for means of continuous variables.

Statistical significance of our primary outcome, the between group difference in pre- to post-test aphasia severity after 3 weeks as measured by the WAB-AQ, will be evaluated with a 2-sample t-test. Although successful randomization should render it unnecessary, the pre- to post-test WAB-AQ score difference will also serve as the dependent variable in multivariate regression that includes a dummy variable for group
(MMIT or usual care) assignment, baseline aphasia severity, center fixed effects, and other baseline characteristics that may confound results. The coefficient on the group assignment dummy variable is the estimated adjusted score difference, and its significance will be evaluated with a t-statistic.

We will also perform secondary analysis of additional outcomes. Within group pre- to post-test scores at 3 weeks (with matched pair t-test to evaluate significance) will reveal the order of magnitude of communication improvement over this period. Between group difference in pre- to post-test scores at 6 months will be used to evaluate persistence of treatment benefit with 2-sample t-test to evaluate significance. We will also compare mortality rates at hospital discharge and 6 months between groups and between group drop-out rates at 6 months using a $\chi^2$ test for difference in proportions, and between group differences in treatment volume at 6 months using a 2-sample t-test.

The level of statistical significance for all tests will be set to p<.05. Analysis will be performed on intention-to-treat basis.

3.10 Timeline, Location, and Resources

Timeline: Pending IRB approval, study enrollment will commence on January 1, 2019, and continue on a rolling basis until June 27, 2020, the last date at which new patients may be enrolled. Data collection will be completed on December 31, 2020, and data analysis will commence on January 1, 2021.

Personnel: Study-specific research personnel include 2 central research assistants, 1 statistician, and 1 research assistant per site. Study-specific clinicians include 3 outcome assessors and at least 2 SLPs trained in MMIT per site.
Location: The study coordination center will have headquarters at the Neurology Department of the West Haven, CT VAMC at 950 Campbell Avenue, where principle investigators Jason Sico, MD and Faye Steiner, PhD, PA-SII will be in residence.
CHAPTER 4: CONCLUSION

4.1 Strengths and Advantages

The primary strength of our study is our choice of intervention: MMIT is pathophysiologically motivated and supported by abundant case studies and a few underpowered RCTs, and its early initiation not only coincides with a period of maximal neuroplasticity, but it allows for a test of efficacy since formal therapy is not a part of usual care in that period.

Our use of VAMCs for study setting also confers many advantages. The VAMC provides a homogenous institutional setting with consistency across centers, clinicians, and reimbursement in a country where healthcare delivery, settings, and insurance coverage vary tremendously and may confound estimates of treatment effects. Additionally, using VAMCs we can ensure continuity of care across inpatient and clinic settings, so that patients receiving MMIT can be treated by the same SLP over the course of their 3-week intervention. Finally, patient data has been meticulously recorded in the VA’s VistA EHR software, facilitating collection of patient baseline characteristics, whereas in other hospital settings, such data may be missing if a patient is unable to communicate and has never presented prior to acute stroke.

Finally, we use sound methodology. Using a prospective RCT, we minimize risk of selection bias. Our use of multiple centers allows recruitment of a larger sample, increasing precision, and greater geographic diversity, increasing generalizability. Our use of reliable, validated standard assessment instruments and blinded assessors prevents detection bias, enhances reproducibility, and facilitates comparison with other studies.
4.2 Limitations and Disadvantages

The source of many advantages also confers one of our primary limitations: our use of the VAMC setting constrains the external validity of our study as the veteran population is not representative of the non-veteran U.S. population, and is only 9.4% female. While our sample will underrepresent women, gender has undergone considerable scrutiny as a potential confounder, and it has no evidence of an independent association with aphasia recovery. We therefore feel that the many advantages to using the VAMC setting are worth this compromise of generalizability.

Our other limitations are shared with the SLT literature more generally. Like our predecessors, we are likely to lose substantial numbers of patients to withdrawal, death, and failure to adhere to protocol. Because recruitment of eligible PWA after stroke is challenging, while driven by ex-ante power calculation, our sample size is small. While randomization should yield comparable groups that allow identification of treatment effects, in small samples, randomization is more likely to result in baseline differences across study groups. Additionally, we must exert caution in interpreting performance on language assessments; even in healthy persons without aphasia, individual heterogeneity in hearing ability, literacy, premorbid intelligence, and medical risks may influence performance, so all errors on language assessments are not due to aphasia. However, our use of randomization should eliminate any systematic variation in these factors. Finally, as is true of all SLT studies, our results do not generalize to other types, timing, or intensity of therapy, so our contribution to the deficient SLT evidence base will still be incremental.
4.3 Clinical Significance

An estimated 180,000 individuals in the U.S. are newly diagnosed with aphasia each year.\textsuperscript{10} Aphasia is associated with high morbidity and mortality that can persist into the long term.\textsuperscript{3,11-13} Many patients recover at least incompletely,\textsuperscript{3} and clinical guidelines recommend SLT,\textsuperscript{14} but they provide no insight into its optimal parameters. Our study is a response to numerous calls for an adequately powered RCT to shed light on the ideal type and timing of SLT. With individual heterogeneity across patients, SLT can never be “one size fits all.” However, if our results support the efficacy of MMIT compared to the common practice of deferring therapy in patients within the first days after stroke, they may motivate providers to start MMIT therapy before patients are discharged from their acute hospital stays, either as a precursor or adjunct to longer term aphasia therapies, and they might motivate insurers to reimburse such treatment.
REFERENCES

# APPENDIX A: ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>VAMC</td>
<td>Veterans Administration Medical Center</td>
</tr>
<tr>
<td>VA/DoD</td>
<td>Veterans Administration/ Department of Defense</td>
</tr>
<tr>
<td>AHA/ASA</td>
<td>American Heart Association/ American Stroke Association</td>
</tr>
<tr>
<td>PWA</td>
<td>persons with aphasia</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>SLP</td>
<td>speech language pathologist</td>
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<tr>
<td>MIT</td>
<td>Melodic Intonation Therapy</td>
</tr>
<tr>
<td>SLT</td>
<td>speech language therapy (broadly speaking, includes all therapeutic approaches)</td>
</tr>
<tr>
<td>MMIT</td>
<td>Modified Melodic Intonation Therapy</td>
</tr>
<tr>
<td>WAB-AQ</td>
<td>Western Aphasia Battery-Aphasia Quotient</td>
</tr>
<tr>
<td>PICA</td>
<td>Porch Index of Communicative Ability</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusor Tensor Imaging</td>
</tr>
<tr>
<td>PET</td>
<td>positive emission topography</td>
</tr>
<tr>
<td>AAT</td>
<td>Aaschen Aphasia Test</td>
</tr>
<tr>
<td>ANELT</td>
<td>Amsterdam-Nijmegen Everyday Language Test</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary Stroke Center</td>
</tr>
<tr>
<td>UC</td>
<td>usual Care</td>
</tr>
<tr>
<td>ITT</td>
<td>intention to treat</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
</tr>
<tr>
<td>VistA</td>
<td>Veterans Health Information System and Technology Architecture</td>
</tr>
<tr>
<td>AHCPR</td>
<td>Agency for Health Care Policy and Research</td>
</tr>
<tr>
<td>REDCap</td>
<td>Research Electronic Data Capture</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
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</table>
APPENDIX B: LETTER TO INSTITUTIONS

(Date)

Dear ________________,

This letter is to inform you of an upcoming single-blinded, randomized, controlled trial to assess the impact of Melodic Intonation Therapy (MIT), a structured therapy that makes use of melody, rhythm, and emphasis, on patients with aphasia following an acute stroke.

While the American Heart Association/American Stroke Association (AHA/ASA) recommends speech and language therapy for individuals with stroke-induced aphasia, there are no guidelines for timing, format, intensity, frequency, or duration of treatment. Patients typically do not start receiving speech and language therapy until several weeks after stroke. Case studies and observational studies and a small scale RCT suggest that patients who receive MIT showed language improvement, and MIT is a therapy that seems especially well suited to the critical period of neuroplasticity in the first few weeks after stroke. We are proposing a randomized control trial to compare MIT to usual care in patients with aphasia due to a stroke during the first three weeks following a stroke. We suspect that MIT will improve the patients’ aphasia severity.

Entry Criteria:

Inclusion
1. Age >= 18
2. First ever acute stroke, radiologically confirmed (CT or MRI)
3. Left sided lesion
4. NIHSS language score of 1 or 2 within 24 hours of admission
5. Able to react to verbal commands (need not be fully alert)
6. Native/primary English speaker
7. Able to consent/undergo treatment

Exclusion
1. Age >= 18
2. Requiring ICU transfer or hospice care
3. Concurrent ACS or decompensated heart failure
4. Right sided or bi-hemispheric lesion
5. Prior stroke, lesions, neurological or communication disorders, severe dementia, severe depression
6. Uncorrectable hearing deficit
7. Prior exposure to MIT
8. Unable to consent/undergo treatment

Patients who meet the entry criteria will then be randomized to one of two arms in the study. Patients randomized to the MIT arm will receive a modified form of MIT. The
dose of our intervention will be a total of 45 minutes per day, 5 days per week, over the 3-week experimental period, and the 45 minutes per day may be accomplished through three time-spaced sessions that takes 10-15 minutes to complete. During the first three weeks of the study, patients in the control arm will receive usual care, which consists of a swallow study and a speech assessment per the usual protocol at the VAMC. After the initial three week period, patients in both arms will be scheduled for outpatient therapy PRN as usual. The main outcome of this study is the difference between groups of the mean difference from baseline in aphasia severity as measured by the Western Aphasia Battery, at 3 weeks and at 6 months after enrollment.

The participation of your institution in this study would help with recruitment and would be greatly beneficial in determining the impact of early MIT therapy on aphasia recovery. You will be receiving a follow-up phone call in the next two weeks to answer any specific questions or concerns your facility may have regarding the involvement in this study. Please do not hesitate to contact us (information below) prior to speaking on the phone.

Thank you for your time and we look forward to working with you.
Faye Steiner, PhD, PA-SII
Co-Principal Investigator
(XXX)XXX-XXXX
faye.steiner@yale.edu
APPENDIX C: INFORMED CONSENT FORM

VA Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Subject Name: __________________________

First Name  MI  Last Name

Title of Study: Early Melodic Intonation Therapy vs Usual Care For Aphasia

Principal Investigators: Jason Sico, MD and

Faye Steiner, Ph.D.  VA Connecticut Healthcare System/689 (v.07/19/18)

SECTION I: THE PURPOSE OF THE STUDY AND HOW LONG IT WILL LAST.

You are invited to participate in a research project designed to look at whether music therapy helps patients regain communication capabilities after having had a stroke. You have been invited because you have recently suffered a stroke and some of your speaking abilities have been affected. Your participation in the study will last for approximately six months.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study which a member of the research team will discuss with you. This discussion will go over all aspects of this research; its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate, if so, you will be asked to sign this form.

SECTION II: DESCRIPTION OF THE STUDY INCLUDING PROCEDURES TO BE USED.

This study will be comparing the effect of two types of speech and language therapy on the recovery of communication abilities after a stroke, specifically comparing a form of music therapy called "Melodic Intonation Therapy" or "MIT" to the usual standard speech and language therapy administered as part of stroke rehabilitation therapy.

The study will be administered at 2 Veterans Administration Medical Centers, and the therapies will be administered by speech language therapists who work at these centers on both an inpatient and outpatient basis. We will be asking a total of 76 patients to enroll in the study. The study’s sponsors are Dr. Jason Sico and Faye Steiner, Ph.D.

If you decide to participate in this research study, you will be randomly assigned to one of two treatment groups through a method similar to flipping a coin, and you will have an equal chance of being in either group.

Patients in both treatment groups will receive be seen by a speech therapist who will conduct an interview with the patient (and where possible, family), and do some standardized testing to identify what aspects of communication have been affected by the stroke and how severely they are affected. The standardized test mostly involves speaking and it usually takes no more than 45 minutes. The speech therapist will then recommend a treatment plan that is follows standard VA practices and is individualized to each patient’s needs. Patients will then be assisted in scheduling their prescribed therapy sessions to begin 3 weeks after stroke for up to 6 months. The therapy sessions may occur in and/or outside the hospital, and may include a variety of speaking and language comprehension exercises, working one on one with the therapist, with a computer, or in a group. The patient may also be asked to do some exercises as homework outside of the therapy sessions with the speech language therapist.

In one of the two treatment groups, patients will additionally have regular music therapy sessions during the first 3 weeks after stroke while they wait to begin the "usual" individually tailored speech
therapy that was just described. The music therapy sessions will take a total of 45 minutes per day that can be split into 3 shorter sessions, and they will occur five days per week. Patients in this group will have the music therapy sessions in the hospital until they are discharged, and will then continue with the same certified VA therapist outside the hospital after discharge.

For all patients in the study, approximately three weeks after stroke, a speech language therapist will repeat the standardized testing that was done 3 days after stroke. For the remainder of the six-month study, all patients will continue with their individualized treatment plan, and the plan will be adjusted to meet changing needs over that time period. Towards the end of the six months after stroke, a speech language therapist will schedule and conduct a final round of standardized testing.

If you participate, throughout the study, you and your speech language therapist will be asked to record how much time you have spent doing any therapy activities in sessions with your therapist and also at home. We will give you a diary to keep track of your time spent on homework.

SECTION III: DESCRIPTION OF ANY PROCEDURES THAT MAY RESULT IN DISCOMFORT OR INCONVENIENCE.

The music therapy we will be administering is non-invasive, as is the case for all of the language therapy that will be a part of this study. There are no significant risk factors associated with the therapy in this study, however the mentally demanding intensity can cause some patients to become bored and/or tired. Additionally, this therapy has a significant time demand for the participating patient and care givers after the patient is released from the hospital.

SECTION IV: EXPECTED RISKS OF STUDY:

There are no known risks associated with participating in this study.

Confidentiality of Information:

Participation in research may involve a loss of privacy. From your medical records, we will be collecting information about you and your stroke including gender, education, age, medical problems, and we will summarize details and imaging results from your stroke. Your research records will be kept as confidential as possible. The code number used to record information for this study will not be based on any information that could be used to identify you (for example, social security number, initials, birth date, etc.) The master list linking names to code numbers will be kept separately from the research data.

All research information will be secured in locked files. Your identity will not be revealed in any reports or publications resulting from this study. Only authorized persons will have access to the information gathered in this study. Authorized persons may include regulatory agencies such as the Food and Drug Administration (FDA), the Government Accountability Office (GAO), the Office for Human Research Protections (OHRP), Office of Research Oversight (ORO), VA Connecticut Healthcare System Research Office, and Yale University Human Investigation Committee.

The Department of Veterans Affairs (VA) requires some information to be recorded in the VA electronic medical record for veteran and non-veteran research subjects. Therefore, if you participate in this study, a medical record will be created if you do not already have one. Notes from your visits, procedures, and laboratory tests will be included in this record. In addition to the research team, and the VA staff who provide clinical services, other researchers may be granted approval to access this.
information in the future. Federal laws and regulation that protect privacy of medical records will apply to your VA record.

SECTION V: EXPECTED BENEFITS OF STUDY.

This trial is the first of its kind for using this type of music therapy in the first 3 weeks after stroke. There is no set guideline on when to start therapy following a stroke, nor on what the therapy should entail. Case studies have shown that this music therapy may be beneficial, and that some patients improve their communication after this type of therapy. Our goal in this study is to determine if starting music therapy early can be more beneficial in improving communication function.

You may or may not be personally be helped by taking part in this study, but your participation may lead to knowledge that may help others.

SECTION VI: ALTERNATIVE THERAPY OR DIAGNOSTIC TEST.

The alternative is to not participate in this study, in which case you will receive standard language therapy in accordance with your needs and the VA guidelines and standard procedures.

Participation in this study is voluntary, and you may withdraw from the study at any time for any reason.

SECTION VII: USE OF RESEARCH RESULTS.

If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. Your medical records will be maintained according to VA requirements.

SECTION VIII: SPECIAL CIRCUMSTANCES.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

There will be no charge for care received as part of your participation in this study. However, some Veterans are required to pay a co-payment for medical and other services provided by the VA Connecticut Healthcare System that are not part of the study. These co-pay requirements will continue to apply to medical care and services provided by VA that are not part of this study.

If you are injured as a direct result of your participation in this research study, VA will provide necessary medical treatment at no cost to you. Except in very limited circumstances, this medical treatment will be provided in a VA Medical facility. There are no plans to provide compensation for disability or other losses occurring over the long term or if an injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation. If you have any questions about your rights as a subject, you may contact the Chairman of the Human Studies Subcommittee at 203-932-5711, extension 3350. If you have any complaints, concerns or pertinent questions regarding the conduct of this study, or if you have any questions about compensation for injury, you may contact the Human Studies Coordinator in the Research Office at 203-937-3830.
RESEARCH SUBJECTS' RIGHTS

I have read or have had read to me all of the above and I voluntarily consent to participate in this study. The study has been explained to me and my questions have been answered. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled. I will receive a signed copy of this consent form.

The results of this study may be published, but my records will not be revealed unless required by law.

In case there are medical problems, a research related injury or complaints, concerns, or pertinent questions about the research. I have been told I can call Dr. Jason Sico at (203-932-4724) during the day and the VA Clinic after hours at (203-932-5711).

__________________________________________
Signature of Subject Date

__________________________________________
Signature of Person Obtaining Consent Name of Person Obtaining Consent (Print) Date

__________________________________________
Signature of Principal Investigator Date

The signature of Subject's Representative is required if patient is not competent or has been assigned a Conservator of Person.

HSS Approval Stamp

VACHS FORM March 2015
### APPENDIX D: NATIONAL INSTITUTE OF HEALTH STROKE SCALE

#### NIH stroke scale

<table>
<thead>
<tr>
<th>Admission date:</th>
<th>Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
</tbody>
</table>

1. **Level of consciousness**
   - **0** Alert
   - **1** Not alert, but arousable with minimal stimulation
   - **2** Not alert, requires repeated stimulation to attend
   - **3** Coma

2. **LOC questions**
   - **0** Answers both correctly
   - **1** Answers one correctly
   - **2** Both incorrect

3. **LOC commands**
   - **0** Obey’s both correctly
   - **1** Obey’s one correctly
   - **2** Both incorrect

4. **Best gaze**
   - **0** Normal
   - **1** Partial gaze palsy
   - **2** Forced gaze palsy

5. **Visual field testing**
   - **0** No visual field loss
   - **1** Partial hemianopia
   - **2** Complete hemianopia
   - **3** Bilateral hemianopia (blind, incl. Cortical blindness)

6. **Facial palsy**
   - **0** Normal symmetrical movement
   - **1** Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
   - **2** Partial paralysis (total or near total paralysis of lower face)
   - **3** Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

7. **Motor function arm**
   - **0** Normal (extends arm 90° or 45° for 10 sec without drift)
   - **1** Drift
   - **2** Some effort against gravity
   - **3** No effort against gravity
   - **4** No movement
   - **9** Untestable (joint fused/limb amputated) (do not add score)

8. **Motor function leg**
   - **0** Normal (holds leg in 30° position for 5 sec without drift)
   - **1** Drift
   - **2** Some effort against gravity
   - **3** No effort against gravity
   - **4** No movement
   - **9** Untestable (joint fused/limb amputated) (do not add score)

9. **Limb ataxia**
   - **0** No ataxia
   - **1** Present in one limb
   - **2** Present in two limbs

10. **Sensory**
    - **0** Normal
    - **1** Mild to moderate decrease in sensation
    - **2** Severe to total sensory loss

11. **Best language**
    - **0** No aphasia
    - **1** Mild to moderate aphasia
    - **2** Severe aphasia
    - **3** Mute

12. **Dysarthria**
    - **0** Normal articulation
    - **1** Mild to moderate slurring of words
    - **2** Severe aphasia
    - **3** Mute

13. **Extinction and inattention**
    - **0** Normal
    - **1** Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities
    - **2** Hemi-inattention, severe or to more than one modality

14. **Distal motor function**
    - **0** Normal
    - **1** At least some extension after 5 sec but not fully extended
    - **2** No voluntary extension after 5 sec

**Total score:**
APPENDIX E: WESTERN APHASIA BATTERY SCORE SHEET

### SCORE SHEET

<table>
<thead>
<tr>
<th></th>
<th>Maximum</th>
<th>Patient's Subscores</th>
<th>Total For AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous Speech</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information Content</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluency</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comprehension</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes/No Questions</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Word Recognition</td>
<td>60</td>
<td></td>
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</tr>
<tr>
<td>Sequential Commands</td>
<td>80</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Divide By 20 For AQ)</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Divide By 10 For CQ)</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Repetition</strong></td>
<td>100</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(Divide By 10)</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Naming</strong></td>
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<td></td>
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<tr>
<td>Object Naming</td>
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<tr>
<td>Word Fluency</td>
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<tr>
<td>Sentence Completion</td>
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<tr>
<td>Responsive Speech</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<tr>
<td>(Divide By 10)</td>
<td>10</td>
<td></td>
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</tr>
<tr>
<td><strong>Aphasia Quotient</strong></td>
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<td></td>
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<tr>
<td>(Add Totals And Multiply By 2 For AQ)</td>
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<tr>
<td><strong>Reading And Writing</strong></td>
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<td></td>
</tr>
<tr>
<td>Reading</td>
<td>100</td>
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<tr>
<td>Writing</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Divide By 10)</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Praxis</strong></td>
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<td><strong>Total</strong></td>
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<td>(Divide By 6)</td>
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<td><strong>Construction</strong></td>
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<td>Drawing</td>
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<td>Calculation</td>
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<tr>
<td><strong>Total</strong></td>
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<td></td>
<td></td>
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<tr>
<td>(Divide By 10)</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cortical Quotient</strong></td>
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<tr>
<td><strong>Add Totals</strong></td>
<td>100</td>
<td></td>
<td></td>
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</tbody>
</table>

### References
APPENDIX F: SAMPLE SIZE CALCULATION

> # Sample Size Calculation
> # Godecke difference at 4 weeks or discharge
> godecke.difference <- 15.1
> # Standard Deviation using properties
> # We get the standard deviation for the difference between groups using
> properties of Standard Deviation and the 4-week estimate of Intensive vs Standard
> from Bakheit
> intensive.vs.nhs.fourweek <- sqrt(11.8^2+13.2^2)
> # Compute the power
> godecke.power <- power.t.test(delta=godecke.difference,
> sd=intensive.vs.nhs.fourweek,
> +    sig.level=0.05, power=0.8, alternative="two.sided")
> 
> print(godecke.power)

Two-sample t test power calculation

n = 22.58389  
delta = 15.1  
sd = 17.70537  
sig.level = 0.05  
power = 0.8  
alternative = two.sided

NOTE: n is number in *each* group

>
APPENDIX G: ESTIMATED PATIENTS BY CENTER

<table>
<thead>
<tr>
<th>Stroke Patients Admitted (a)</th>
<th>Forecasted to be eligible based on NIHSS and lesion site (b)</th>
<th>Forecasted to complete primary outcome and be analyzed (c)</th>
<th>Cumulative total across centers forecasted to be usable in analysis</th>
<th>Included</th>
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<tbody>
<tr>
<td>Houston</td>
<td>266</td>
<td>82.46</td>
<td>50.30</td>
<td>50.30</td>
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<tr>
<td>San Juan</td>
<td>216</td>
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<td>Dallas</td>
<td>166</td>
<td>51.46</td>
<td>31.39</td>
<td>81.69</td>
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<td>Central Arkansas</td>
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<td>Memphis</td>
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<td>45.26</td>
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<td>Indianapolis</td>
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<td>Bay Pines</td>
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<td>36.58</td>
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<td>34.41</td>
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<td>31.31</td>
<td>19.10</td>
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<td>Tampa</td>
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<td>31.00</td>
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<td>Cincinnati</td>
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<td>30.69</td>
<td>18.72</td>
<td>390.30</td>
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<td>Kansas City</td>
<td>98</td>
<td>30.38</td>
<td>18.53</td>
<td>408.83</td>
</tr>
</tbody>
</table>


(b) Assumes 31% (midpoint of 24-38 from epidemiological studies) of acute stroke patients will present with aphasia based on the National Institute of Health Stroke Scale (NIHSS)

(c) Assumes 61% (midpoint of 45-77 from RCTs with CONSORT diagrams) of screened patients will complete primary end point and be usable in analysis


70. La Caze A, Duffull S. Estimating risk from underpowered, but statistically significant, studies: was APPROVe on TARGET? *Journal of clinical pharmacy and therapeutics.* 2011;36(6):637-641.


135. Wertz RT, Deal, Jon L., Robinson, Alice J. Classifying the aphasias: A comparison of the Boston Diagnostic Aphasia Examination and the Western Aphasia Battery. Clinical Aphasiology Conference; 1984; Seabrook Island, SC.


