**Enhanced Medical Rehabilitation in Older Adults (EMR R01)**
**Statistical Analysis Plan (Final)**

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Roles and Responsibilities

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Abbreviations:

**EMR**: Enhanced Medical Rehabilitation

**SOC**: Standard of Care

**SNF**: Skilled Nursing Facility

**OT:** Occupational Therapy

**PT:** Physical Therapy

**PI:** Principal Investigator

**AE:** Adverse Event

**SAE:** Serious Adverse Event

**MADRS**: Montgomery and Asberg Depression Rating Scale.

**CIRS-G**: Cumulative Illness Rating Scale for Geriatrics

**SBT**: Short Blessed Test

**SAS:** Statistical Analysis Software

**ANCOVA**: Analysis of Covariance

Introduction:

i. Background and Rationale:

Americans are aging and having more medical events such as heart attack, stroke, and hip fracture. More than ever, older adults are surviving these events and leaving the hospital, alive but severely disabled. The solution for these highly disabled older adults is rehabilitation in the post-acute care setting, a large and rapidly-growing sector of care. Post-acute rehabilitation consists of daily physical therapy (PT) and occupational therapy (OT) to achieve restoration (e.g., regain walking ability and counteract bone and muscle loss by gait and muscle strengthening exercises), and adaptation (e.g., learn to perform activities of daily living and safely live at home). The most common setting for post-acute rehabilitation is a skilled nursing facility (SNF). Length of stay is about 3 weeks, a narrow window in which to recover and return home or be institutionalized.

Post-acute rehabilitation is low-intensity, low-engagement and too often fails to achieve functional recovery, especially in the most vulnerable individuals. This problem should be remediable by applying the science of behavior change to this setting. We therefore developed Enhanced Medical Rehabilitation.

ii. Objectives:

1. Aim 1 (Primary): Examine the effectiveness of EMR for improving functional outcomes in older adults admitted to SNFs for post-acute rehabilitation.

   H1: EMR will improve functional recovery to a greater extent than standard-of-care rehabilitation.

   Explanation: The purpose of H1 is to examine the effectiveness of EMR. If H1 is supported, this could establish EMR as the gold-standard practice for post-acute rehabilitation. Our primary analysis is the change from baseline to Discharge. This single primary endpoint allows for an effectiveness test that is not confounded by length of stay differences or post-discharge issues beyond the reach of EMR.

2. Aim 2: Examine EMR's ability to overcome patient-level barriers to successful rehabilitation.

   H2: The effectiveness of EMR for functional recovery will be greatest in: (a) patients with clinical depression; (b) patients with high levels of medical comorbidity; (c) patients with cognitive impairment.

   Explanation: EMR was designed to overcome barriers to rehabilitation (for example, due to depression); therefore, the difference in functional recovery between EMR and SOC should be greater in the most vulnerable older adults. If H2 is supported, we will demonstrate that older adults with these common comorbidities benefit the most from high intensity, high engagement rehabilitation. If so, this would refute conventional wisdom in post-acute rehabilitation, codified in admission criteria for rehabilitation facilities, regarding the appropriate candidates for rehabilitation (as described in Significance).

3. Aim 3 (Secondary): Effect of EMR on MADRS scores on individuals with clinical depression.

4. Calculated a rate of clinical depression (SCID for those with elevated MADRS score):

   *22 participants had the SCID administered.*
   *8 did not have depression diagnosis while 14 did have depression diagnosis.*

   Conclusion: only 14 individuals in the study had a clinical depression (ie, a diagnosis of depression). No further analyses to be done.

Additional Variables/Outcomes

6-Minute Walk/Gait Speed: Administered at Baseline and Discharge. Two components for 6-Minute Walk:

1) Distance Ambulated (feet): text box. If unable to complete, distance was entered as a 0.
2) Time: options are 6 minutes, Other time (MM:SS), and N/A

Two components for Gait Speed (Baseline, Day 30, Discharge):

1) Distance: radio button (10 meters, 4 meters, 0 meters). If unable, 0 meters selected.
2) Time (seconds): text box (if unable, time is 0).

Disposition (i.e., discharge to community vs. not)

Rehospitalization (rate).

Secondary analyses (not for main paper):

1. PANAS (A positive and a negative affect score).

2. PROMIS (Ability to Participant in Social Roles and Activities).
3. OARS IADL.

Process data: Measures of the dosage of intervention (# of EMR steps done in each therapy activity; PAT %; Rehab Participation Scale Score) before and after training.

Study Methods:

i. Trial Design:

This was a randomized, parallel-group trial where patients received either EMR or SOC therapy.

Patients who received EMR received therapy only from therapists who were trained and supervised in EMR. Their therapy sessions followed the EMR protocol. Otherwise, their SNF care did not differ from usual care.

Patients who received SOC received therapy only from PT/OTs (or assistants) who were not trained nor supervised in EMR. These therapists were monitored (videotaped or observed) but were not asked to do anything differently with their patients.

ii. Randomization:

Randomization (blocks…2 and 4 patients). was 1:1 to EMR or SOC with stratification by SNF site and by baseline depression status.

iii. Sample Size:

The sample size was based on 80% power to detect a Cohen's d=0.4 effect size on the ANCOVA difference in treatments at primary endpoint, based on a two-tailed p<0.025 (because two outcome measures are used). G*Power 3.1.2 was used for power calculations. A Cohen's d=0.4 is between "small" (0.2) and "medium" (0.5) effect sizes. Effect sizes for function were in the "large" range, d=0.7-0.9, but we acknowledge that these observed effect sizes are qualified by the small sample size, and it makes most sense to be more cautious regarding likely effect sizes in a full-scale study, hence our choice to power at d=0.4. Such an effect size is clinically relevant for the functional outcomes. *We will only examine affective recovery as an outcome for those who are "affectively impaired" to begin with; i.e., those with clinical depression at baseline; with this reduced N, we are powered at 80% for a d=0.54. This same power analysis would apply for any subgroup analysis of depressed; i.e., if we wish to demonstrate that EMR is effective both in the case of clinical depression and in "non-depressed" older adults.*

iv. Statistical Interim Analyses/Stopping Guidance:

Not applicable; we did not have any interim data analysis or early stopping plans.

v. Timing of Final Analysis:

All outcomes will be analyzed collectively.

vi. Timing of Outcome Assessments (including windows):

| | **Schedule of Assessments** | **SNF admit (baseline)** | **Day 7** | **Day 30** | **SNF discharge** | **Day 60** | **Day 90** |
|---|---|---|---|---|---|---|---|
| **Outcomes** | *Function* | | | | | | |
| | **Barthel Index (primary outcome)** | X | | X | X | X | X |
| | Gait speed | X | | X | X | | |
| | 6-minute walk | X | | | X | | |
| | *Depression* SCID (given if indicated by MADRS) | X | | | | | |
| | **MADRS** | X | | X | | | |
| | 17-item positive and negative affect scale | X | X | X | | X | X |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Processes** | *Rehabilitation intensity* | | | | | | |
| | Patient active time & actigraphy (at 20% of sessions at random) | collected each session throughout stay | | | | | |
| | *Treatment engagement* | | | | | | |
| | Observer-rated Rehabilitation Participation Scale (at 20% of sessions at random) | collected each session throughout stay | | | | | |
| | Fidelity data (at 20% of session at random) | collected each session throughout stay | | | | | |
| | Post-Treatment Affect | | | | | | |
| | Self-Assessment Moniker (at 20% of session at random) | collected each session throughout stay | | | | | |
| | Patient Satisfaction and Treatment Fidelity Survey | Collected after therapy sessions | | | | | |
| | *Other rehabilitation variables* | | | | | | |
| | Rehospitalization | | | X | X | X | X |
| | Disposition (home, long-term care) | X | | X | X | X | X |
| | Social Participation (PROMIS Ability to Participate in Social Roles and Activities) | | | | | X | X |
| | Instrumental Activities of Daily Living (OARS IADL) | | | | | X | X |
| | Executive Functioning (Clock Drawing Test) | X | | | | | |
| | Fear of Falling | X | | | | | |
| | Readiness for Rehab | X | X | | | | |
| | Short Blessed Test | X | | | | | |
| | Medical Comorbidity (CIRS-G) | X | | | | | |
| | Barthel Index: Pre-morbid version | X | | | | | |

Statistical Principles:

i. Confidence Intervals and P-Values

Level of significance is 5%

ii. Adherence and protocol deviations

Protocol Deviation:
Any alteration or modification to the IRB-approved research without prospective IRB approval. The term research encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

Therapist adherence and competence was tracked two times per participant.

Variables: number of EMR principles used per therapy session; PAT.

iii. Analysis Populations

Trial Population:

i. Screening data to describe representativeness of trial sample will include age, gender, race and ethnicity.

ii. Eligibility

Inclusion Criteria:

a. 65 years of age and older
b. Admitted to a skilled nursing facility for post-acute care from PT and OT for 2 weeks or more.

Exclusion Criteria:

a. Language, visual or hearing barriers to participation (e.g. unable to communicate with research staff).
b. Medical illness preventing study participation or accurate data collection (e.g., highly unstable cardiac illness such that early re-hospitalization is expected; metastatic or other cancer such that hospice is recommended or survival is limited.
c. Moderate-severe dementia (demonstrated by chart diagnosis and/or short blessed score greater than 13).
d. Progressive neurological condition such that recovery of function is not feasible.
e. Patient did not have the ability to walk prior to hospitalization (e.g. paraplegic).
f. Schizophrenia or other chronic or current psychotic disorder.
g. Patient normally resides in a long-term care facility.

iii. Recruitment: the numbers that will be presented in a CONSORT diagram include:

1. # Screened/Consented and reasons for ineligibility.
2. # Randomized to EMR vs SOC.
3. # Present at each follow-up time point (i.e., Day 30, Discharge, Day 60, and Day 90); reasons for discontinuation/lost to follow-up.
4. # Included in Final Analysis; reasons excluded from final analysis.

iv. Withdrawal/follow-up

No follow-up was done for withdrawn participants. If a participant was withdrawn, then an attempt was made to obtain final prognosis information using clinical data available from the chart unless explicitly told not to do so by the participant.

v. Baseline Patient Characteristics

In addition to the screening variables described above, the variables below will also be summarized in a Baseline Characteristics Table. Continuous variables will be summarized using median and IQR while categorical variables will be summarized using counts and percentages. These statistics will be provided by condition (EMR Vs SOC) and as a whole.

- Barthel Index
- MADRS Score
- Gait Speed (Distance in meters and Time in seconds)
- 6-Minute Walk (Distance Ambulated, in feet)
- PANAS Score
- Short Blessed Test Score
- CIRS-G Score
- Clock Drawing Score

Analysis:

i. Outcome Definitions

1) Aim 1: Examine the effectiveness of EMR for improving functional outcomes in older adults admitted to SNFs for post-acute rehabilitation.

   H1: EMR will improve functional recovery to a greater extent than standard-of-care rehabilitation.

   The primary measure employed for assessing functional improvement will be The Barthel Index. This index is a 10-item scale used to ascertain the degree of independence of normal daily activities. This will be done by taking the sum of these 10 items. A high score indicates a high degree of independence, and a score can range from 0 to 100.

2) Aim 2: Examine EMR's ability to overcome patient-level barriers to successful rehabilitation.

   H2: The effectiveness of EMR for functional recovery will be greatest in: (a) patients with clinical depression; (b) patients with high levels of medical comorbidity; (c) patients with cognitive impairment.

   Part (a) will be assessed using the MADRS, which is a 10-item scale used to assess for major depression. Each item is rated on a scale of 0 to 6, where a 6 is worse. The total score (i.e., sum of these 10 items) will be

used to assess for major depression and can range from 0 to 60.

Part (b) will be assessed using the CIRS-G, which is a 13-item scale used to assess for disease in all major body systems. Each item is rated on a scale of 0 to 4, with a 4 indicating severe impairment. The total score (i.e., sum of these 10 items) will be used to assess for medical comorbidity and can range from 0 to 52.

Part (c) will be assessed using the SBT Scores. The SBT is a 6-item scale used to assess for memory/concentration deficits. A total score, which is obtained after applying a weighting factor to each item then summing up the final item scores, can range from 0 to 28. A high score indicates impairment consistent with dementia.

ii. Analysis Methods

The primary outcome analysis for functional recovery will use a marginal model with time (baseline and discharge), condition (E-MR vs. SOC) and time x condition as fixed effects and with a covariance structure specified based on the Bayesian Information Criterion (BIC). Employing a marginal model allows for a more robust approach in the handling of missing data compared to the traditional ANCOVA model.

For H2 under Aim 2, each potential continuous moderator will be individually inserted into the primary model. The term of interest will be the time x condition x moderator interaction.

The secondary analyses for Six-Minute Walk distance and Gait Speed will use a Mann-Whitney U Test to test for differences in means between groups. In addition, a Chi-Square test will be employed to test for independence between condition and the secondary outcome variable re-hospitalization. Finally, the outcome of self-reported function will use a marginal model using time (30, 60, and 90 days), condition and time x condition as fixed effects, with a covariance structure specified based on BIC.

Exploratory analyses will also test whether the effects of age, gender, race and site (i.e., Barnes Jewish Extended Care Vs Alexian Brothers Sherbrooke Village) altered the conclusions of the primary results as well as the conclusions of the moderator results.

Note: we will not look at the nesting of subjects within therapists who are then nested within site as this is not possible due to the inconsistency of assigning therapists to participants.

iii. Missing Data

We use a marginal model which accounts for missing data (no multiple imputation was used).

iv. Harms

An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

AEs will be labeled according to severity (i.e., mild, moderate or severe), which is based on the AE's impact on the participant.

AEs will be categorized according to the likelihood that they are related to the study intervention or other study procedures (i.e., definitely unrelated, definitely related, probably related, or possibly related).

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IRB, and NIMH in accordance with requirements. Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NIMH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NIMH Program Official within 15 days. Anticipated SAEs will be handled in a less urgent manner but will be reported to the IRB in accordance with their requirements.

v. Statistical Software

All analyses will be performed using SAS and/or R.

vi. References

none