STUDY TITLE: **C3FIT (COORDINATED, COLLABORATIVE, COMPREHENSIVE, FAMILY-BASED, INTEGRATED, AND TECHNOLOGY-ENABLED CARE): A COMPARATIVE EFFECTIVENESS RANDOMIZED TRIAL TO IMPROVE STROKE CARE DELIVERY**

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Statistical Analysis Plan (SAP)
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Coordinated, Collaborative, Comprehensive, Family-based, Integrated, Technology-enabled Stroke Care (C3FIT) Study

1. Introduction

C3FIT is a cluster -randomized clinical trial randomizing 24 sites (21 of which provided data and will be included) to assess the effectiveness, defined at 12-months post-stroke discharge, of post-stroke care delivered using the Joint Commission (JC)-certified Comprehensive or Primary Care (CSC/PSC) model compared to an integrated, coordinated, technology-enabled Integrated Stroke Practice Unit (ISPU) model (that includes CSC/PSC care). The trial has two primary outcomes, the modified Rankin score (mRS) and the Stroke Impact Scale (SIS), both assessed at baseline (for SIS, only in approximately 50% of the participants), and at 3, 6 and 12 months. Any beneficial treatment effect of the ISPU approach on the mRS and SIS is presumed to be through a beneficial effect on "intermediate" factors, specifically better control of: 1) systolic blood pressure (SBP) to levels below 130 mmHg, 2) LDL levels to levels below 70 mg/dL, 3) HbA1c to levels below 7%, 4) smoking cessation, 5) adherence to AHA diet guidelines by following a Mediterranean-type or DASH diet, and 6) adherence to AHA exercise guidelines by a usual exercise level of moderate or above. Each of these intermediate factors will be assessed among those failing to be in control at hospital discharge (i.e., for SBP, among those with discharge SBP≥130 mmHg; for LDL, among those with discharge LDL levels above 70 mg/dL, etc.). Because of this presumed pathway for potential effects, the assessment of treatment effects on these six intermediate factors is considered an integral part of the assessment of primary outcomes. Because the cluster-randomization may fail to balance the treatment groups on key factors potentially affecting outcome, treatment differences will be assessed after a series of incremental models, first in a crude model with no adjustment, then with adjustment for measures of stroke severity, then with further adjustment for demographic factors, and then with further adjustment for major cardiovascular risk factors. Treatment differences for both the two primary outcome variables and the six intermediate factors will be assessed using a mixed model approach including the assessments at baseline, 3 months, 6 months and 12 months.

Beyond the intermediate factors above, the study also has secondary outcomes including mortality, recurrent stroke, rehospitalization, time at home, depression, caregiver strain, and perceived support.

2. Definitions and classification of covariates

The covariates used in the incremental models include measures of stroke severity, demographic factors, and traditional cerebrovascular risk factors.

- Measures of stroke severity
  - Discharge location, classified as discharged home vs. not home (skilled nursing, rehabilitation center, etc.).

  - Discharge mRS, categorized as 0, 1, 2, 3 or 4 or more (noting relatively few patients with discharge mRS of 5).
  - Discharge NIH Stroke Scale (NIHSS), categorized into approximate quartiles of 0, 1, 2-4 or 5+
  - Stroke subtype (hemorrhage vs. infarction)
- Demographic factors
  - Age, considered as a continuous factor
  - Male sex
  - Race/Ethnicity, categorized as non-Hispanic white (NHW) versus not NHW (including both other races and Hispanic participants)
  - A summary neighborhood index of socio-economic status (nSES) based on previously published methods, including six variables representing wealth/income, education and occupation: (1) log of median household income, (2) log of median value of owner-occupied housing units, (3) proportion of households receiving interest, dividend, or net rental income, (4) proportion of adults aged ≥25 years with a high school diploma, (5) proportion of adults aged ≥25 years with college degree, and (6) proportion of people employed in executive, managerial or professional occupations.[1,2]
- Baseline cerebrovascular risk factors
  - Cigarette smoking, categorized as current vs. non-current (past or never)
  - Hypertension as a dichotomous variable
  - Dyslipidemia as a dichotomous variable
  - Diabetes as a dichotomous variable
  - Atrial fibrillation or irregular heartbeat as a dichotomous variable
  - Sedentary activity (defined as a score of 0-No Physical Activity or 1-Sedentary or sitting most of the time)

Because the mixed models will include baseline assessment of the outcome variable (i.e., outcomes include measures at times 0, 3, 6, and 12 months), covariates directly related to the outcome being assessed will be excluded from the model. That is, variables will not be used as both an outcome and as a predictor in the same model. For example, discharge mRS will not be included in the models predicting treatment differences in mRS, and baseline hypertension will not be included in models assessing treatment differences in SBP. Rather, changes from baseline to the 3, 6 and 12-month visits will be assessed using contrast statements.

3. Primary Outcome Analyses

3.1. Analysis of intermediate factors

Because the ISPU intervention was targeted to specific groups determined by baseline assessments, the primary analysis of the six intermediate factors will be restricted to the estimation of treatment differences among patients who were not in control at discharge, specifically assessing the percentage of patients with:

1) SBP below 130 mmHg at 3, 6, and 12-months among those with SBP of 130 mmHg or above at discharge
2) LDL below 70 mg/dL at 3, 6, and 12-months among those with LDL of 70 mg/dL or above at discharge

3) HbA1c below 7% at 3, 6, and 12 months among those with HbA1c of 7% or above at discharge
4) Smoking cessation at 3, 6, and 12-months among those smoking at dischargement,
5) Adhering to a Mediterranean or DASH diet among those not adhering at baseline
6) Having regular exercise levels of moderate or above among those with lower levels at baseline.

The primary hypothesis will focus on compliance/adherence at the 12-month visit, but mixed models will be used with assessments at the 3 time points (3, 6, and 12 months) and treatment differences reported at all three follow-up times.

Analyses will generally take the approach of using a mixed model approach with: 1) repeated measures at 3, 6 and 12 months, and 2) a random effect for patient and site (if models do not converge, site will be considered as affixed effect). As all of the intermediate factors will be dichotomized for the follow-up assessments, outcomes will be assessed using PROC GLIMMIX. Treatment differences will be assessed in a series of incremental models: 1) crude, 2) adjusted for stroke severity, 3) further adjustment for demographics, and 4) adjustment for cerebrovascular risk factors (see section 2 for factors in each group). The temporal pattern of treatment differences at 3, 6 and 12-months will be described by the treatment-specific proportion adherent/compliant with 95% confidence intervals. The primary assessment of treatment efficacy will be the p-value and confidence intervals for the treatment difference in the proportion at the 12^{th} months; however, p-values and confidence intervals for months 3 and 6 will also be reported.

In addition to this primary analysis of the intermediate factors that is restricted to those not compliant/adherent at discharge, a supplemental analysis will assess the proportion compliant at 3, 6, and 12 months regardless of compliance at month 0 (i.e., proportion compliant/adherent in the entire population). This analysis will consider a mixed modeling approach with outcomes at 4 time points (0, 3, 6, and 12 months). The focus of this analysis will be on the change in the proportion compliant between month 0 and 12 months (but also reporting the change in the proportion to 3 and 6 months). In addition to assessing treatment differences in the change in the proportion, the treatment differences in the proportions at the 4 time points will be assessed.

For all six factors, analyses assessing the potential for bias from missingness will be performed using inverse probability weighting (for both the analysis restricted to those not compliant/adherent and for the entire population analysis). This will be conducted by first developing a logistic regression model estimated in all subjects predicting the probability of observing the 12-month observation. Predictors in the model will be site (with cluster randomization, implicitly including treatment effect), age, NHW race/ethnicity, sex, NIHSS and nSES. The inverse of this probability will be standardized by dividing by the sum of the inverses, standardizing the inverse probabilities to have the same sum as the sample size; hence, not inflating or deflating statistical power. The analysis for the factor will then be repeated using the inverse probability weights. Should the interpretation of results differ between the weighted and unweighted analyses, the primary interpretation will be based on the weighted analysis, and the weighted analysis will be the basis for figures and estimates in the manuscript will focus on the weighted results.

Effect modification will be assessed by age, sex, race/ethnicity, stroke sub-type, stroke severity (discharge NIHSS dichotomized at 0 to 1 versus 2+), and nSES.

3.2. Modified Rankin Score (mRS)

The mRS is a 7-point scale, ranging from 0 (normal) to 6 (dead), where at baseline the scores were from 0 to 5 (discharged dead were excluded from the study). During follow-up, patients were scored a 6 at the 3, 6 and 12-month follow-up if the patient died before the respective follow-up (even if the patient missed intervening visits. The mRS will be dichotomized as "good outcomes" of 0 to 2 points, and "poor outcomes" of 3 to 6 points. Analysis will use a mixed model approach (implemented through GLIMMIX) with the treatment-specific proportion of "good outcomes" modeled at months 0, 3, 6, and 12 (reported with the p-value for treatment differences at each time point). The primary outcome will be treatment differences in the change in the proportion with good outcomes between months 0 and 12, but differences to months 3 and 6 will also be estimated. These differences will be estimated with the same 4-level incremental adjustments, and with both unadjusted and inverse-probability weighted adjustment. Effect modification will be assessed by age, sex, race/ethnicity, stroke sub-type, stroke severity (discharge NIHSS dichotomized at 0 to 1 versus 2+), and nSES. With the discharge mRS as an outcome, the analysis will not be adjusted for baseline mRS.

3.3. Stroke Impact Scale (SIS)

The SIS is a continuous outcome variable with a range from 0 to 100 which will be analyzed identically to continuous intervening factors measured at 4 timepoints (including the analysis with inverse probability weighting). We do note that: 1) after approximately half the patients were recruited, a decision was made to not collect SIS at baseline; however, it is quite reasonable to assume that this decision will give rise to data missing at random and the missingness will be addressed by the mixed models, and 2) the baseline SIS collected were the "long form" of the questionnaire (96 items); however, the 16 items in the short form used at 3, 6 and 12 months are a subset of the long form, and these items will be extracted and scored identically with the follow-up assessments. The analysis of SIS will employ analysis for a continuous factor, but will follow the modeling approach described above for mRS, specifically reporting treatment differences in mean SIS rather than treatment differences in the proportion with good mRS outcome (primary outcome as treatment difference in the change in mean SIS between baseline and 12 months, 4-level incremental models, with/without inverse probability weighting, assessment of effect modifiers, etc.).

4. Secondary Outcomes

4.1. Time-to-event secondary outcomes (mortality, recurrent stroke, and rehospitalization)

The number of days between discharge and death, recurrent stroke or rehospitalization will be calculated, and treatment differences in the times will be assessed using hierarchical proportional hazards models (i.e., using a RANDOM statement for site if conversion, or fixed effect with no conversion). The same incremental modeling approach (crude, adjusted for stroke severity, further adjusted for demographics, and finally adjusted for risk factors) will be employed. It is possible that the number of events may be relatively small (particularly for death and recurrent

stroke), introducing concerns for the use of too many covariates relative to the number of predictors. Should this be the case, a "restricted" number of covariates will be considered, specifically using NIHSS as the single index of severity, using age and race/ethnicity as the indexes of demographics, and hypertension as the single index of risk factors. These will be added in this order up to the point where there are at least 10 events for each factor introduced (i.e., perhaps, not even all these predictors can be considered).

4.2. Time-at-home

The proportion of the "time at risk" (defined as the patient being alive and with known status) to be at home will be calculated for each patient, where patients with a no time at risk will be excluded from analysis. Time at home is defined by subtracting time during hospitalization, rehabilitation, skilled nursing from the follow-up time (defined as the time from discharge to last follow-up, death or withdrawal date). Treatment differences in the time-at-home will be assessed in a hierarchical regression model (patients within sites). A 4-level incremental modeling approach like that used for other outcomes will be employed, with the modification that the time at risk will be considered in all models. The first step in considering the time at risk is to assess an interaction with treatment, and should this interaction be significant ($p < 0.10$) the analysis will be stratified and the median value for time at risk. After this determination, the analysis will proceed in a similar manner as other outcomes with the exception that time at risk will be included as a covariate in all models.

4.3. Depressive symptoms

Depressive symptoms will be assessed using the PHQ-9 dichotomized at scores of 0 to 9 versus 10 and above[3] (note that if fewer than 10% of patients present with depressive symptoms the score will be dichotomized at the median). The analysis of this outcome will then follow the approaches described above for dichotomous outcomes measured only at follow-up (i.e., adherence to exercise and diet guidelines).

4.4. Caregiver strain index (mCSI)

The (modified) CSI is assessed at the 3, 6 and 12-month follow-up (not at month 0) and is a 13-item scale, producing a score from 0 to 26. The analysis will focus on the difference at month 12, but will used a mixed model approach incorporating data from the 3 and 6 month timepoints (note that without data at month 0, change from discharge is not defined). The analysis will follow the approaches for the primary outcome with the 4-level incremental models.

4.5. Perceived level of support

The perceived level of support was assessed through the study at the 3, 6 and 12-month visit and is measured on 5 point scale. The differences in the mean score at each follow-up time will be assessed using a mixed model in a manner similar to the mCSI above.

1. Diez Roux AV, Merkin SS, Arnett D, et al. Neighborhood of residence and incidence of coronary heart disease. *The New England journal of medicine*. Jul 12 2001;345(2):99-106. doi:10.1056/NEJM200107123450205
2. Diez-Roux AV, Kiefe CI, Jacobs DR, Jr., et al. Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies. *Annals of epidemiology*. Aug 2001;11(6):395-405.
3. Levis B, Benedetti A, Thombs BD, Collaboration DESD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *Bmj*. Apr 9 2019;365:l1476. doi:10.1136/bmj.l1476