COMPASS

COMPREHENSIVE POST-ACUTE STROKE SERVICES

Phase 1
Statistical Analysis Plan

May 15 2018

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Phase 1 Statistical Analysis Plan

STUDY TITLE: Comprehensive Post-Acute Stroke Services (COMPASS) Study

COMMUNICATING PI: Pamela Duncan, PhD

JOINT PIs: Cheryl Bushnell, MD; Wayne Rosamond, PhD

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AUTHOR: Matthew A. Psioda, PhD

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Name	Role	Signature	Date
Pamela Duncan	Principal Investigator	Pamela W Duncan	5/16/2018
Cheryl Bushnell	Co-Principal Investigator	Cheryl Bushnell, MD, MHS	5/17/2018
Wayne Rosamond	Co-Principal Investigator	Wayne Rosamond	5/17/2018
Matthew Psioda	Lead Statistician; Co-Investigator		5/15/2018
Ralph B. D'Agostino Jr.	Sn. Statistician; Co-Investigator	Ralph B. D'Agostino Jr.	5/23/2018

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1 LIST OF ABBREVIATIONS

Term	Abbreviation
COMPASS	Comprehensive Stroke Services
NCSCC	North Carolina Stroke Care Collaborative
SIS-16	Stroke Impact Scale - 16
PHQ	Patient Health Questionnaire
MOCA	Montreal Cognitive Assessment
MGLS	Morisky Green Levine Scale
CSI	Caregiver strain index
PROMIS	Patient reported outcome measurement information system
CAHPS	Consumer Assessment of Healthcare Providers and Systems
LMM	Linear mixed model
MICE	Multiple imputation by chained equations
PCP	Primary care provider
PP	Per protocol
CACE	Complier average causal effect
SACE	Survivor average causal effect
IV	Instrumental variable
Blood Pressure	BP
Intent-to-Treat	ITT
Transient Ischemic Attack	TIA

2 INTRODUCTION

The COMPASS Study is a pragmatic, cluster-randomized trial of 41 hospitals in North Carolina and is designed to evaluate the effectiveness of a model of post-acute stroke care (i.e. the COMPASS Care Model Intervention) compared with usual care (control). The COMPASS Study includes two phases. Forty-one hospitals were randomized as 40 units to either receive the COMPASS Intervention at the beginning of the trial (Phase 1) or at the start of Phase 2 (two hospital were randomized together as one unit). Hospitals transition into Phase 2 after approximately 1 year of enrollment or when key enrollment milestones are met. Hospitals randomized to receive the COMPASS Intervention during Phase 2 represent the usual care comparator group during Phase 1. This statistical analysis plan addresses the analysis of data collection during Phase 1 of the trial. A separate analysis plan will be written for Phase 2. A separate addendum to this analysis plan will be prepared for the analysis of claims-based secondary endpoints.

3 STUDY DESIGN

3.1 Study Population

In 2013, data from hospitals in the North Carolina Stroke Care Collaborative (NCSCC) indicated that 46% of patients were discharged directly home from the hospital after a stroke or TIA (our proposed study population). In that population, the mean age was 65.0 years (SD 14.4), 25% were African American, and 48% were women. Stroke severity, measured by the NIH Stroke Severity score and ranging from 0 (no deficit) to 42 (maximum deficits), was on average 3.2 for those discharged home.

3.2 Randomization

Individual stroke patients cannot easily be randomized to receive the COMPASS Intervention. Accordingly, the COMPASS Study utilizes stratified cluster randomization with each of the 41 individual hospitals being randomized to either receive the COMPASS Intervention at the beginning of the study (Phase 1) or in Phase 2. Two of the participating 41 hospitals required paired randomization due to having shared staff, resulting in a total of 40 randomized units. The randomization of hospitals was stratified by annual stroke patient volume (2 levels: Large, Medium or Small) and whether the hospital is a primary stroke center (2 levels: primary or comprehensive stroke center, neither) resulting in a total of four strata.

3.3 Sample Size Calculations & Statistical Power

Details on sample size calculations and statistical power for the COMPASS study can be found in Duncan et al [1]. Calculations were based on sample size of 6000 participants from 40 randomization units. Under these assumptions, the study will have 83.2% power to detect a 4.17 unit difference in the SIS-16 score for patients in the two groups (assuming a standard deviation of 16.1)[2]. This assumes that 90% of patients will be evaluated at 90 days, an intra-class correlation of 0.036 (based on preliminary data from NCSCC hospitals), and a detectable effect of 0.192 times the within-group standard deviation. The COMPASS Study was also designed to detect differences within subgroups of interest that comprise at least 20% of the overall sample (e.g., stroke subtype, severity, insurance status, geographic area of residence, race, and gender).

Based on preliminary data during the first year of the COMPASS study, it became apparent that approximately 60%-65% of participants would have an ascertained outcome and that the distribution of sample sizes across the clusters was more heterogeneous that originally expected. Therefore, the data analysis core re-estimated the statistical power based on the following revised assumptions:

1. Final enrollment for each hospital could be accurately predicted based on the hospital's average enrollment rate at that point in the trial.
2. The number of hospitals enrolling participants would be 39.
3. The total number of participants enrolled would be approximately 5973.
4. Response rate for the primary outcome would be approximately 65% and would be consistent across hospitals leading to an effective sample size of approximately 3882 participants.

In order to make optimal use of the available information, updated power calculations were based on simulation studies using a linear mixed model rather than a simple formula and using the estimation methods to be used for the primary endpoint analysis. Table 1 presents simulation-based estimates of power for several different scenarios.

Table 1: Power Analysis based on Initial and Revised Assumptions

Within-Cluster Standard Deviation σ	Intraclass Correlation	Mean Difference μ	Effect Size μ/σ	Power[1]	
				Initial Assumptions[2]	Updated Assumptions
16.1	0.036	4.17	0.26	0.96	0.91
		4.59	0.28	0.99	0.96
		5.00	0.31	0.99	0.98
		5.42	0.34	0.99	0.99
16.1	0.072	4.17	0.26	0.78	0.70
		4.59	0.28	0.85	0.79
		5.00	0.31	0.90	0.86
		5.42	0.34	0.94	0.90

[1] Each power estimate is based on 20,000 simulated trials.
[2] Initial power estimates are based on simulation.

4 PRIMARY AND SECONDARY OBJECTIVES

4.1 Primary Objective

The primary objective of the COMPASS Study is to evaluate the comparative effectiveness of the COMPASS Intervention compared to usual care with respect to improving stroke survivor functional status (measured by the Stroke Impact Scale) at 90 days post-discharge.

4.2 Secondary Objectives

The key secondary objectives of the COMPASS Study are as follows:

1. Evaluate comparative effectiveness of the COMPASS Intervention with respect to reducing caregiver strain (measured by the Modified Caregiver Strain Index) at 90 days post-discharge.
2. Using responses from the 90-day patient survey, evaluate whether the COMPASS Intervention improves general health, global disability, physical activity, depression (PHQ2), cognition (Mini MOCA), medication adherence (MGLS-4), management of blood pressure, incidence of falls, incidence of fatigue, and satisfaction with care.
3. Evaluate the effectiveness of the COMPASS Intervention in key patient subgroups based on race, sex, age, diagnosis (stroke versus TIA), stroke severity, and type of health insurance.
4. Endpoints to be addressed in SAP Addendum: Using claims data from multiple payer sources up to 12 months after stroke hospitalization, evaluate comparative effectiveness of the COMPASS Intervention with respect to the following outcomes:
    a. all-cause hospital readmissions at 30 days, 90 days, and 1 year post-discharge
    b. all-cause mortality up to 1 year post-discharge
    c. healthcare utilization (emergency department visits, admissions to skilled nursing facilities/inpatient rehabilitation facilities) up to 1 year post-discharge
    d. use of transitional care management billing codes

5 PRIMARY AND SECONDARY ENDPOINTS

5.1 Primary Endpoint – Stroke Impact Scale 16

The primary endpoint for the COMPASS Study is physical functioning as measured by the Stroke Impact Scale 16 (SIS-16)[2] at 90 days post-discharge. The SIS-16 instrument is a 16-item survey that assesses the difficulty level of performing basic physical activities (e.g., dressing oneself) over the most recent two week period. For each item, responses are provided on the following 5-point Likert scale:

Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
5	4	3	2	1

A raw score is obtained for each participant by summing individual item scores. For participants who complete all 16 items, the maximum possible raw score is 80 and the minimum possible raw score is 16. A survey is considered scoreable if a participant answers at least 12 of the 16 items. Standardized scores are computed for each valid raw score using the following formula:

$$\text{analysis score} = \frac{\text{raw score} - n}{5n - n} \times 100,$$

where n is the number of items answered by the participant. Thus, the standardized scores for all participants will have a possible range from 0 to 100 with larger scores corresponding to outcomes that are more favorable.

Ninety-day patient outcomes were assessed through telephone interviews by trained and blinded interviewers using Computer Assisted Telephone Interviewing (CATI) software. For participants who could not be reached by phone (e.g., invalid phone number, 10 call attempts with no answer), an abbreviated survey was subsequently sent by mail to the participant address on record. This mailed survey included only the SIS-16, self-rated health, and last measured blood pressure. In the rare event that a participant completed a telephone and mailed survey, the SIS-16 from the telephone survey was selected as the participant's SIS16 outcome unless fewer than 12 items were completed. In such cases, the SIS-16 outcome from the mailed survey was selected. Although the 90-day survey would ideally be completed approximately 90 days after discharge, all scoreable surveys will be included in the primary analysis regardless of the precise time of completion.

5.2 Secondary Endpoints Based on 90-day Surveys

5.2.1 Modified Caregiver Strain Index

The Modified Caregiver Strain Index (CSI) can be used to assess caregiver strain with familial caregivers [3]. This tool measures strain that caregivers may experience in the following domains: Financial, Physical, Psychological, Social, and Personal. To complete the survey, caregivers respond to 13 statements regarding the care they provide. Example statements include "My sleep is disturbed (For example: the person I care for is in and out of bed or wanders around at night)" and "Caregiving is inconvenient (For example: helping takes so much time or it's a long drive over to help)". Responses to each of the 13 statements are scored according to the following criteria:

- 2 = Yes, on a regular basis
- 1 = Yes, sometimes
- 0 = No

For participants who complete all 13 items, the maximum possible raw score is 26 and the minimum possible raw score is 0. A survey is considered scoreable if a caregiver answers at least 10 of the 13 items. Standardized scores are computed for each valid raw score using the following formula:

$$\text{analysis score} = \frac{\text{actual raw score}}{2\text{n}} \times 100,$$

where n is the number of items answered by the participant. Thus, the standardized scores for all participants will have a possible range from 0 to 100 with larger scores indicating more caregiver burden.

The caregiver survey is mailed to all eligible caregivers on record approximately 95 days after patient discharge. Not all participants indicated having a caregiver. Caregivers of patients who died prior to 90 days, are residing in a facility, or who withdraw from the study are not mailed a survey.

5.2.2 Self-Reported General Health

Participants are asked to self-rate their general health since their stroke or TIA using the following 5-point Likert scale:

Compared to others your age, how would you rate your health since your stroke using a scale between 1 and 5 with 1 being “poor” and 5 being “excellent?”	**Poor**	**Fair**	**Good**	**Very Good**	**Excellent**

Self-reported general health will be analyzed as a continuous variable. Following [4], these responses will be transformed for analysis according to the following criteria:

- Excellent = 95
- Very Good = 90
- Good = 80
- Fair = 30
- Poor = 15

5.2.3 Secondary Prevention – Home Blood Pressure Monitoring

Participants are asked whether they monitor their blood pressure at home (yes or no) and, if they answer in the affirmative, how frequently (daily, weekly, and monthly). Home blood pressure monitoring will be analyzed as a dichotomous endpoint (monitoring with any frequency versus no monitoring).

5.2.4 Self-Reported Blood Pressure

Self-reported systolic and diastolic BP will each be analyzed as a continuous endpoint. In addition, self-reported systolic and diastolic BP will be used to create a dichotomous hypertension endpoint (systolic BP >= 140 versus systolic BP < 140).

5.2.5 Cognition – Montreal Cognitive Assessment (MoCA) 5-Minute Protocol

The MoCA 5-minute protocol is a brief cognitive protocol for screening for vascular cognitive impairment [5], [6]. The tool includes 4 items from the full MoCA and examines attention, verbal learning and memory, executive functions/language, and orientation. Each of the four items are scored separately and the scores are summed to obtain a total score that falls between 0 and 30 for analysis as a continuous variable.

5.2.6 Depression

The PHQ-2 is a 2-item questionnaire that inquires about the frequency of depressed mood and anhedonia over the past 2 weeks [7]. The first question asks how often the participant had little interest or pleasure in doing things and the second asks how often the participant felt down, depressed, or hopeless. Each of the two questions are answered using a Likert scale with the following scoring rubric:

- 0 = Not at all
- 1 = Several days
- 2 = More than half the days
- 3 = Nearly every day

The total score is the sum of the scores for the two questions and ranges from 0-6. For analysis, following standard screening criteria [7], the total score will be dichotomized (total score >= 3 versus total score <3).

5.2.7 Physical Activity

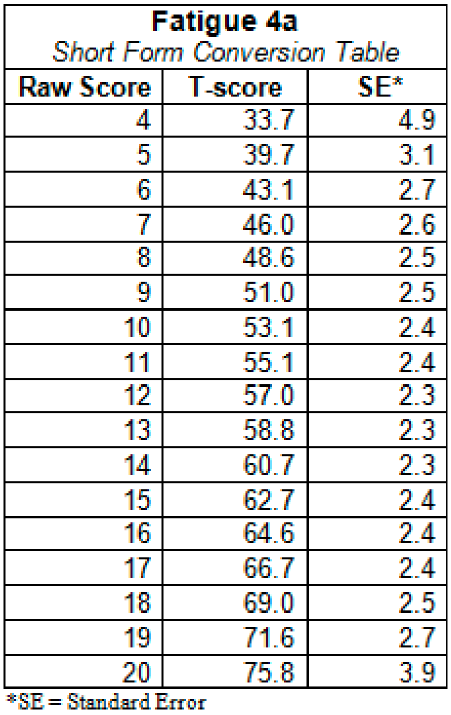
Physical activity is assessed in several ways. Patients are asked whether they walked continuously for at least 10 minutes on any of the last seven days, how many of those days they walked continuously for at least 10 minutes and how many minutes they walked, on average, each day. The physical activity endpoint will be self-reported total number of minutes walked during the past seven days. Total number of minutes walked will be log-transformed prior to analysis.

5.2.8 Fatigue

Degree of fatigue will be assessed using the PROMIS Fatigue Instrument [8]. This 4-question self-report instrument asks participants about their level of fatigue over the past 7 day period. Each of the 4 questions are answered using a Likert scale with the following scoring rubric:

1	2	3	4	5
Not at all	A little bit	Somewhat	Quite a bit	Very much

The total raw score is obtained by summing individual question scores and has a range of 4-20. For analysis, raw scores are translated into T-scores using the table show on the right. The T-score rescales the raw score into a standardized score with a mean of 50 and a SD of 10.



Fatigue 4a
Short Form Conversion Table

Raw Score	T-score	SE*
4	33.7	4.9
5	39.7	3.1
6	43.1	2.7
7	46.0	2.6
8	48.6	2.5
9	51.0	2.5
10	53.1	2.4
11	55.1	2.4
12	57.0	2.3
13	58.8	2.3
14	60.7	2.3
15	62.7	2.4
16	64.6	2.4
17	66.7	2.4
18	69.0	2.5
19	71.6	2.7
20	75.8	3.9

*SE = Standard Error

5.2.9 Falls

Participants are asked whether they have fallen (yes versus no) since hospital discharge, whether or not the fall resulted in a doctor/emergency room visit, whether they have fallen multiple times since discharge, and how many times they have fallen since discharge. Analysis of falls will be based on incidence of any fall since hospital discharge (no falls versus at least one fall).

5.2.10 Disability and Dependence – Modified Rankin Scale

The Modified Rankin Scale measures the degree of disability or dependence in daily activities for people who have suffered a stroke [9]. The scale ranges from 0-6 according to the following criteria:

0 - No symptoms

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent

6 - Dead

Since 90-day survey respondents are alive at the time of survey completion, survey responses will fall between 0 and 5. A value of 6 will be assigned for all participants who are confirmed to have died prior to completion of the 90-days outcomes protocol based on the North Carolina state mortality database.

5.2.11 Four-Item Morisky Green Levine Scale (MGLS-4)

The Morisky Green Levine Scale (MGLS-4) is a generic self-reported, medication-taking behavior scale, validated for hypertension, but used for a wide variety of medical conditions. The instrument consists of four items with yes/no response options [10] which are scored as 1/0, respectively. The items are summed to obtain a total score that is classified into the following groups:

- High adherence – total score = 0
- Medium adherence – total score = 1 or 2
- Low adherence – total score = 3 or 4

Medication adherence will be analyzed as a three category ordinal variable.

5.2.12 Satisfaction with Care

Participant satisfaction with care will be assessed using the Consumer Assessment of Health Plans and Services Clinician and Group Survey (CG-CAHPS, version 3.0). This instrument includes 6 questions that ask about how often the patient's doctors explained concepts in a way that was easy to understand, listened carefully, knew important medical history, showed respect for what the patient had to say, spent sufficient time with the patient, and talked about all of the patient's prescription medications. The individual questions are answered using a Likert scale with the following scoring rubric:

- 1 = Never
- 2 = Sometimes
- 3 = Usually
- 4 = Always

A total raw score is obtained by summing the individual question scores and has a range of 4-24 if all questions are answered. Standardized scores will be computed for each valid raw score using the following formula:

$$\text{analysis score} = \frac{\text{actual raw score}}{4\text{n}-\text{n}} \times 100,$$

where n is the number of items answered by the participant. Thus, the standardized scores for all participants will have a possible range from 0 to 100 with greater scores indicating more satisfaction with care.

6 ANALYSIS POPULATIONS

In the COMPASS Study, data are collected during the initial hospital stay, follow-up clinical assessments for the intervention arm (by telephone and at an in-person clinic visit), during a telephone survey, and potentially by mailed survey. Use of the data from different sources are subject to different patient consent requirements per the study IRB. The analysis populations defined below specify broad collections of patients that will be used for analyses. Particular analyses may be further restricted based on specific consent requirements for the data being analyzed.

6.1 Intent-to-Treat Analysis

The Intent-to-Treat (ITT) population will include all patients who are enrolled in the study. Participants re-enrolled for subsequent stroke or TIA events are not included in the ITT population. This population will be used for the analysis of primary and secondary endpoints unless otherwise stated. For all intent-to-treat analyses, participants in the intervention arm of the study will be analyzed as having received the intervention regardless of which components, if any, they actually received. Intent-to-treat analyses will compare outcomes for intervention patients to those from usual care patients.

6.2 Per-Protocol Intervention Analysis

Participants in the intervention arm of the study will be subdivided into two categories: (1) participants receiving an eCare plan at the COMPASS clinic visit within 30 calendar days of hospital discharge, and (2) participants not meeting the criteria in (1). Participants meeting criteria (1) are referred to as Per-Protocol Intervention (PPI) participants and those meeting criteria (2) are referred to as non-PPI participants.

The goal of the Per-Protocol (PP) analysis is to estimate the complier average causal effect (CACE) of the COMPASS intervention compared to usual care. That is, the effect of the

COMPASS intervention compared to usual care among those patients who would comply with treatment recommendations (e.g., attend the clinic visit to receive an eCare Plan for intervention arm participants). This is done through the framework of compliance principle stratification [11]. Formal details of the analysis strategy are given in Section 7.5.

7 INTENT-TO-TREAT ANALYSIS OF THE PRIMARY ENDPOINT

As standardized SIS-16 scores are semi-continuous in nature, the primary analysis will be based on a *weighted* linear mixed model (LMM) that includes a hospital-specific random effect (i.e., random intercept), a four-level stratification variable (see Section 3.2), a treatment effect, a patient-level effect for diagnosis type (stroke versus TIA) and other patient-level potential confounders (or surrogates thereof) for which there is a meaningful imbalance between the two study arms (see Section 7.4.3).

The case-weights used for the LMM will be case-specific inverse probabilities for ascertainment of the primary outcome. This approach is commonly referred to as inverse probability weighting (IPW) or simply weighting using propensity scores. Estimation of the case-specific propensities is described in Section 7.1. Estimation of the weighted LMM will be performed using restricted maximum likelihood methods. Degrees of freedom for tests of the treatment effect will be estimated using the method of Kenward and Roger [12]. The pre-planned adjustment for diagnosis type is justified by the fact that TIA patients (on average) are hypothesized to have better functional outcomes than stroke patients and by including this covariate, the analysis should have added precision and increased power.

Since the COMPASS Study randomizes hospitals and not patients, the randomization does not ensure balance with respect to patient characteristics across the two study arms. As a result, statistical analyses that do not adjust for potential confounders may be biased. In order to assure that analysis of the primary endpoint is robust, we will consider adjustments for potential confounders that are both meaningfully imbalanced across the two study arms and potentially casually related to the primary outcome. Candidate confounders include the following: race (white versus non-white), age, diagnosis (stroke versus TIA), NIH Stroke Scale Score (NIHSS), history of stroke or TIA, presence of multiple comorbidities, ability to ambulate prior to admission, ability to ambulate at discharge, having a primary care provider (PCP), whether the patient has medical insurance, and number of and type of therapy referrals prior to discharge.

7.1 Primary Outcome Ascertainment and Bias Correction through IPW

Based on preliminary data from the COMPASS Study, we expect that primary outcome ascertainment will occur for approximately 60%-65% of patients and >=60% of patients in each study arm. Due to the significant number of missing primary outcomes, a complete case analysis could be biased. Accordingly, the primary analysis will account for primary outcome nonresponse by weighting cases with an observed outcome based on the inverse of their propensity for outcome ascertainment as estimated using a logistic regression model. If the data suggest a cluster-specific effect on outcome ascertainment, we will consider conditional logistic regression which has been shown to avoid bias due to cluster-specific nonignorable nonresponse [13].

Propensities will be estimated separately for each study arm using common set of covariate predictors. The set of predictors will be selected prior to any unmasked analyses of any primary or secondary endpoint data. Candidate predictors include the following: race (white versus non-white), age, diagnosis (stroke versus TIA), NIHSS, history of stroke or TIA, presence of multiple comorbidities, ability to ambulate prior to admission, ability to ambulate at discharge, having a PCP, whether the patient has medical insurance, and number and type of therapy referrals prior to discharge.

Patients who die prior to the date of the 90-day survey will be excluded from the analyses that estimates case-specific propensities and from the actual primary analysis. Thus, the primary analysis will effectively be performed *conditional on 90-day survival*.

7.2 Multiple Imputation to Address Covariate Missingness

Preliminary data from the COMPASS Study suggest that several important baseline characteristics will be missing for 10% to 30% of patients. These characteristics include NIHSS (approximately 15%) and ambulatory status at discharge (22%). We will use multiple imputation by chained equations (MICE) [14] to impute missing NIHSS, ambulatory status at discharge, and other potential confounders as necessary. Primary and secondary endpoint analyses will be based on 100 imputed datasets. For each imputed dataset, the IPW analysis procedure described above will be performed and the parameter estimates will be combined across imputed datasets using standard techniques [15]. Thus, the primary ITT analysis can be viewed as a combination of multiple imputation to address covariate missingness and inverse probability weighting to address failed outcome ascertainment.

7.3 Assessment of a Treatment by Diagnosis Interaction

While we *a priori* expect for both stroke and TIA patients to benefit comparably from the COMPASS Intervention, it is plausible that the benefit to TIA patients could be less than that for stroke patients owing to the comparatively less severe nature of TIAs. To that end, we will assess the degree to which the data support the assumption of a homogeneous intervention effect for both stroke and TIA patients as a first step in the primary analysis. This will be done by fitting an augmented weighted LMM that includes a treatment by diagnosis type interaction and by formally testing the interaction at significance level 0.10. If the interaction is not statistically significant at level 0.10, the primary ITT analysis will be performed at level 0.05 as described above. However, if the interaction is significant at level 0.10 the primary ITT analysis will be performed by assessing the impact of the COMPASS Intervention on both stroke and TIA patients separately from a single model with the familywise type I error rate controlled using the Hommel's method [16].

7.4 Supplemental/Sensitivity ITT Analyses for the Primary Endpoint

7.4.1 Possible Ceiling/Floor Effect & Other Violations of LMM Assumptions

Because of the bounded nature of standardized SIS-16 scores and the significant proportion of TIA patients enrolled in the COMPASS study (approximation 35%), there is a potential for a ceiling effect whereby a non-negligible proportion of the patient population experience the most extreme outcomes supported by the instrument. In these cases, the assumption of normality for the weighted LMM is not tenable though the linear model in known to provide robust inference in many cases. If 15% or more of cases have a SIS-16 outcome equal to the ceiling of the instrument, we will perform a secondary analysis based on a categorical SIS-16 outcome with categories defined using the quintiles of the observed SIS-16 scores. A weighted ordinal logistic regression model will be used for this analysis. More generally, we will use standard diagnostic tools to assess the appropriateness of the normality assumption (e.g., QQ-plots) and, if approximate normality of the residuals is not tenable, similar sensitivity analyses will be performed to supplement the primary analysis that do not make that assumption.

7.4.2 Primary Endpoint Truncation by Death

Some deaths are expected to occur prior to the 90-day outcomes period. For these patients the 90-day SIS-16 outcome is not missing, it is simply undefined. To explore the impact of the COMPASS Intervention on 90-day mortality, we will perform an analysis of 90-day mortality using a logistic mixed regression model with hospital-specific random effect. Since morality will be assessed by linkage with the North Carolina mortality database, IPW methods will not be required for this analysis. In order to assure this analysis is robust, we will consider adjustments for potential confounders that are both meaningfully imbalanced across the two study arms and potentially related to the death. Candidate confounders include the following: race (white versus non-white), age, diagnosis (stroke versus TIA), NIHSS, history of stroke or TIA, presence of multiple comorbidities, ability to ambulate prior to admission, ability to ambulate at discharge, having a PCP, whether the patient has medical insurance, and number of and type of therapy referrals prior to discharge.

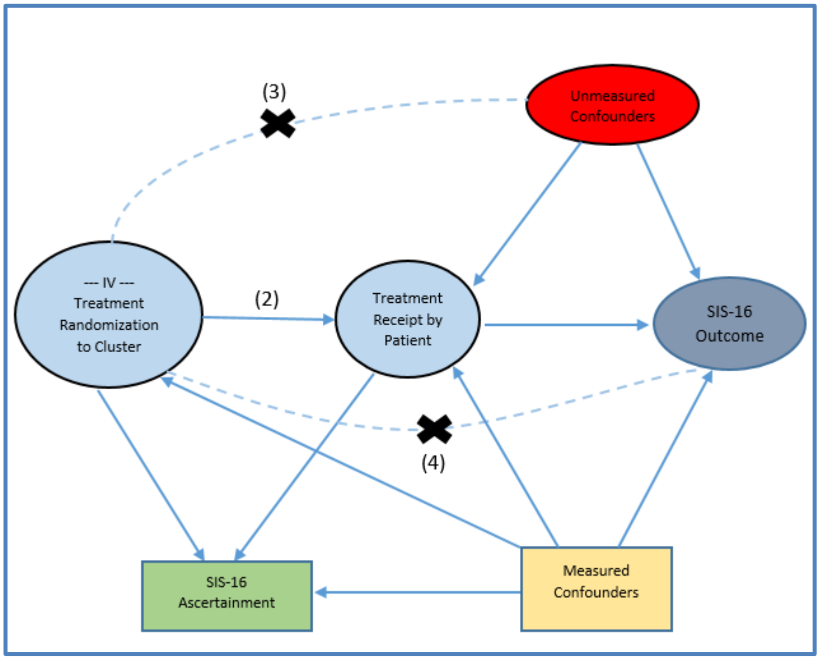
As described in Section 7.1, the planned ITT analysis will include patients who survive at least 90 days after discharge. Based on our preliminary linkage with the NC state death index, a blinded look at the percentage of participants who died within the first 90 days post-discharge suggests that the observed mortality rate will be very low for the COMPASS Study (approximately 1.5% - 2.5%). When death rates are this low, the planned analytic approach emits an approximate estimator for the Survivor Average Causal Effect (SACE). Deriving an unbiased estimator of the SACE in our study is complicated by the fact that 35% - 40% of outcomes will not be ascertained for reasons other than death. There are a dearth of statistical methods that formally address SACE estimation in the presence of failed outcome ascertainment where a small portion of non-ascertained outcomes are due to death.

Our statistical methods team has begun work to develop an extension of the work of Hayden et al. [14] that appropriately addresses the challenges presented by failed outcome ascertainment mainly due to participant refusal but due to death in a small number of cases. This approach weights observations by the probability of survival for a given participant (under the alternative treatment) and inversely by the probability of having an ascertained outcome conditional on survival to 90-days (c.f. equation (6) on page 306 of Hayden et al.) but relies on additional assumptions. Our analytic team will implement this new methodology as a sensitivity analysis to the planned ITT analysis.

7.5 Per-Protocol Analysis of the Primary Endpoint

The goal of the per-protocol analysis (PP) is to estimate the complier average causal effect (CACE) for the COMPASS intervention. To do this, we take an approach based on instrumental variables (IV)[17], viewing the randomization of treatment to hospital cluster as an instrument. Figure 1 presents the directed acyclic graph illustrating the relationship between COMPASS intervention randomization to hospital cluster, receipt of COMPASS care model (i.e., eCare Plan) by patient, the primary outcome, and unmeasured confounders.

Figure 1: Instrumental Variable Directed Acyclic Graph



There are several core assumptions of IV analysis:

(1) Stable Unit Treatment Value Assumption [18], [19] – The assumption that the treatment affects only the subjects taking the treatment and that there are not different versions of the treatment that have different effects.

(2) IV is positively correlated with treatment received.

(3) IV is independent of unmeasured confounders (conditional on covariates)

(4) Exclusion Restriction – The assumption that the IV affects outcomes only through its effect on the treatment received. There is no direct effect of treatment assignment on the outcome.

(5) Monotonicity – The assumption that there are no "defiers" who would only receive the intervention if they were randomized to usual care.

Each of these assumptions is tenable for the COMPASS study as discussed below:

(1) Assumption 1: The COMPASS care model is delivered primarily through a patient-specific eCare Plan constructed from a standardized battery of assessments by trained

medical personnel who receive comprehensive training during a startup Bootcamp and consistent reinforcement through ongoing webinars, all of which are led by the COMPASS Study Implementation Team. There is considerable effort to ensure the model is implemented consistently across enrolling hospitals. While there is variability in system-level resources, all hospitals that take part in the COMPASS study have sufficient infrastructure to administer the care model effectively.

(2) Assumption 2: This assumption holds since one cannot receive the COMPASS care model at hospitals other than those randomized to the intervention arm in Phase I and many of the patients who are enrolled at hospitals randomized to administer the COMPASS intervention do receive the care model as designed.

(3) Assumption 3: The COMPASS study randomization was stratified by whether a hospital was a primary stroke center and by stroke volume to ensure these important system level characteristics are independent of treatment assignment.

Our PP analysis will consider adjustment for several patient-level characteristics, which are believed to be potential confounders to minimize the possibility that any unmeasured confounder remains correlated with treatment assignment after covariate adjustment. Candidates for covariate adjustment include: race (white versus non-white), age, diagnosis (stroke versus TIA), NIHSS, history of stroke or TIA, presence of multiple comorbidities, ability to ambulate prior to admission, ability to ambulate at discharge, having a PCP, whether the patient has medical insurance and/or the type of medical insurance (e.g., private, Medicare, Medicaid, etc.), and number and type of therapy referrals prior to discharge, and number of and type of therapy referrals prior to discharge.

(4) Assumption 4: The core component of the COMPASS care model is receipt of an eCare Plan at the COMPASS clinic visit. Patients are unlikely to benefit meaningfully from the intervention unless they attend this visit and receive an eCare Plan and so it is unlikely that patient outcomes are affected by hospital assignment to the COMPASS intervention by means other than receipt of the customized eCare Plan.

(5) Assumption 5: The assumption of monotonicity (5) is met for the COMPASS Study since no participants at usual care hospitals are able to receive the COMPASS eCare Plan. Though there is potential for a participant to enroll at a usual care hospital, experience a subsequent event and reenroll at an intervention hospital, such an occurrence should be exceedingly rare.

Two-Stage least squares estimation will be performed for the instrumental variables analysis as described in [17]. To account for the clustered nature of our data, robust standard errors will be computed as described in [20]. The first stage regression model will regress the outcome *receipt of an eCare plan at the clinic visit within 30 calendar days* onto the hospital-level characteristics (e.g., stroke volume, primary stroke center status) and a subset of the following patient-level characteristics: race (white versus non-white), age, diagnosis (stroke versus TIA), NIH Stroke Scale Score (NIHSS), history of stroke or TIA, presence of multiple comorbidities, ability to ambulate prior to admission, ability to ambulate at discharge, having a primary care provider (PCP), whether the patient has medical insurance and/or the type of medical insurance (e.g., private, Medicare, Medicaid, etc.), and number and type of therapy referrals prior to discharge.

7.5.1 Correction for Selection Bias Due to Missing Outcomes

Use of instrumental variables offers no protection from selection bias related to outcome ascertainment [21]. Since the SIS-16 outcome is only ascertained for a subset of patients and because we have observed a modest imbalance between the two study arms in ascertainment rates, it is also important to account for any characteristics that influence outcome ascertainment that are potentially causally related to the outcome of interest. To account for selection bias associated with outcome ascertainment, we will use the IP weights from the Intent-to-Treat analysis in the two-stage least squares estimation procedure. This has been shown to improve the quality of IV estimation in the presence of selection bias [22].

7.5.2 Missing Covariate Data

Due to missing values of some covariates, the two-stage least squares process will be repeated for 100 datasets with missing data filled in by multiple imputation using MICE. Robust standard errors will be estimated for each imputed dataset. The results will be combined using standard techniques [15].

8 ANALYSIS OF SECONDARY ENDPOINTS BASED ON 90-DAY SURVEY DATA

Analysis of the secondary endpoints described in Section 5.2 will be performed using an analogous strategy to that described for the ITT and PP analyses for the primary outcome.

8.1 Analysis of Modified Caregiver Strain Index Endpoint

The modified CSI is assessed using a caregiver survey that is administered separately from the 90-day participant outcomes survey. The set of factors that influence a caregiver's propensity to respond to the caregiver survey may be different from those that influence a participant's propensity to response to the 90-day outcomes survey. Accordingly, weighted LMM analyses of the CSI will weight caregivers based on the inverse of their propensity for CSI outcome ascertainment estimated using the same procedure as for the primary endpoint. Candidate predictors for inclusion in the IPW model include the following patient characteristics: race (white versus non-white), age, diagnosis (stroke versus TIA), NIHSS, history of stroke or TIA, presence of multiple comorbidities, ability to ambulate prior to admission, ability to ambulate at discharge, having a PCP, whether the patient has medical insurance, and number and type of therapy referrals prior to discharge, and number of and type of therapy referrals prior to discharge. For this endpoint, we will also consider adjustment for gender of the caregiver and relationship with the participant. Just as with the SIS-16 instrument, the CSI is subject to a potential ceiling (or floor) effect. Therefore, as necessary, we will perform sensitivity analyses mirroring those described in Section 7.4.1 for the CSI.

8.2 Analysis of Other Patient-Reported Secondary Endpoints

The mailed survey that is sent after sufficient unsuccessful attempts to complete the 90-day outcomes call only collects the SIS-16, self-rated health, and blood pressure endpoint data. For analysis of these secondary endpoints, the propensity scores from the primary endpoint analysis will be used. For secondary endpoints only collected by phone, separate propensity scores will be estimated. Depending on the nature of the secondary endpoint, the analysis model will be a linear mixed model (continuous endpoints), a logistic mixed model (binary endpoints), or an ordinal logistic mixed model (multi-category ordinal endpoints). The set of potential confounders that are relevant to the analysis of each of the secondary endpoints will vary (e.g., history of hypertension will be highly relevant to BP related outcomes but not so for many other secondary endpoints).

Several secondary endpoints are defined based on a standardized instrument that has a small number of items (e.g., MoCA, PROMIS Fatigue Instrument, MGLS-4, and PHQ-2). In these cases, partial completion of the instrument results in a sizeable fraction of missing information on the outcome. In instances where one or more items on such instruments are missing, remaining missing items will be imputed using MICE for analysis. The imputation model will be based on the non-missing items for the instrument and baseline characteristics relevant to the endpoint in question. Because partially completed instruments will have missing values imputed, propensity score models will include partial completion as an observed outcome.

9 SUBGROUP ANALYSES

For reasons described in Section 7.3, the primary analysis will assess the degree to which the effect of the COMPASS Intervention varies with patient diagnosis (stroke versus TIA). In addition to this assessment, it is of *a priori* interest to examine the comparative effectiveness of the COMPASS Intervention in key subgroups of the studied population. We will examine the comparative effectiveness of the COMPASS Intervention in the following subgroups:

- Race – White, Non-White
- Sex – Male, Female
- Age – <45, 45-<55, 55-<65, 65-<75, >=75
- Stroke severity – NIHSS=0, NIHSS=1-4, NIHSS>4
- Type of Health Insurance – Insured versus uninsured

For each of the characteristic above (e.g., race) and to the extent that samples size permits, we will evaluate the comparative effectiveness of the COMPASS Intervention against usual care within each of the corresponding subgroups (e.g., for whites and non-whites) using methodology analogous to that previously described for the primary and secondary endpoints. For a given endpoint and characteristic, a single model will be fit for all subgroups and will include subgroup-specific treatment effects.

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