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

DOCUMENTS:

1. Integrated Stroke Practice Unit (ISPU; Intervention) Model of Care Protocol
2. Comprehensive or Primary Stroke Center (CSC/PSC; Control) Model of Care Protocol

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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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PRINCIPAL INVESTIGATOR:

Kenneth Gaines, MD, MBA
Professor of Neurology
Vanderbilt University Medical Center

Barry Jackson, BA
Patient Co-PI

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TABLE OF CONTENTS **Page**

SUMMARY ……..

1. STUDY OBJECTIVES ……..

A. Hypotheses ……..

B. Primary and Secondary Outcomes……..

2. BACKGROUND……..

A. Rationale ……..

B. Supporting Data ……..

3. PATIENT AND STAKEHOLDER ENGAGEMENT……..

4. STUDY DESIGN ……

A. Disease-specific Enrollment Criteria……..

B. Randomization……

C. Site Selection……..

D. Patient Eligibility……

E. Study Aims……..

F. Patient Enrollment Procedures..……..

5. MODEL OF CARE – THE ISPU INTERVENTION……..

6. BASELINE AND FOLLOW-UP ASSESSMENTS AND LABORATORY EVALUATIONS……..

A. On-Study/On-Intervention Evaluations ……..

7. MANAGEMENT OF ADVERSE EXPERIENCES ……

8. STUDY MONITORING……

A. Data and Safety Monitoring Board (DSMB)……

B. Adjudication Committee (AC)……

C. Criteria for Intervention Discontinuation……

9. STATISTICAL CONSIDERATIONS ……

A. Sample Size……

B. Analyses……..

10. HUMAN SUBJECTS PROTECTIONS……..

A. Adequacy of Protection Against Risks……

B. Potential Risks to Subjects and Protections……..

C. Potential Benefits of the Proposed Research ……

D. Risk-to-Benefit Ratio……

E. Inclusion of Women and Minorities……..

F. Subject Confidentiality……..

G. Study Modification/Discontinuation……..

11. PUBLICATION OF RESEARCH FINDINGS ……

12. REFERENCES ……

SUMMARY

Patient support after stroke requires a long-term commitment, supporting the patient as they move through "nodes" of acute care, post-acute in-hospital care, subacute care (inpatient rehab, extended stay, etc.), and chronic care. The current standard of stroke care is the Joint Commission (JC)-certified Comprehensive Stroke Center or Primary Stroke Center (CSC/PSC) care system, a collection of proven processes of care, but an approach with a focus on acute care (and to a lesser extent the post-acute in-hospital care), with little coordination of care of the patient after discharge. The overall goal of C3FIT is to assess if patient outcomes are improved when the CSC/PSC system is supplemented with an Integrated Stroke Practice Unit (ISPU) system of care, a patient-centric model of care involving the patient's caregiver that coordinates care from the acute management through the rehabilitation and recovery of the patient.

The specific aim of this project is to assess superiority of patient-centric outcomes between the CSC/PSC and ISPU models in a cluster-randomized pragmatic trial conducted at approximately 18 clinical sites in the United States (US). The primary aim focuses on differences in 12-months post stroke quality of life (QOL) using the Stroke Impact Scale (SIS) and patient function using the Simplified Modified Rankin Scale (smRS). Secondary aims include other patient/caregiver-centered outcomes, including: (1) short-term function and QOL using the SIS and smRS; (2) control of stroke risk factors; (3) mortality, recurrent stroke rates, and hospital readmission rates; (4) Time At Home; (5) patient depression, using the Patient Health Questionnaire (PHQ-9); and (6) caregiver strain, using the Caregiver Strain Index (CSI). Finally, we aim to determine whether there are patient subgroups specifically responsive or resilient to the intervention, according to effect modification by age, race, sex, and socio-economic status (income and education).

Study Design. C3FIT is a multicenter, randomized, single blinded, Phase III, cluster randomized trial. Sites will be stratified by patient admission volume and geographic location; subsequently, each site will be randomized to one of two patient care management strategies: the CSC/PSC versus ISPU model.

Outcomes. C3FIT's primary outcomes are the SIS and smRS at 12 months.

Sample Size and Population. Based on the primary outcome, the study was originally designed for a total sample size of approximately 1800 patients, with approximately 18 sites. However, due to the challenges of the COVID-19 pandemic the sample size was decreased to 1,262 and the number of sites were increased to 22. The Statistical and Data Coordinating Center (SDCC) at the University of Alabama determined the change in sample size would not influence the study statistical measures and/or study power, and our funder, PCORI, approved of the changes.

Interventions. Coordinated care (including in-home/in-patient rehabilitation and skilled nursing or extended care facility visits) will be provided based on protocol-based coordination of post-acute in-home/facility care for ISPU Site patients, while CSC/PSC patients will be managed per standard CSC/PSC protocol with no additional study related management post discharge. Clinical site personnel will be provided with training specific to the arm to which they are randomized.

Duration. Patients will be followed at the site level for one year after enrollment.

1. STUDY OBJECTIVES

The current standard of stroke care is the JC-certified CSC/PSC care system, a collection of proven individual processes of care, but a system that lacks coordination for the post-stroke care of patients. The C3FIT trial serves as the opportunity to assess potential impact on patient QOL and functional outcomes resulting from the improved integration of care provided by the ISPU approach.

C3FIT's overall goal is to assess if patient outcomes are improved when the CSC/PSC system is supplemented with an Integrated Stroke Practice Unit (ISPU) system of care, a patient-centric model of care involving the patient and caregiver/family that coordinates care from the acute management through the rehabilitation and recovery of the patient.

A. Hypotheses

C3FIT's *Primary Hypothesis* is that the ISPU model of care will show improved mean level SIS and smRS scores at 12 months compared to the CSC/PSC model of care.

The *Secondary Hypotheses are*:

(1) The ISPU approach will improve secondary stroke outcomes relative to the CSC/PSC approach, including: SIS and smRS at 3 and 6 months, risk factor control, stroke recurrence rates, hospital readmission rates, mortality in the first 12 months, time at home, patient depression, and caregiver strain.

(2) The ISPU benefit in SIS and smRS will persist after the protocol-based post-acute coordination of in-home/facility care is terminated (at 12 months).

(3) Patient characteristics (specifically age, race, sex, income, and education) will affect the primary or secondary intervention differences.

B. Primary and Secondary Outcomes

Primary and secondary outcomes are documented in Table 1 and described below.

- *Primary outcomes* include patient function and QOL using the SIS and smRS at 12-months post-stroke.
- *Secondary outcomes* are patient/caregiver-centered and include: (1) short-term patient function and QOL using the SIS and smRS (at 3 and 6 months); (2) the proportion of patient with risk factors controlled at target (at 3, 6, and 12 months); (3) mortality in the first 12 months, time to first recurrent stroke, and number of hospital readmissions per participant month over the first 12 months; (4) Time At Home (proportion of survival time spent at home); (5) patient depression, using the Patient Health Questionnaire (PHQ-9; at 3, 6, and 12 months); and (6) caregiver strain, using the Caregiver Strain Index (CSI; at 3, 6, and 12 months).

Table 1. Study Outcome Measures and Assessment Frequency					
		ASSESSMENT FREQUENCY (By Month)			
C3FIT OUTCOMES	**VARIABLES**	**H**	**3**	**6**	**12**
Functional Assessment	Stroke Impact Scale	X	X+	X+	X+
Quality of Life	Simplified Modified Rankin Scale	X	X+	X+	X+
Stroke Risk Factors					
(1) Blood pressure control at target*	Standard Systolic and Diastolic Measurement	X	X	X	X
(2) Lipid control at target*	Standard Lipid Panel or, at a minimum, LDL (Blood Draw, repeated only if patient's cholesterol is elevated at baseline, if LDLC%≥70mg/dl, or if patient is on a statin)	X	X	X	X
(3) Diabetes control at target*	Standard HBA1c (Blood Draw, repeated only if patient's blood glucose is elevated at baseline or if HBA1C%≥7mg/dl)	X	X	X	X
(4) Smoking status*	Question(s) to assess patient smoking status	X	X	X	X
(5) Body Mass Index (BMI)*	Weight and hip circumference	X	X	X	X
(6) Diet	Question(s) to assess patient adherence to recommendations of the American Heart Association (AHA).	X	X+	X+	X+
(7) Exercise	Question(s) to assess patient adherence to recommendations of the AHA.	X	X+	X+	X+
Mortality*	Will be assessed at visits. If needed, medical records will be collected from site, and the Adjudication Committee will review.		X	X	X
Recurrent Stroke*			X	X	X
Rehospitalization*			X	X	X
Time at Home	Assesses Time at Home (patient or caregiver home) versus at institution (for hospitalization, IPR, and/or SNF).		X+	X+	X+
Depression (Patient)	Patient Health Questionnaire (PHQ-9)		X	X	X
Caregiver Strain	Caregiver Strain Index		X	X	X

*Results of these measures will be reported back to patient's treatment team for information/action.
+SRU only.
H: Collected at the Hospital prior to discharge by site personnel
IPR: In-patient rehabilitation facility
SNF: Skilled Nursing Facility

2. BACKGROUND

A. Rationale

Stroke is the 5th leading cause of death and the leading cause of adult disability[1-2], and approximately 780,000 have a stroke or transient ischemic attack (TIA) in the US each year. As many as 90% of the 5 million stroke survivors (roughly the population of South Carolina) have some functional deficit and live with sequelae of stroke[3]. The impact of stroke risk does not end there, as 17% of TIA patients and 18% of those with non-disabling stroke will experience a recurrent stroke within three months[4] and nearly one-third will have a recurrence within five years[5]. About 23% of annual stroke incidence is recurrent stroke, and mortality is greater after a second stroke than the first (24-month survival rates are 48% versus 57%)[1,6]. Persisting physical

and cognitive impairments affect not only the patient, but the caregiver and family experience both psychological and health quality impact[2,7,8].

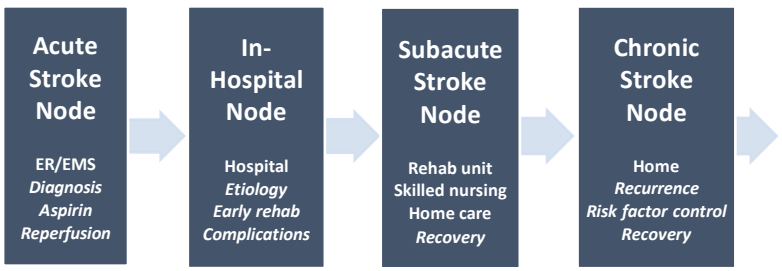
B. Supporting Data

The care delivery system for a typical US stroke patient during the first-year post-stroke is fragmented into four distinct Nodes of Care - from acute stroke through in-hospital care and then discharged to rehabilitation or skilled nursing facility (SNF) and/or finally (for most patients) home; see Figure 1. Each Care Node has distinct care delivery geography, personnel, and focus. This dissociated system fosters miscommunication and inefficient, uncoordinated care to the detriment of patient health[9].

Across these Stroke Nodes of Care, there is clear evidence of the effectiveness of therapies in isolation. For example,

- In the Acute Node, tissue plasminogen activator (tPA) and interventional therapies have been shown effective for stroke care[10-14,37].
- In the In-hospital Node, stroke units and quality improvement programs have been promulgated by the American Heart Association (AHA) [37] Get-With The Guidelines (GWTG)[34], JC[15,33], and CMS[35].
- In the Subacute or Chronic Care Nodes that follow hospital discharge, comprehensive risk factor management[16,17] and early rehabilitation[37] has been shown to work[60]. Effective secondary prevention is fostered by patient and caregiver/family engagement, medication compliance, and caregiver engagement, particularly during the first year[16,17].

Figure 1. Nodes of Stroke Care Across the Continuum



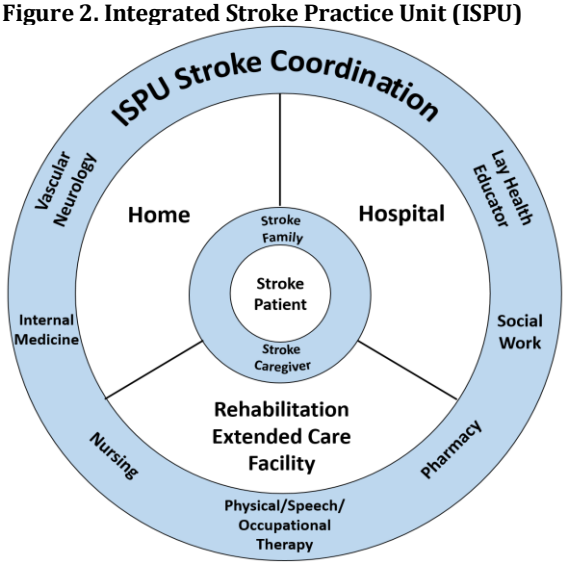
A review of post-stroke risk factor management projects from the scientific literature was conducted that included the most difficult targets, for example, smoking cessation, exercise, diet, and risk factor education. Standard stroke care often includes variable risk factor control patient education and limited team-based and caregiver/family focus, as well as a clinic-based focus. Joint Commission (JC)-certified Comprehensive and Primary Stroke Center (CSC/PSC) care offers some improvements on the acute, in-hospital side, defining risk factor management at discharge only and incorporating in-patient education but limits outpatient care to only a 30-day clinic visit with no team based coordination or caregiver/family focus[15]. Studies like ICARRUS[18], SAMMPRIS[23,24], WASID[19], PROTECT[44], PREVENTION[20], Stop Stroke[45], and COMPASS[36] have incorporated various aspects of integrated care models. These studies have clearly documented improved outcomes and lower risk of subsequent stroke associated with the proper post-discharge management of risk factors; however, control of post-stroke risk factors at target remains at low levels.

While there are interventions proven effective in each of the nodes of care, it remains unknown whether a comprehensive system that coordinates care across the four nodes would improve patient and caregiver outcomes. It could be argued that such a coordination would better inform the down-stream nodes regarding the patient status and progress through the first year of care, and with this information the caregivers can provide more effective care of the patient. Alternatively, it could be argued that the interventions known to be effective in each of the nodes can operate effectively as independent activities, and efforts to coordinate care would only introduce confusion and complications that would lead to worse outcomes for the patient. The overarching goal of C3FIT is to address specifically this question, that whether the coordination of care across the four nodes of care provides better outcomes for the patient and his/her caregivers. There is clinical equipoise on this question in the stroke community. Background about the ISPU model of care will be discussed in further detail.

The IPU model of care provides the coordination and integration of care not found in any other previous design. Based on a concept originally proposed by Porter and evaluated in joint replacement, spine and cancer[26,28,29], the IPU model incorporates components of team-based care[26] (i.e. coordinated care in multiple specialty areas with a specified communication mechanism, like regular in-person/ virtual team meetings[25]), which have shown care delivery improvement[27] Combined with technology-enabled, home/facility-based access to multiple layers of care and more timely access to care, these represent key elements in delivering improved patient-centered outcomes. Given that caregivers also experience negative health-related QOL, engagement of both the patient and caregiver unit is also important to deliver positive outcomes[2,8] in an IPU.

Our research group conducted a three-year, single-site pilot study as part of a CMS HCIA (#1C1CMS331043). Post-stroke care that was both integrated and coordinated showed a positive impact on long-term outcomes, as well as higher patient satisfaction and improved risk factor control[46]. First devised as a NIH Office of Minority Health-funded grant in South Carolina (#CPIMP071044; PI: K Gaines)[47] and based on the IPU concept, we implemented a stroke-specific care model called an *ISPU (*see Figure 2) that informed and largely directed design of the ISPU arm of C3FIT. This pilot ISPU included two coordinated units that addressed the entire spectrum of care, from acute assessment, diagnosis and intervention (called *Stroke Central*) through hospital discharge to 1-year post-discharge care (called *Stroke Mobile*). Stroke Central was the care coordination component that extended from acute to hospital to home/facility, impacting complications, length of stay, and readmissions. The Stroke Mobile Care Team, comprised of a Registered Nurse (RN) and a Lay Health Educator, engaged patients and caregivers in their home and/or skilled nursing or rehabilitation facility. The Stroke

Figure 2. Integrated Stroke Practice Unit (ISPU)



Mobile Team was linked by telemedicine to higher levels of care (i.e., internal medicine, vascular neurology, rehabilitation physicians and therapists, pharmacists, and/or advanced practice providers) to address management issues in real time. We enrolled a large population of patients in tele-stroke (n=3000) at 30 spoke sites, in Stroke Central (n=3800), and in Stroke Mobile (n=547). Primary results were presented at the 2017 *International Stroke Conference*, and publications have been prepared and/or submitted. Figure 3 documents increased blood pressure (BP) control at target in our demonstration sample over one year of the ISPU design intervention. Table 3 documents decreases in urinary tract infections, stroke recurrence rates, readmission rates, cost per case, as well as, risk factor control for key stroke risk factors[22-24]. It should also be noted that patients in the CMS HCIA pilot who were on intervention and at goal exceeded published reports of both community and research populations, including SAMPRISS[24]. However, this project was not randomized, and assessment of change was restricted to a limited number of outcomes because of a demonstration project design. Unfortunately, there are not prospective randomized controlled US data documenting that implementation of a more-broad coordinated system developed as a natural extension of our pilot work will result in improved outcomes relative to the currently accepted intervention approaches. This is a critical area of needed research[2].

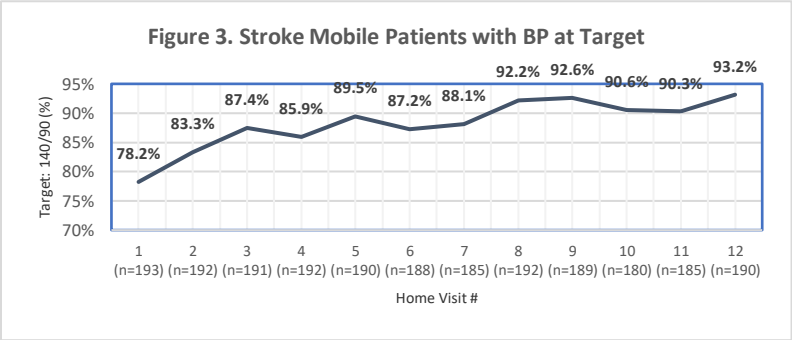


Table 3. Key Outcome Data CMS HCIA Pilot Study – Stroke Central and Stroke Mobile (ISPU Model)

STROKE CENTRAL: In-hospital Stroke Care Delivery Issues (Before/After Comparator)	EFFECTS ATTRIBUTED TO STROKE CENTRAL	STROKE MOBILE: Post-hospital Stroke Care Delivery Issues (Literature/Data Comparator[6])	On Intervention	Controlled	EFFECTS ATTRIBUTED TO STROKE MOBILE (Controlled At Target)
Complications occur in 85% of in-hospital strokes[1]	**UTI ↓ by 19%**	BP management	80%	27-44%	**95%**
Stroke recurrence occurs in 20% of cases in 90 days[2]	**↓ by 11%**	Smoking cessation	67%	15%	**57%**
Stroke readmission occurs in 12.7% of cases[3,4]	**↓ by 15%**	Statin	47%	42%	**80%**
Cost per case (retrospective before & after control)	**↓Total direct cost 8%**	Diabetes	76%	30%	**85%**

[1]Langhorne, 2000; [2]Oxfordshire. Stroke 1994; [3]Medicare Linkage Study. Stroke, 2011; [4]JAMA 2014; [5]AHA/ASA; [6]Mouradian, 2002; Kernan, 2000; Joseph, 1999; VISP, 2006.

3. PATIENT AND STAKEHOLDER ENGAGEMENT

Patient/caregiver research partners and other stakeholder partners are foundational to C3FIT and bring diverse perspectives and/or personal experience as stroke survivors, caregivers/family, care providers, clinical researchers, national clinical experts and organizational stakeholder partners such as payers and national advocacy groups.

We have developed a four-committee structure for engaging stakeholders in all aspects of C3FIT. Each Committee is described below.

- C3FIT's Steering Committee will provide overall supervision of study operations, procedures, fidelity of the intervention, and progress for the study. It will be jointly chaired by the Patient Co-PI and the physician Co-PI. Committee members include each Clinical Site PI, the Project Manager, the SDCC PI, the Chief Research Scientist, and the Chairperson of the Stakeholder Engagement Committee.
- C3FIT's Scientific Advisory Committee will oversee the study's scientific integrity and will be chaired by C3FIT's Chief Research Scientist. This committee includes stakeholder partners who are national experts in their fields. Broad representation consistent with a complex disease state will safeguard scientific rigor and trial integrity and included groups who are critical to dissemination and implementation of C3FIT results.
- C3FIT's Central Stakeholder Engagement Committee (SEC) will ensure that patient partner and stakeholder partner priorities are reflected in the study design, data analysis, and dissemination of study findings. It will include patient and caregiver/family partners along with care providers from multiple disciplines and representatives from two national patient advocacy groups. The Committee will be facilitated by the Engagement Coordinator, who will report the Committee and Clinical Site Engagement Groups' recommendations to the Steering Committee.
- Selected ISPU and CSC/PSC Sites will develop Clinical Site Stakeholder Engagement Groups, which will identify specific supplemental recruitment strategies, study implementation issues, and provide practical tips to support study subjects and care providers at their clinical sites. Each will include patients and caregivers/family along with care providers from multiple disciplines. The group will meet in-person two times per year at their respective sites and will be facilitated by clinical site personnel. Group input will be directed to the central study Stakeholder Engagement Committee.

4. STUDY DESIGN

C3FIT is a randomized comparative effectiveness trial (CET) of two care delivery methodologies at approximately 18 clinical sites. Primary and secondary outcomes are described in Section 1.

A. Disease-specific Enrollment Criteria

Clinical Indicators. Definitive stroke will be defined by ICD-10 code criteria. Definitions will be based on ICD-10 criteria (see Table 4). Investigators will use tests and assessments deemed appropriate for an individual patient to determine the appropriate diagnosis. Additional stroke subtype categorization will occur using the TOAST Criteria as performed by C3FIT clinical site investigators.

Prior Therapy. There is no exclusion for prior therapy.

Demographic Characteristics. The clinical sites have been carefully selected with the goal of providing nationwide representation, urban and rural representation, inclusion of both men/women and all race/ethnic groups affected by stroke. Patients aged 18 and older are eligible with no upper age exclusion criterion.

Contraindications. Since no drugs or experimental devices are utilized in this trial there are no specific contraindications.

Pregnancy Exclusions. There is no exclusion for pregnancy or planned lactation and no inherent risk from the proposed intervention.

B. Randomization

C3FIT is randomized at the facility (clinical site) level rather than the individual patient level. Randomization at the facility level is appropriate, as the proposed comparator arms could not be reasonably instituted at the patient level for a system change design. Sites will be stratified by patient volume and geography and randomized to management using the CSC/PSC or ISPU model.

C. Site Selection

C3FIT clinical site eligibility for inclusion is the JC CSC/PSC certification (or operating as such), which ensures that all sites will have well-established in-hospital care delivery programs and documented success in guideline-driven delivery of care that introduces a level of homogeneity among clinical sites. Sites with sufficient volume of stroke admissions were identified with selection was made with special consideration given to sites with populations that include diverse race/ethnic groups. At the patient level, all stroke patients with a stroke diagnosis who reside in a defined geographic region are potential candidates. Though JC CSC/PSC clinical sites tend to be located in largely urban areas, we will include geography in the target population that encompasses the index county and contiguous counties to include both a more diverse and more rural population.

D. Patient Eligibility

Inclusion and Exclusion Criteria are detailed below.

Inclusion Criteria:

- Age 18+.
- Clinical diagnosis of acute stroke with or without brain imaging compatible with intracerebral hemorrhage or ischemic stroke; see ICD 10 codes in Table 4.
- English or Spanish speaking subjects.
- Patient admitted within 7 days of their index stroke event.
- Patient is discharged alive and not to hospice care.
- Patient living at discharge within the geography of recruitment for that C3FIT site.
- Pre-morbid mRS/smRS of 0-1.
- Patient and/or surrogate give consent to participate after an informed consent process.
- Patients who go to rehabilitation inpatient therapy or other care facilities are eligible, as long as they reside in the geographic are of recruitment and do not go to hospice care.

Exclusion Criteria:

- Clinical transient ischemic attack (TIA)[38-41] is ***excluded*** even if there is a computerized tomography (CT) or magnetic resonance imaging (MRI) lesion corresponding to the clinical syndrome at presentation.
- Already enrolled or planned enrollment in another clinical trial for which participation in C3FIT would be compromised with regard to follow-up assessment of outcomes or continuation in C3FIT.
- Patients with a planned admission to hospice care prior to consent.
- Patients not anticipated to survive for 1 year due to neurological or other medical status (i.e., advanced cancer, hospice care, heart disease, etc.).
- Patients who in the opinion of the site investigator cannot be involved in follow up care.
- Inability or unwillingness of subject or legal guardian/representative to understand and cooperate with study procedures or provide informed consent.

Table 4. ICD 10 Codes for Stroke Included and Excluded from C3FIT

ICD 10 Codes for Stroke Included in C3FIT[48]: • I 60; non-traumatic subarachnoid hemorrhage • I 61: Non-traumatic intracerebral hemorrhage • I 62: Other and un-specified non-traumatic intracerebral hemorrhage • I 63: Cerebral infarction: • I 64: Stroke, not specified as hemorrhage or infarction
ICD 10 Codes Excluded from C3FIT[48]: • I 65: Occlusion and stenosis of pre-cerebral arteries, not resulting in cerebral infarction Cerebral artery stenosis without cerebral infarction • I 66: Occlusion and stenosis of cerebral arteries, not associated with cerebral infarction. (Cerebral artery stenosis without cerebral infarction) • I 67: Other cerebrovascular diseases (Cerebral arteries dissection, cerebral aneurysm non ruptured, hypertensive encephalopathy, Moya disease, Non-pyogenic thrombosis of intracranial venous system, cerebral arteritis, acute cerebrovascular insufficiency, posterior reversible encephalopathy syndrome, cerebral vasospasm and vasoconstriction, Reversible cerebrovascular vasoconstriction syndrome). • I 68: Cerebrovascular disorders in diseases classified elsewhere (cerebral amyloid angiopathy) • I 69: Sequelae of cerebrovascular disease (Multi infarct dementia) • G 45 (unless they meet criteria for I63) (Transient Ischemic attacks and related syndromes).

E. Study Arms

The proposed project will involve randomization to: (1) the ISPU model developed and tested in the CMS pilot, versus (2) the CSC/PSC model implemented as part of the program overseen by the JC. Specific differences between the two interventions are detailed in Table 5. During hospital stay, clinical care and risk factor management in the ISPU arm (and also the CSC/PSC arm) will continue to operate per existing JC and American Stroke Association (ASA) national guidelines.

Table 5. CSC/PSC Care compared to ISPU Care

Parameter	CSC/PSC	ISPU
Time Focus	Acute care hospital door-to-door and follow-up over 1 year	Continuum of care for 1-year
Goals	Process compliance	• Patient-centered QOL • Patient centered functional outcome
Measurement	Performance measures	• Functional outcome
Geography of Care Delivery	• Hospital • Post-hospital clinic Home health	• Hospital • Home- and caregiver/family-based post-stroke care (Stroke Mobile)
Integration with Rehabilitation	• Discharge summary and clinic follow-up	• Stroke Connect active in in-patient rehab centers and extended care facilities thru Stroke Mobile
Focus of Modification	Providers	Patient and family
Post-hospital Follow-up	Clinic	Home
Patient/Caregiver/Family-centered Care	No	Yes
Patient-centered Outcome	No	Yes

F. Patient Enrollment Procedures

In both CSC/PSC and ISPU Sites, study personnel will be responsible for approaching suspected stroke patients, describing the study, and providing an IRB-approved informed consent process for the patient and caregiver. Admission records will be reviewed frequently by the site personnel, and discharge diagnosis and zip code of residence of all patients admitted with stroke will be identified to determine inclusion.

During hospital discharge or within 5 business days post discharge ideally (to a maximum of 14 total days) patients meeting all inclusion/exclusion criteria for enrollment in C3FIT will be involved in an informed consent process, and once consent is obtained the subject will be given a unique identifier. After consent has been obtained, study personnel will obtain the location to which the patient will be discharged, discharge diagnosis by ICD code, primary and secondary outcomes and other baseline data. Caregivers may be consented at any time during the C3FIT study, but no data will be collected from them until consent is obtained.

In conjunction with our patient and caregiver stakeholders, we will develop and utilize a protocol-driven approach for approaching patients and caregivers about the study and where possible, both patients and caregivers will participate in the consent process. Training on patient identification and a video on the informed consent process will be developed at the Clinical Coordinating Center (CCC) based on the pilot experience. If questions arise from an individual approached for recruitment, our patient/caregiver research partners at each C3FIT Site may be engaged to assist.

Screening for potential recruitment to C3FIT will progress during the hospital stay. Stroke patient admission logs will be checked frequently by Stroke Central for cases meeting the inclusion/exclusion criteria above. Data establishing eligibility will be obtained from the hospital admission sheet and progress notes. Functioning levels pre-stroke will be determined to establish a pre-stroke mRS/smRS of 0 or 1. Those deemed to fit the inclusion/exclusion criteria will be approached to initiate the informed consent process. Study personnel will obtain the location to which the patient will be discharged, for patients who consent, and baseline assessments will be obtained after consent is obtained. In addition, to data collected from the patient, the patient's caregiver and other contacts will be identified and collected to ensure recontact for future research visits and study goals and schedule will be reviewed. Informed consent will be obtained from both the patient and the caregiver or their legal surrogate."

Informed Consent Process. The patient and caregiver/family will not be enrolled until verbal discussion (in-person, by phone, or virtually) that describes the purpose of the study, study interventions, risks and benefits associated with study procedures, and other human subjects' protections (contained in the informed consent document) occur; consent forms can be sent by mail or email for signature, and virtual e-Consent can be used. For patients without access to audio/video capabilities, a Vivify Samsung Tablet may be provided without any cost to the patient to complete virtual visits. Participation in the study will not affect patient or caregivers' in-hospital or post-discharge care, and, as such, discussions of alternatives to participating are not necessary. Potential patients will be informed that the alternative to participating in the C3FIT follow-up will be the standard post-discharge recovery care paradigm provided by the clinical site. Informed consent will be obtained by the PI or via their designated study personnel. Consent may be obtained from the patient if, in the opinion of the Site Investigator, the patient is capable of participating in the informed consent process or from the appropriate legal surrogate based on applicable law. Personnel obtaining consent will be appropriately certified by the University of Miami's Collaborative Institutional Training Initiative (CITI) certification or appropriate certification as deemed by the clinical site. The informed consent document will be reviewed periodically; changes will be approved by the Steering Committee, as well as the IRB and Data Safety Monitoring Board (DSMB). Documentation of the signed informed consent will be maintained at the clinical site.

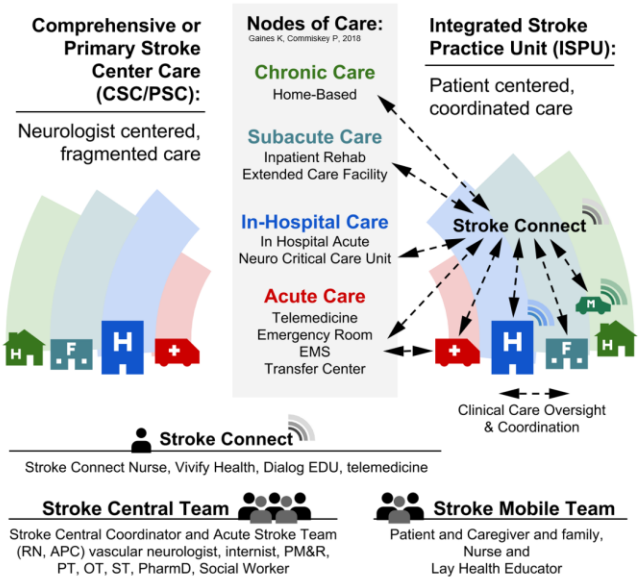
Management of Patients. For patients in both arms of the trial, the study aims to utilize the standard in-hospital management of all stroke patients for the site, and all patients at the site will be treated using this standard management. This implies that participation in C3FIT does not directly affect the care and intervention provided to individual patients enrolled in the study at the site during the hospital stay, and that informed consent for follow-up by C3FIT can be obtained during discharge planning or within 5 business days post discharge ideally (to a maximum of 14 total days) for the subject.

Once consented, study personnel will obtain the location to which the patient will be discharged, and baseline assessments will be obtained. In addition, to data collected from the patient, the patient's caregiver and other contacts will be identified and collected to ensure recontact for future research visits and study goals and schedule will be reviewed. Informed

consent will be obtained from both the patient and the caregiver or their legal surrogate prior to data collection.

Participant Retention. Monitoring of potential patient dropout and loss to follow up at each clinical site will be conducted at an early stage (in-person, by phone, or virtually using the Vivify Health Go App, Samsung Tablet, or other audio/video capabilities) to allow intervention. Both will be mitigated by having C3FIT's site personnel encourage and maintain participation and patient engagement, providing monthly feedback reports, having the Clinical Site PI contact patients/caregivers to discuss feelings about continuing participation, and utilizing other techniques identified in our demonstration project. Data from monitoring visits, GWTG, and the SDCC will be used by the CCC to monitor fidelity of the intervention during the period of enrollment and follow-up.

Figure 5. Stroke Nodes and Systems of Care: CSC/PSC versus C3FIT's ISPU



Participant Reimbursement. Research participants can be reimbursed for their time and effort on C3FIT at a rate of $25 for the collection of study outcomes at baseline, 3, 6, and 12 months by completing a SRU call and an intervention research visit for a total of $100. For each follow up intervention research visit (1,2,4,5,7,8,9,10,11 months) the participant will receive $20 which equals $180. Compensation will be provided in a method in alignment with each sites' institutional policies.

5. MODEL OF CARE – THE ISPU INTERVENTION

The ISPU is an innovative care model that builds on the JC-certified CSC/PSC design by increasing coordination of care using a patient/caregiver-centric design. C3FIT's ISPU two coordinated units, *Stroke Central* and *Stroke Mobile*, are connected by a technology-enabled coordinating bridge, *Stroke Connect* that addresses the entire care continuum for the patient, from acute through hospital care to 1-year post-discharge care. Stroke Central and Stroke Mobile can be thought of as components of Stroke Connect; see Figure 5.

- Stroke Connect is comprised of Stroke Central and Stroke Mobile personnel and technology working in synergy to provide coordination and integration of care delivery and communication across the 1-year episode of care (see Figure 4). Stroke Mobile can access Stroke Central's specialist input through this key care coordination system.
- Stroke Central is the acute and in-hospital-based component of the ISPU. Responsible for the patient during EMS routing, ED care, and management while in-hospital, Stroke Central is comprised of a licensed health professional Coordinator and many key

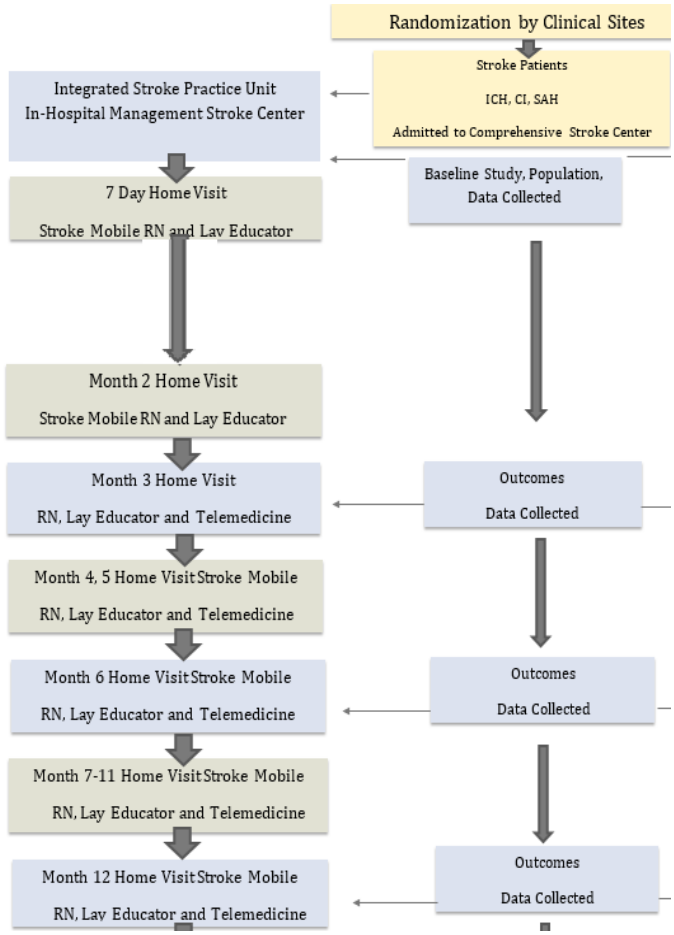
specialist care delivery professionals. The Acute Stroke Team resides in Stroke Central and includes key personnel and functions of a CSC/PSC (that currently reside in the hospital setting) but in the IPU model also extends coordination of their care delivery into the Subacute and Chronic Nodes for management of care.

- The Acute Stroke Team expands into post-discharge recovery through Stroke Mobile, a care delivery team comprised of a licensed health professional and lay health educator who work directly with the patient and caregiver/family. During monthly visits in their home or care facility, Stroke Mobile's Care Team follows patients through their final phases of in-hospital stay and remains engaged during any post-hospital care at a rehabilitation unit or extended care facility and/or in their home. Stroke Mobile can access Stroke Central's specialist input virtually at any time through C3FIT's key care coordination system, Stroke Connect.

Technological facilitators will be utilized as part of the Stroke Connect coordination and integration mechanism, including:

- A data management and data collection portal, Vivify Health, which will be used by Stroke Central and Stroke Mobile to facilitate chronic disease management post-stroke, to monitor risk factor control, and to facilitate new symptom and/or complication recognition.
- Telemedicine audio-video capability to allow Stroke Central providers the capability to assist the Stroke Mobile team in evaluation and management in the home/facility, which facilitates real time communication and collaboration and allows virtual evaluation of the patient/caregiver for a higher level of care as required.
- An educational portal called dialogEDU provides a common educational platform for professional (RN, physician, EMS, pharmacist, etc.) and patient and caregiver education around stroke symptoms, complications, recovery and risk factor management, and lifestyle changes.

Figure 4. C3FIT Patient Flow Diagram – ISPU Arm Only



Outcome visits = blue; Scheduled visits = gray.

The ISPU intervention is designed to coordinate and integrate patient-centric, multidisciplinary, team-based initiatives that engage patients and caregivers/family members in care and recovery from arrival at the ED through 1-year post-stroke at home or facility. Initiatives in Stroke Central include: (1) daily (M-F) multidisciplinary rounds in the hospital (including physicians, residents, physical, speech, and occupational therapists, pharmacists, nursing unit representatives, and Advanced Practice Nurses); (2) use of a daily ("airline-type") checklist administered by Stroke Central to evaluate guideline compliance; (3) use of proactive real-time care evaluation with a feedback loop for immediate correction of care deficiencies targeting complications; and (4) a central coordinating mechanism (Stroke Central) to enhance collaboration between professionals across the nodes of care.

Initiatives in Stroke Mobile include: (1) enrolling all stroke subtypes (ischemic (small and large vessel, embolic, and other), intracerebral hemorrhage, and subarachnoid hemorrhage; (2) utilizing a home/facility-based care delivery model that reduces the need for clinic visits; (3) invoking a home/facility-based model that focuses on caregiver/family (in addition to patients) to increase patient/caregiver/family engagement; (4) utilizing a lower cost care delivery team that broadly involves multiple layers of care (i.e. vascular neurology, internal medicine, rehabilitation physicians/therapists, nursing, advanced practice nursing, and lay educators); (5) tackling multiple risk factors in the management paradigm post-stroke; and (6) Involving a comprehensive care model that reflects the longitudinal care needs of the stroke patient for 1-year post-stroke.

Ensuring both implementation and fidelity is essential to ensuring our results can be attributed to the intervention. To this end, specific monitoring will be undertaken by the CCC and the Steering Committee to ensure intervention components are conducted as intended, including recording and assessment of training attendance, completion, and knowledge attained; monitoring of meeting frequency and attendance; and determining home visit procedure/visit compliance, completion, drop-out rates, and other strategies. We will closely monitor these and other components at the site level and intervene with their personnel if not performing.

6. BASELINE AND FOLLOW-UP ASSESSMENTS AND LABORATORY EVALUATIONS

The following outlines the Data Paradigms for Stroke Mobile based on obtained values for various scales and data points utilized. The guidelines establishing blood pressure and cholesterol goals are from the American Heart and Stroke Association.[8]

A. On-Study/On-Intervention Evaluations

The schedule of evaluations occurring after randomization while the subject is on-study and on (or about to start) intervention along with allowable time window in which evaluations may take place (±30 days with a target of ±14 days) is shown in Tables 7 and 8. Primary and secondary outcomes are considered a mandatory part of the protocol; remaining measures will be collected if patient/caregiver are able and/or available.

Table 7. Data Collection Paradigm: ISPU Arm, Stroke Central and Stroke Mobile

Item/Metric	In Hospital Prior to Discharge	Post Discharge Visit											
		Day 0-14	Month of Visit to Home/Facility										
		1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent Confirmed	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographics (Age, Gender, Race/Ethnicity, Marital Status, Zip Code of Residence, Income, and Education)*	X			X			X						X
Caregiver/Family identified*	X			X			X						X
Medical Record Number (MR #)*	X												
Get-With-The-Guidelines (GWTG) in-hospital data*	X												
Patient Medical History	X			X			X						X
Complications*[1]	X			X			X						X
National Institutes of Health Stroke Scale (NIHSS)*	X	X	X	X	X	X	X	X	X	X	X	X	X
Stroke Subtype*	X												
Prior stroke/Transient Ischemic Attack (TIA)*	X												
Risk factor profile*[2]	X												X
Cholesterol panel or LDL*	X			X			X						X
Hemoglobin A1C (HBA1C)*	X			X			X						X
Perceived Support				SRU			SRU						SRU
Stroke Impact Scale (SIS)				SRU			SRU						SRU
Simplified Modified Rankin Scale (smRS)	X			SRU			SRU						SRU
Blood Pressure (BP) Control: at target	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid Control: LDL, at target	X			X			X						X
Diabetes Control: HBA1C, at target	X			X			X						X
Smoking Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Mass Index (BMI)	X	X	X	X	X	X	X	X	X	X	X	X	X
Diet Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Exercise Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Mortality surveillance		X	X	X	X	X	X	X	X	X	X	X	X
Recurrence surveillance		X	X	X	X	X	X	X	X	X	X	X	X
Readmission surveillance		X	X	X	X	X	X	X	X	X	X	X	X
Time at Home		X		SRU			SRU						SRU
Depression History	X												
Depression: Patient Health Questionnaire (PHQ-9)		X	X	X	X	X	X	X	X	X	X	X	X
Caregiver Strain Index (CSI)		X		X			X			X			X

RED=Primary and Secondary Outcomes, BLACK=Additional Assessments by Stroke Mobile
SRU=UAB's Survey Research Unit
[1]Complications monitored: Urinary tract infection, pneumonia, aspiration, deep vein thrombosis, skin breakdown, fall, myocardial infarction, depression, fever/other infection, and Afib.
[2]Risk factor profile: hypertension, diabetes, hyperlipidemia, smoking status, BMI, CHADS2VASC score, CRP, Afib, family history.
*Will be collected if patient/caregiver are able and/or available.

Table 8. Data Monitoring Paradigm: ISPU Arm, Stroke Mobile Visits 1-12

Item/Metric	In Hospital Prior to Discharge	Post Discharge Visit to Home/Facility											
		Day 0-14	Month of Visit										
		1	2	3	4	5	6	7	8	9	10	11	12
Glasgow Coma Scale (GCS)*	X												
Barthel Index*	X	X					X						X
Stroke education*	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/OT/ST visits scheduled*	X												
Patient Medical History	X												
4-item Medication Adherence Scale*		X					X			X			X
Hill-Bone Compliance*		X					X						X
Epworth Sleepiness Scale*		X					X						X
Montreal Cognitive Assessment (MoCA)*		X					X						X
Frenchay Activities Index*		X					X						X
Antiplatelet use assessed, if appropriate*		X	X	X	X	X	X	X	X	X	X	X	X
Anticoagulant use assessed, if appropriate*		X	X	X	X	X	X	X	X	X	X	X	X
INR at-target, if appropriate*		X	X	X	X	X	X	X	X	X	X	X	X
Antihypertensive assessed, on intervention*		X	X	X	X	X	X	X	X	X	X	X	X
Antihypertensive assessed, at target*		X	X	X	X	X	X	X	X	X	X	X	X
Statin assessed, on intervention*		X	X	X	X	X	X	X	X	X	X	X	X
Hyperglycemia assessed, on intervention*		X	X	X	X	X	X	X	X	X	X	X	X
Hyperglycemia assessed, at target*		X		X			X						X
Smoking Cessation: On intervention, At target*		X	X	X	X	X	X	X	X	X	X	X	X
BMI: Discussed, at target*		X	X	X	X	X	X	X	X	X	X	X	X
Diet: Discussed, at target*		X	X	X	X	X	X	X	X	X	X	X	X
Exercise: Discussed, At target*		X	X	X	X	X	X	X	X	X	X	X	X
DVT assessed*		X	X	X	X	X	X	X	X	X	X	X	X
Skin assessed*		X	X	X	X	X	X	X	X	X	X	X	X
Mobility assessment*[1]		X					X						X
Depression intervention, if needed*		X	X	X	X	X	X	X	X	X	X	X	X
Caregiver Intervention, if needed*		X	X	X	X	X	X	X	X	X	X	X	X
Document tele- or phone consult to Stroke Central*		X	X	X	X	X	X	X	X	X	X	X	X
Stroke Mobile Team Conference attendance (monthly)*		X	X	X	X	X	X	X	X	X	X	X	X
Stroke Central Check-in with Stroke Mobile (daily)*		X	X	X	X	X	X	X	X	X	X	X	X
Establish plans for post intervention follow-up*													X
Self-reported Assessment of Life's Simple Seven*		X											X

SRU=UAB's Survey Research Unit
[1]Mobility Assessment includes: Berg Balance Test, Functional Reach Test, Timed Up and Go.
*Will be collected if patient/caregiver are able and/or available.

Intervention Discontinuation Evaluations. If the patient or caregiver/family declines follow up in-person visits, we will offer follow-up phone or virtual evaluations for primary and secondary outcomes and other assessments. If consent not provided for this, no follow up will occur.

Special Instructions and Definitions of Evaluations. Evaluations to be performed include: SIS and smRS, NIHSS, GCS, 4-item Medication Adherence, medication side effects, Hill Bone Compliance, Frenchay, MoCA, Barthel's Index, Epworth Sleepiness Scale, PHQ-9 depression scale, Caregiver Strain Index, blood pressure, Cholesterol panel, Hemoglobin A1c, INR (as appropriate), BMI, Smoking cessation, exercise assessment, diet assessment, readmission, recurrence, bleeding assessment and INR assessment (see Tables 7 and 8).

Final On-Study Evaluations. On study evaluations will be completed by Stroke Mobile and the University of Alabama Birmingham (UAB) SDCC Survey Research Unit (SRU) to include SIS and smRS and other assessments (see Table 5).

Concomitant Interventions. None.

Study Intervention Modifications. None.

Assessments. Tables 7 and 8 identify and define the assessments and the timeframe for each measurement parameter.

Other Laboratory Studies. None.

7. MANAGEMENT OF ADVERSE EXPERIENCES

Adverse experiences are anticipated to be rare. This study does not involve agents or interventions that are likely to be associated with adverse experiences. This study will use the standardized JC and ASA national guidelines for stroke care management. As revisions occur to the national guidelines these will be made available to clinical sites to modify their clinical site stroke patient care management strategies.

8. STUDY MONITORING

A. Data and Safety Monitoring Board (DSMB)

A formal Data and Safety Monitoring Board (DSMB) will be convened at regular intervals (for example, twice a year) to review recruitment, data security, and patient safety. We do not anticipate adverse events from this intervention, but the DSMB will monitor overall outcomes, including the following: death, recurrent stroke, rehospitalization, serious hemorrhage, recurrent or new ischemic event, serious adverse experiences, and premature withdrawal from the study. This study does not involve agents that likely will be associated with adverse experiences; as such, the DSMB will have a follow-up schedule and Significant Adverse Effects (SAE) reporting schedule that will include regular meetings with possible emergency meetings.

Data and Safety Monitoring Plan. The DSMB is tasked with mandating specific data required for independent analysis. A formal DSMB Plan will be developed by the DSMB Chair and the CCC and SDCC PIs that includes a framework for monitoring of study data and process, clinical and primary/secondary outcomes and will be submitted to the full DSMB. The frequency of data and safety monitoring will be determined in consultation with PCORI.

B. Adjudication Committee (AC)

In addition to the PI, two vascular neurologists will be charged with adjudicating stroke-related hospitalizations reported during the follow up period. This group (the Adjudication Committee) will review specific outcomes, including recurrent stroke, including subtype; and serious hemorrhage, including site.

C. Criteria for Intervention Discontinuation

- Revocation of informed consent.
- Subjects moving substantial distance from the original geographical location.
- Morbidity or mortality giving rise to insurmountable barriers to continued assessment.

9. STATISTICAL CONSIDERATIONS

C3FIT will compare the effectiveness of the *JC-certified CSC/PSC care system with the ISPU care system* in improving patient outcome and quality of life post-stroke. The primary outcome is the SIS-3.0 at 12 months, while assessment at 3 and 6 months are part of secondary outcomes. The primary analysis will focus on intervention differences in mean SIS score at 12 months. Mixed models will be used to assess the SIS outcome at 12 months, allowing the hierarchical nature of the data to be reflected (patients within Sites), and providing an accounting for data that are not missing completely at random. We anticipate (and trust) that randomization will balance potential confounding factors; however, secondary analysis will be performed with adjustment for baseline factors that could be imbalanced and potentially confound the estimated intervention differences, specifically adjusting for factors assessed at baseline that are known to be strongly associated with stroke outcomes (specifically age and stroke severity). Patients who die or cannot return due to morbid conditions will be assigned to "floor" score for poor outcome (and hence does not reduce the number of evaluable patients). With these patients not representing missing data, we anticipate there will be relatively little additional missing data and that these data will be generally missing at random (i.e., patients not returning because of other conditions, like moving); however, missing data that is present will be addressed by including baseline, 3, and 6 month data in the model and allowing the mixed model to adjust estimates for the missing data at 12 months by incorporating information available through the correlation between measurements.

A. Sample Size

The total sample size for the primary outcome for this study will be approximately 1,800 patients (each arm anticipated to have approximately 900 patients with approximately 100 patients at each clinical site, although some sites will enroll up to 140 consented participants due to limited enrollment by other sites due to institutional COVID PANDEMIC issues). We have intentionally restricted clinical site participation to those Sites certified as a TJC CSC/PSC (or acting as such). This restriction is important not only to provide CSC/PSC intervention "state of the art" comparator group, but also to increase the homogeneity of Sites and, thereby, reduce intraclass correlation coefficient in the hierarchical models. We do not have information on the intraclass correlation coefficient of the SIS, but given this restriction, we would suggest it is quite small (0.01); however, for power calculations, we have conservatively assumed it is of modest size (0.05) and also provide estimates should it be large (0.10). These larger intraclass

correlations would arise if there is larger than anticipated heterogeneity of intervention effect, and that there is adequate power for these larger intraclass correlation coefficients shows that we are well-positioned to detect intervention even in the presence substantial heterogeneity of the effect. Under this assumption and with the standard deviation of the SIS being approximately 8[49], if the interclass correlation is 0.05 then mean intervention differences of 2.7 and 3.2 can be detected with 80% and 90% power respectively (power calculations by PASS, NCSS, Kayville, UT); 2.7 was chosen based on evidence from Lin et al[30]. Even if the intraclass correlation is 0.10, differences of 3.7 and 4.3 can be detected with 80% and 90% power. As such, we have quite good power to detect clinically significant differences generally smaller than half of a standard deviation of the outcome scale.

B. Analyses

Analysis of the primary analysis will focus on intervention differences in mean SIS and smRS scores at 12 months. In addition, the mixed models will be used to assess the SIS and smRS outcomes at 12 months, allowing the hierarchical nature of the data to be reflected (patients within Sites), and providing an accounting for data that are not missing completely at random. Analyses of the secondary outcomes of time either rehospitalization or subsequent stroke will be assessed using proportional hazards analysis. In order to incorporate the hierarchical nature of these data, this analysis will be implemented using packages such as the SURVIVAL procedure from the SUDAAN package (Research Triangle Institute, Research Triangle Park, NC).

Analysis of the QOL secondary outcome will follow the analysis approach as the primary analysis and will have similar power (i.e., ability to detect intervention differences of magnitude of a half-standard-deviation). The study will also focus on identifying specific subgroups who are particularly responsive or resilient to intervention differences.

10. HUMAN SUBJECTS PROTECTIONS

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the Steering Committee, IRB, and DSMB responsible for oversight of the study. A signed consent form will be obtained from the subjects.

The total sample size for the primary outcome for this study will be approximately 1800 patients (approximately 100 patients at each clinical site, although some sites will enroll up to 140 consented participants due to limited enrollment by other sites due to institutional COVID PANDEMIC issues) who have consented to participate.

- Participating patients at a clinical site randomized to ISPU arm will be followed by Stroke Central to collect the same acute in-hospital metrics to measure care quality, health status, and outcomes and will also be contacted via telephone by the blinded personnel at the UAB SDCC SRU to assess primary outcomes. However, ISPU patients will also be assessed monthly by Stroke Mobile for 1-year in their home to collect specific metrics that will evaluate the patient and caregiver/family for potential issues and provide follow-up care and targeted education and support.
- The patient and their caregiver (or their legally authorized representative, if patients are unable to provide consent) will be approached to participate in the study ideally during hospitalization or within 5 business days of hospital discharge ideally (to a

maximum of 14 total days) to allow for data collection of specific acute in-hospital metrics. Caregivers may be consented at any time during the C3FIT study, but no data will be collected until consent is obtained. At research visits, the following will be obtained: (1) demographic and other data collection; (2) follow-up data collection specific to the ISPU arm; and (3) contact via telephone survey to collect SIS and smRS outcome data.

- C3FIT's population will include patients with all stroke subtypes and levels of severity, regardless of gender, race, ethnicity, or socioeconomic status. Each Site will recruit from their geographically eligible patients (who have a discharge diagnosis of stroke according to their ICD-10 code) until approximately 100 patients are consented, although some sites will enroll up to 140 consented participants due to limited enrollment by other sites due to institutional COVID PANDEMIC issues.

A. Adequacy of Protection Against Risks

Recruitment and Informed Consent. The acute in-hospital study sample will include patients admitted to the hospital with suspected stroke symptoms. Potential participants (both patient and caregiver if available) will be approached for recruitment ideally within 5 business days post discharge ideally (to a maximum of 14 total days) for the participant. In the event that the patient is unable to provide consent, their surrogate can be consented. Patients will be identified by study personnel from ED and stroke service admission logs; pilot data suggests nearly complete case ascertainment. To assure that acute in-hospital recruitment and informed consent procedures are followed consistently across Sites, a guidance document will be prepared in consultation with Site PI's and other patient, caregiver and organizational stakeholders, and Site personnel will be trained consistently by CCC staff.

The post-hospital discharge study sample will include patients and caregivers who have a discharge diagnosis of stroke and who reside in each clinical site's defined geographic area. Potential participants will be approached prior to hospital discharge regarding their interest in participating in the study, and every effort will be made to consent both patient and caregiver at that time.

Patients and caregivers at an ISPU Site who participate in Stroke Mobile will receive 12 in-home visits from Stroke Mobile. At each visit, Stroke Mobile will conduct a physical assessment and administer specific clinical scales to determine functional status, medication adherence, fall risk, daily activity level, depression, and caregiver strain, among others. A phlebotomy (draw blood) will occur (cholesterol and HbgA1c) according to the study time schedule.

The consent process will begin at hospital admission at a C3FIT clinical site. The PI at the site or his/her Co-I designee will provide information to the patient and/or caregiver about the nature of the trial, the two arm comparator groups and the randomization of the site. The fact that the C3FIT study does not involve an investigational drug or device will be discussed with the patient and caregiver. Potential participants will be made aware of the scientific basis for the comparison of methods of care delivery, and the clinical equipoise of the investigators. Information on the requirements of the participants will be discussed: (1) to allow appropriate outcome scales to be obtained, (2) the approximate time involved in obtaining these scales based on or pilot experience, (3) that some of the outcome scales will be obtained by phone by

blinded interviewers at the UAB SDCC SRU, (4) and that common laboratory tests will be obtained that would be appropriate for monitoring any person who suffered a stroke.

Potential and enrolled participants will: (1) be assured that they may withdraw consent at any time and do not have to provide a reason for their withdrawal; (2) have the right to speak with a member of our patient/stakeholder advisory group if they so choose to obtain additional information; and (3) be provided access to study personnel at their C3FIT clinical site (including the PI) to answer any questions or address concerns. In addition, the C3FIT personnel at the CCC are available for any questions or issues they identify. Potential participants will be assured that study personnel will be well trained, are familiar with guidelines for human subject's protection, and will have completed appropriate human subject's protection training as required by their site and the C3FIT Central IRB. A member of the Stakeholder Committee for C3FIT is a medical ethicist who has assisted in the design of the pilot study and, as such, will be available as a resource to C3FIT study personnel if specific ethical issues arise.

B. Potential Risks to Subjects and Protections

Potential risks for C3FIT participants and proposed methods to reduce these risks are described below. A member of the Stakeholder Committee for C3FIT is a medical ethicist who has assisted in the design of the pilot study and, as such, will be available as a resource to C3FIT study personnel if specific ethical issues arise.

1) *Breach of confidentiality of medical information in the acute in-hospital or outpatient setting – minimal risk.* All data will be stored in encrypted, password-protected databases that meet mandated IT security standards and will include subject identifiers (name, address, date of birth, and medical record numbers) necessary to maintain contact during the study.
2) *Anxiety/discomfort – minimal risk.* Participants will be assured that all study-related data and information (including both outcome assessment and monitoring data) will be kept confidential by the PI and study personnel, any questions and concerns can be addressed at any time, and participants can refuse to answer any question or not participate at any time during the study.
3) *Harm from physical and clinical assessments or measurements conducted as part of the outpatient ISPU program – minimal risk.* Physical assessments like the National Institutes of Health Stroke Scale and smRS are standard clinical assessment scales utilized in clinical practice. C3FIT study personnel will undergo training and certification in these scales, which have no recognized physical harm. Other scales used, including the primary outcome scale (SIS), have been used in many clinical situations/studies with no recognized harm.
4) *Discomfort and/or harm from blood draws to assess cholesterol level and HbgA1c – minimal risk.* Standard phlebotomy techniques will be used as in typical care. The minimal pain and risk of fainting will be acknowledged to potential participants, and participants may decline some or all of the blood draws.

Since no investigational device is involved in the C3FIT study, we anticipate few adverse events. However, our conservative approach is to provide several layers of protection for our study participants: (1) the informed consent process itself; (2) access to the C3FIT personnel, including the C3FIT nurses and physician Site PI; (3) access to the CCC staff, including the C3FIT

PI; (4) a Central IRB at Vanderbilt to provide consistency across 18 C3FIT Sites; and (5) a Data and Safety Monitoring Board (DSMB) that will review patient outcome data; and (6) human subjects research protections using the CITI certification as required by the Central IRB.

Adverse events (physical, behavioral, or psychological) will be reported to the Clinical Site PI or the SDCC; they will report these adverse events per guidelines in a timely fashion to the CCC, where they will be reviewed by the PI, Project Manager and forwarded to the DSMB.

C. Potential Benefits of the Proposed Research

Benefits for Patients. The major benefit to patients will accrue to future patients who benefit from the information gained from this study to design a patient-centered stroke healthcare delivery system that is comprehensive, integrated, and caregiver/family-focused. Many of the current issues faced by stroke patients involve lack of defect free stroke care in the in-hospital phase of care, leading to longer lengths of stay and in-hospital complications. These complications can lead to loss of QOL over many years. Lack of defect free care also plagues the post-hospital phase of care where stroke recurrence leads to readmissions and less Time at Home. Patients can also benefit by access to results of C3FIT to inform their choices in health care based on data that identifies the most effective and efficient care.

Based on positive results of C3FIT, patients could also benefit by having the potential for home care management, avoiding time and travel costs for outpatient clinic visits. Patients will have screening for HbgA1C and cholesterol to measure risk factor control at-target which may help identify targets of therapy. Patients could also benefit by having their caregivers supported by study personnel reducing caregiver strain. Because patients are involved in the design, implementation and dissemination of C3FIT outcomes that matter to them will be foremost in the study design.

Benefits for Caregivers. The major benefit to caregivers will accrue to future caregivers where the information gained from this study can be used to design a patient-centered stroke healthcare delivery system that is comprehensive, integrated, and caregiver/family-focused. Such a system may encourage recovery in their associated patient and limit stroke recurrences and readmissions.

If results from C3FIT are positive, caregivers could have the potential advantage of home visits, avoiding the stress, time commitment, and travel costs of clinic visits. Caregivers could potentially benefit by having a team that monitors their stress level and offers support.

Benefits for Organizational Stakeholders and Society. Organizational stakeholders will benefit by having access to high quality data to inform decisions regarding design and implementation of the most efficient and effective stroke delivery system.

D. Risk-to-Benefit Ratio

C3FIT risks to participants are reasonable. C3FIT does not involve any investigational drug or device, so the risks of unknown or unrecognized side effects of investigational drugs and devices are not an issue. C3FIT involves several blood specimen collections (HBA1C and cholesterol) with associated pain from the needle stick. This discomfort is transient and considered minimal. These tests would be considered standard of care in a stroke patient. The collections themselves are to obtain lab values that will be used to document control at target of risk factors and inform decisions about best medication or other therapy based on nationally

accepted guidelines. Testing procedures involve only grading scales often used in practice (i.e., NIH Stroke Scale, Simplified Modified Rankin Scale (smRS), or scales that are commonly used in stroke clinical trials for outcome). The information requested will include some information about sexual, urinary, and bowel function but will be obtained by trained medical personnel with a minimum of patient distress. The time involved in obtaining information from patients and caregivers is carefully considered. Only those scales determined critical to patient management and documentation of key functional and QOL outcomes are utilized. The timing of administration of these scales is also carefully chosen to not provide undue time commitment or stress at any visit. Given the minimal risks and significant potential benefits the risk benefit ratio seems reasonable and quite acceptable.

Importance of the Knowledge to be Gained. We have discussed the opportunity to improve stroke care delivery given the lack of defect free care, complications, recurrences, and lack of risk factor control documented for stroke patients. In addition, the opportunity to focus on stroke outcomes that are patient-centered will significantly improve patient and caregiver engagement in their intervention and recovery journey resulting from stroke. Organizational stakeholders such as the JC and the ASA, who are tasked with offering improvement programs that are informed by high quality scientific evidence, will find data from C3FIT invaluable, as Level 1 evidence to assist in identifying the appropriate focus for resources and effort does not currently exist. Vascular neurologists (VNs) and rehabilitation and internal medicine physicians will find that the results of this trial will help design care delivery approaches that provide the most appropriate patient centered functional and QOL outcomes rather than depending on compliance with process measures that may not contribute to these more important outcomes.

As in any research effort, much of the time, stress, and risk of the project is born by participants. It is hoped that including them as Research Partners may help to ally some of this burden. In any event, they are to be honored for their involvement.

Data and Safety Monitoring Plan. A formal Data and Safety Monitoring Board (DSMB) will be convened at regular intervals (for example, twice a year) to review and monitor recruitment, data security, and patient safety. The DSMB and development of the formal DSMB Plan is described in Section 8.

ClinicalTrials.gov. This randomized trial will be registered, and results will be reported in ClinicalTrials.gov as encouraged by NIH and required by Public Law 110-85.

E. Inclusion of Women and Minorities

This study has no exclusion criteria based on gender, race, or ethnicity. We anticipate that patients recruited to our study will reflect the demographic profile of the general stroke population, which proportionally includes more older adults than younger and good representation of minorities. While the age-adjusted incidence of stroke (primarily ischemic stroke) in men is approximately 30% higher than in women, because women live longer than men, more women have stroke than men. However, because they are older at time of stroke, women have more co-morbidities so they may be less likely to meet some of inclusion/criteria.

F. Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain

subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, PCORI, or the DSMB.

G. Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, PCORI, or the DSMB as part of their duties to ensure that research subjects are protected.

11. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Publication Subcommittee of the Steering Committee. Presentations, abstracts, or manuscripts will be submitted to PCORI within 30 days of acceptance.

12. REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive Summary: Heart Disease and Stroke Statistics-2016 Update: A report from the American Heart Association. Circulation. 2016 Jan 26;133(4):447-54. doi: 10.1161/CIR.0000000000000366.
2. Bakas T, Clark P, Kelly-Hayes M, et al. AHA/ASA scientific statement. Evidence for stroke family caregiver and dyad interventions. A statement for healthcare professionals from the American Heart Association and American Stroke Association. Stroke. 2014;45:2836-52.
3. Rosamund W, Flegal K, Furie K, et al. Heart Disease and Stroke Statistics – 2008 Update: A report from the American Heart Association Statistics Committee and Stroke Statistics Committee. Circulation. 2008;117:e25-146.
4. Coull A, Lovett J, Rothwell P. Population based study of early risk of stroke after transient ischemic attack or minor stroke: Implications for public education and organization of services. BMJ. 2004; 328:326-8.
5. Petty G, Brown R, Sicks J. Survival and recurrence after first cerebral infarction: A population-based study in Rochester, Minnesota, 1975-1989. Neurology. 1998; 50:208-16.
6. Samsa G, Brian J, Lipscomb J, et al. Epidemiology of recurrent cerebral infarction: A Medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. Stroke. 1999; 30:338-49.
7. Tooth L, McKenna K, Barnett A, Prescott C, Murphy S. Caregiver burden, time spent, caring and health status in the first 12 months following stroke. Brain Injury. 2005; 19:963-74.
8. Persson J, Holmegaard L, Kerlberg I, et al. Spouses of stroke survivors report reduced health-related quality of life even in long-term follow-up. Results from Shalgrenska Academy Study on Ischemic Stroke. Stroke. 2015; 46:2584-90.
9. Gaines K, Commiskey P. Stroke: The critical neglected first year post-stroke. J Integr Care. 2018; https://doi.org/10.1108/JICA-09-2017-0030.
10. Emberson J, Lees KR, Lyden P, et al. Effect of intervention delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischemic stroke: a meta-analysis of individual patient data. Lancet. 2014 Nov 29;384(9958):1929-35. doi: 10.1016/S0140-6736(14)60584-5.

11. Choi JC, Jang MU, Kang K, et al. Comparative effectiveness of standard care with IV thrombolysis versus without IV thrombolysis for mild ischemic stroke. J Am Heart Assoc. 2015;4: e001306.
12. Wardlow JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischemic stroke: an updates systematic review and meta-analysis. Lancet. 2012; 379:2364-72.
13. Boudreau D, Guzauskas G, Chen E, Lalla D, Tayama D, Fagan S, et al. Cost-effectiveness of recombinant tissue-type plasminogen activator within 3 hours of acute ischemic stroke. Current evidence. Stroke. 2014; 45:3032-9.
14. Tung C, Win S, Lansberg M. Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke. Stroke. 2011; 42:2257-62.
15. The Joint Commission. 2016. http://www.jointcommission.org/.
16. Lakshminarayan K, Schissel C, Anderson D, et al. Five-year re-hospitalization outcomes in a cohort of patients with acute ischemic stroke. Medicare Linkage Study. Stroke. 2011; 42:1556-62.
17. Roberts CS, Gorelick PB, Ye X, Harley C, Goldberg GA. Additional stroke-related and non-stroke-related cardiovascular costs and hospitalizations in managed-care patients after ischemic stroke. Stroke. 2009; 40:1425-32.
18. Joubert J, Reid C, Barton D, et al. Integrated care improves risk-factor modification after stroke: Initial results of the Integrated Care for the Reduction of Secondary Stroke model. J Neurol Neurosurg Psychiatry. 2009; 80:279-84.
19. Chaturvedi S, Turan TN, Lynn MJ, Kasner SE, Romano J, Cotsonis G, et al., for the WASID Study Group. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology. 2007; 69:2063-68.
20. McAlister FA, Majumdar SR, Padwal RS, Fradetta M, Thompson A, Buck B, et al. Case management for blood pressure and lipid level control after min or stroke: PREVENTION randomized control trial. Canadian Medical Association Journal. 2014; 186:577-84.
21. Billinger S, Arena R, Bernhardt J, et al. AHA/ASA Scientific Statement. Physical activity and exercise recommendations for stroke survivors. A statement for healthcare professionals from the American Heart Association and American Stroke Association. Stroke. 2014; 45:2532-53.
22. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis S, et al., for the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical intervention with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): The final results of a randomised trial. Lancet. 2014; 383:333-41.
23. Chimowitz MI, Lynn MJ, Turan TN, Fiorella D, Lane BF, Janis S, et al., for the SAMMPRIS Investigators. Design of the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis trial. J Stroke Cerebrovascular Dis. 2011; 20:357-68b.
24. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al., for the SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. NEJM. 2011; 365:993-1003a.

25. Carter BL, Rogers, M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension. Arch Int Med. 2009; 169:1748-55.
26. Porter M, Lee T. The strategy that will fix health care. Harvard Business Review. 2013 Oct.
27. Wu RC, Lo V, Rossos P, et al. Improving hospital care and collaborative communications for the 21st century: Key recommendations for general internal medicine. Interact J Med Res. 2012;1: e9.
28. Porter M, Teisberg E. Redefining healthcare: Creating value based competition on results. Boston. Harvard Business School Press. 2006.
29. Porter M. Value-Based healthcare delivery part II: Integrated Practice units, outcome and cost measurement. Medical Leadership Institute. Dec 2010. http://www.medicaidleaders.org/sites/default/files/integrated%20practice%20units.pdf.
30. Lin KC, Fu T, Wu CY, et al. Psychometric comparisons of the Stroke Impact Scale 3.0 and Stroke-Specific Quality of Life Scale. Qual Life Res. 2010; 19:435-443.
31. Sacco R, Boden-Albala B, Gan R, et al. Stroke incidence among whites, blacks, and Hispanics from the same community of Northern Manhattan. Am J Epidemiol. 1998; 147:260.
32. Ramirez L, Kim-Tenser M, Sanossian N, et al. Trends in acute ischemic stroke hospitalizations in the United States. J Am Heart Assoc. 2016;5: e003233. doi:10.1161/JAHA.116.003233.
33. The Joint Commission. Quality Check. 2016. http://qualitycheck.org/StrokeCertificationList.aspx.
34. American Heart Association Get With The Guidelines. Focus on Quality: The More Healthcare Quality Improves the More Patient Outcomes Do Too. 2018. www.heart.org/HEARTORG/Professional/GetWithTheGuidelines/Get-With-The-Guidelines--HFStroke_UCM_001099_SubHomePage.jsp.
35. Centers for Medicare and Medicaid Services. Putting patients first. 2018. https://www.cms.gov/.
36. Duncan P, Bushnell C, Rosamond W, et al. The Comprehensive Post-Acute Stroke Services Study (COMPASS): Design and methods for cluster randomized pragmatic trial. BMC Neurology. 2017; 17:133.
37. Powers WJ, Rabinstein AA, Ackerson T, et al. on behalf of the American Heart Association Stroke Council. Acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018; STR.0000000000000158, originally published January 24, 2018. https://doi.org/10.1161/STR.0000000000000158.
38. Bogousslavsky J and Regli F. Cerebral infarct in apparent transient ischemic attack. Neurology. 1985; 35: 1501-1503.
39. Albers G, Caplan L, Easton J, et al. Transient ischemic attack: Proposal for a new definition. NEJM. 2002; 347: 1713-1716.
40. Alubacher J, Martel P, Mas J. Clinical practice guidelines: Diagnosis and immediate management of transient ischemic attacks in adults. Cerebrovascular Dis. 2005; 20: 220-225.
41. Easton J, Saver J, Albers G, et al. Definition and evaluation of transient ischemic attack. AHA/ASA Scientific Statement. Stroke. 2009; 40: 2276-2293.

42. ACOG Committee Opinion. Guidelines for diagnostic imaging during pregnancy and lactation. Obstetrics & Gynecology. 2017; 130 (4): e210-e216.
43. Toppenberg K, Hill D, Miller D. Safety of radiographic imaging during pregnancy. Am Fam Physician. 1999; 59 (7): 1813-1818.
44. Ovbiagele B, Saver JL, Fredieu A, et al. PROTECT: A coordinated stroke intervention program to prevent recurrent thromboembolic events. Neurology. 2004 Oct 12;63(7):1217-22.
45. Wolfe CD, Redfern J, Rudd AG, et al. Cluster randomized controlled trial of a patient and general practitioner intervention to improve the management of multiple risk factors after stroke: Stop Stroke. Stroke. 2010 Nov;41(11):2470-6. doi: 10.1161/STROKEAHA.110.588046. Epub 2010 Sep 23.
46. Gaines K. Centers for Medicare & Medicaid Services (CMS). Health Care Innovation Award (HCIA) #1C1CMS331043. Jul 2012-Dec 2015.
47. Gaines K. NIH Office of Minority Health. #CPIMP071044.
48. 2019 ICD-10-CM Codes 160-169: Cerebrovascular disease. Retrieved from: https://www.icd10data.com/ICD10CM/Codes/I00-I99/I60-I69/I63-/I63.9.
49. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The Stroke Impact Scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke. 1999 Oct;30(10):2131-40.

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

#NCT04000971

PRINCIPAL INVESTIGATOR:

Kenneth Gaines, MD, MBA
Professor of Neurology
Medical Director, Teleneurology
Vanderbilt University Medical Center

Barry Jackson, BA
Patient Co-PI

STUDY ARM PROTOCOL:

Comprehensive or Primary Stroke Center (CSC/PSC) Model of Care Protocol

VERSION:

Version 11.0
4/3/2025

SUPPORTED BY:

The Patient Centered Outcomes Research Institute (PCORI)
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TABLE OF CONTENTS **Page**

SUMMARY ……

1. STUDY OBJECTIVES ……

A. Hypotheses ……

B. Primary and Secondary Outcomes……

2. BACKGROUND……

A. Rationale ……

B. Supporting Data ……

3. PATIENT AND STAKEHOLDER ENGAGEMENT……

4. STUDY DESIGN ……

A. Disease-specific Enrollment Criteria……

B. Randomization……

C. Site Selection……

D. Patient Eligibility……

E. Study Aims……

F. Patient Enrollment Procedures……

5. MODEL OF CARE – THE CSC/PSC ARM……

6. BASELINE AND FOLLOW-UP ASSESSMENTS AND LABORATORY EVALUATIONS……

A. On-Study/On-Intervention Evaluations ……

7. MANAGEMENT OF ADVERSE EXPERIENCES ……

8. STUDY MONITORING……

A. Data and Safety Monitoring Board (DSMB)……

B. Adjudication Committee (AC)……

C. Criteria for Intervention Discontinuation……

9. STATISTICAL CONSIDERATIONS ……

A. Sample Size……

B. Analyses……

10. HUMAN SUBJECTS PROTECTIONS……

A. Adequacy of Protection Against Risks……

B. Potential Risks to Subjects and Protections…….

C. Potential Benefits of the Proposed Research ……

D. Risk-to-Benefit Ratio……

E. Inclusion of Women and Minorities……..

F. Subject Confidentiality……..

G. Study Modification/Discontinuation…….....

11. PUBLICATION OF RESEARCH FINDINGS …….

12. REFERENCES ……..

SUMMARY

Patient support after stroke requires a long-term commitment, supporting the patient as they move through "nodes" of acute care, post-acute in-hospital care, subacute care (inpatient rehab, extended stay, etc.), and chronic care. The current standard of stroke care is the Joint Commission (JC)-certified Comprehensive Stroke Center or Primary Stroke Center (CSC/PSC) care system, a collection of proven processes of care, but an approach with a focus on acute care (and to a lesser extent the post-acute in-hospital care), with little coordination of care of the patient after discharge. The overall goal of C3FIT is to assess if patient outcomes are improved when the CSC/PSC system is supplemented with an Integrated Stroke Practice Unit (ISPU) system of care, a patient-centric model of care involving the patient's caregiver that coordinates care from the acute management through the rehabilitation and recovery of the patient.

The specific aim of this project is to assess superiority of patient-centric outcomes between the CSC/PSC and ISPU models in a cluster-randomized pragmatic trial conducted at approximately 18 clinical sites in the United States (US). The primary aim focuses on differences in 12-months post stroke quality of life (QOL) using the Stroke Impact Scale (SIS) and patient function using the Simplified Modified Rankin Scale (smRS). Secondary aims include other patient/caregiver-centered outcomes, including: (1) short-term function and QOL using the SIS and smRS; (2) control of stroke risk factors; (3) mortality, recurrent stroke rates, and hospital readmission rates; (4) Time At Home; (5) patient depression, using the Patient Health Questionnaire (PHQ-9); and (6) caregiver strain, using the Caregiver Strain Index (CSI). Finally, we aim to determine whether there are patient subgroups specifically responsive or resilient to the intervention, according to effect modification by age, race, sex, and socio-economic status (income and education).

Study Design. C3FIT is a multicenter, randomized, single blinded, Phase III, cluster randomized trial. Clinical sites were stratified by geography, balanced by patient volume, and randomized to one of two patient care management using the CSC/PSC or ISPU model.

Outcomes. C3FIT's primary outcomes are the SIS and smRS at 12 months.

Sample Size and Population. Based on the primary outcome, the study was originally designed for a total sample size of approximately 1800 patients, with approximately 18 sites. However, due to the challenges of the COVID-19 pandemic, the sample size was decreased to 1,262, and the number of sites were increased to 23. The C3FIT Statistical and Data Coordinating Center (SDCC) at the University of Alabama Birmingham (UAB) determined that this change in samples size does not impact the study's statistical measures and/or study power, and our funder, PCORI, approved of the changes.

Interventions. Coordinated care (including in-home/in-patient rehabilitation and skilled nursing or extended care facility visits) will be provided based on protocol-based coordination of post-acute in-home/facility care for ISPU Site patients, while CSC/PSC patients will be managed per standard CSC/PSC protocol with no additional study related management post discharge. The clinical sites will be provided with training specific to the arm to which they are randomized.

Duration. Patients will be followed at the site level for one year after enrollment.

2. STUDY OBJECTIVES

The current standard of stroke care is the JC-certified CSC/PSC care system, a collection of proven individual processes of care, but a system that lacks coordination for the post-stroke care of patients. The C3FIT trial serves as the opportunity to assess potential impact on patient QOL and functional outcomes resulting from the improved integration of care provided by the ISPU approach.

C3FIT's overall goal is to assess if patient outcomes are improved when the CSC/PSC system is supplemented with an Integrated Stroke Practice Unit (ISPU) system of care, a patient-centric model of care involving the patient and caregiver/family that coordinates care from the acute management through the rehabilitation and recovery of the patient.

A. Hypotheses

C3FIT's *Primary Hypothesis* is that the ISPU model of care will show improved mean level SIS and smRS scores at 12 months compared to the CSC/PSC model of care.

The *Secondary Hypotheses are*:

(1) The ISPU approach will improve secondary stroke outcomes relative to the CSC/PSC approach, including: SIS and smRS at 3 and 6 months, risk factor control, stroke recurrence rates, hospital readmission rates, mortality in the first 12 months, time at home, patient depression, and caregiver strain.

(2) The ISPU benefit in SIS and smRS will persist after the protocol-based post-acute coordination of in-home/facility care is terminated (at 12 months).

(3) Patient characteristics (specifically age, race, sex, income, and education) will affect the primary or secondary intervention differences.

B. Primary and Secondary Outcomes

Primary and secondary outcomes are documented in Table 1 and described below.

- *Primary outcomes* include patient function and QOL using the SIS and smRS at 12-months post-stroke.
- *Secondary outcomes* are patient/caregiver-centered and include: (1) short-term patient function and QOL using the SIS and smRS (at 3 and 6 months); (2) the proportion of patient with risk factors controlled at target (at 3, 6, and 12 months); (3) mortality in the first 12 months, time to first recurrent stroke, and number of hospital readmissions per participant month over the first 12 months; (4) Time At Home (proportion of survival time spent at home); (5) patient depression, using the Patient Health Questionnaire (PHQ-9; at 3, 6, and 12 months); and (6) caregiver strain, using the Caregiver Strain Index (CSI; at 3, 6, and 12 months).

Table 1. Study Outcome Measures and Assessment Frequency					
		ASSESSMENT FREQUENCY (By Month)			
C3FIT OUTCOMES	**VARIABLES**	**H**	**3**	**6**	**12**
Functional Assessment	Stroke Impact Scale	X	X+	X+	X+
Quality of Life	Simplified Modified Rankin Scale	X	X+	X+	X+
Stroke Risk Factors					
(8) Blood pressure control at target*	Standard Systolic and Diastolic Measurement	X	X	X	X
(9) Lipid control at target*	Standard Lipid Panel or, at a minimum, LDL (Blood Draw, repeated only if patient's cholesterol is elevated at baseline, if LDLC%≥70mg/dl, or if patient is on a statin)	X	X	X	X
(10) Diabetes control at target*	Standard HBA1c (Blood Draw, repeated only if patient's blood glucose is elevated at baseline or if HBA1C%≥7mg/dl)	X	X	X	X
(11) Smoking status*	Question(s) to assess patient smoking status	X	X	X	X
(12) Body Mass Index (BMI)*	Weight and hip circumference	X	X	X	X
(13) Diet	Question(s) to assess patient adherence to recommendations of the American Heart Association (AHA).	X	X+	X+	X+
(14) Exercise	Question(s) to assess patient adherence to recommendations of the AHA.	X	X+	X+	X+
Mortality*	Will be assessed at visits. If needed, medical records will be collected from site, and the Adjudication Committee will review.		X	X	X
Recurrent Stroke*			X	X	X
Rehospitalization*			X	X	X
Time at Home	Assesses Time at Home (patient or caregiver home) versus at institution (for hospitalization, IPR, and/or SNF).		X+	X+	X+
Depression (Patient)	Patient Health Questionnaire (PHQ-9)		X	X	X
Caregiver Strain	Caregiver Strain Index		X	X	X

*Results of these measures will be reported back to patient's treatment team for information/action.
+SRU only.
H: Collected at the Hospital prior to discharge by site personnel
IPR: In-patient rehabilitation facility
SNF: Skilled Nursing Facility

2. BACKGROUND

A. Rationale

Stroke is the 5th leading cause of death and the leading cause of adult disability[1-2], and approximately 780,000 have a stroke or transient ischemic attack (TIA) in the US each year. As many as 90% of the 5 million stroke survivors (roughly the population of South Carolina) have some functional deficit and live with sequelae of stroke[3]. The impact of stroke risk does not end there, as 17% of TIA patients and 18% of those with non-disabling stroke will experience a recurrent stroke within three months[4] and nearly one-third will have a recurrence within five years[5]. About 23% of annual stroke incidence is recurrent stroke, and mortality is greater after a

second stroke than the first (24-month survival rates are 48% versus 57%)[1,6]. Persisting physical and cognitive impairments affect not only the patient, but the caregiver and family experience both psychological and health quality impact[2,7,8].

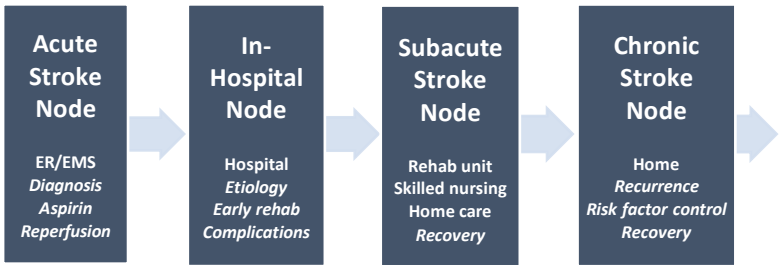
B. Supporting Data

The care delivery system for a typical US stroke patient during the first-year post-stroke is fragmented into four distinct Nodes of Care - from acute stroke through in-hospital care and then discharged to rehabilitation or skilled nursing facility (SNF) and/or finally (for most patients) home; see Figure 1. Each Care Node has distinct care delivery geography, personnel, and focus. This dissociated system fosters miscommunication and inefficient, uncoordinated care to the detriment of patient health[9].

Across these Stroke Nodes of Care, there is clear evidence of the effectiveness of therapies in isolation. For example,

- In the Acute Node, tissue plasminogen activator (tPA) and interventional therapies have been shown effective for stroke care[10-14,37].
- In the In-hospital Node, stroke units and quality improvement programs have been promulgated by the American Heart Association (AHA) [37] Get-With The Guidelines (GWTG)[34], JC[15,33], and CMS[35].
- In the Subacute or Chronic Care Nodes that follow hospital discharge, comprehensive risk factor management[16,17] and early rehabilitation[37] has been shown to work[60]. Effective secondary prevention is fostered by patient and caregiver/family engagement, medication compliance, and caregiver engagement, particularly during the first year[16,17].

Figure 1. Nodes of Stroke Care Across the Continuum



A review of post-stroke risk factor management projects from the scientific literature was conducted that included the most difficult targets, for example, smoking cessation, exercise, diet, and risk factor education. Standard stroke care often includes variable risk factor control patient education and limited team-based and caregiver/family focus, as well as a clinic-based focus. Joint Commission (JC)-certified Comprehensive and Primary Stroke Center (CSC/PSC) care offers some improvements on the acute, in-hospital side, defining risk factor management at discharge only and incorporating in-patient education but limits outpatient care to only a 30-day clinic visit with no team based coordination or caregiver/family focus[15]. Studies like ICARRUS[18], SAMMPRIS[23,24], WASID[19], PROTECT[44], PREVENTION[20], Stop Stroke[45], and COMPASS[36] have incorporated various aspects of integrated care models. These studies have clearly documented improved outcomes and lower risk of subsequent stroke associated with the

proper post-discharge management of risk factors; however, control of post-stroke risk factors at target remains at low levels.

While there are interventions proven effective in each of the nodes of care, it remains unknown whether a comprehensive system that coordinates care across the four nodes would improve patient and care-giver outcomes. It could be argued that such a coordination would better inform in the down-stream nodes regarding the patient status and progress through the first year of care, and with this information the caregivers can provide more effective care of the patient. Alternatively, it could be argued that the interventions known to be effective in each of the nodes can operate effectively as independent activities, and efforts to coordinate care would only introduce confusion and complications that would lead to worse outcomes for the patient. The overarching goal of C3FIT is to address specifically this question, that whether the coordination of care across the four nodes of care provides better outcomes for the patient and his/her caregivers. There is clinical equipoise on this question in the stroke community.

3. PATIENT AND STAKEHOLDER ENGAGEMENT

Patient/caregiver research partners and other stakeholder partners are foundational to C3FIT and bring diverse perspectives and/or personal experience as stroke survivors, caregivers/family, care providers, clinical researchers, national clinical experts and organizational stakeholder partners such as payers and national advocacy groups.

We have developed a four-committee structure for engaging stakeholders in all aspects of C3FIT. Each Committee is described below.

- C3FIT's Steering Committee will provide overall supervision of study operations, procedures, fidelity of the intervention, and progress for the study. It will be jointly chaired by the Patient Co-PI and the physician Co-PI. Committee members include each Clinical Site PI, the Project Manager, the SDCC PI, the Chief Research Scientist, and the Chairperson of the Stakeholder Engagement Committee.
- C3FIT's Scientific Advisory Committee will oversee the study's scientific integrity and will be chaired by C3FIT's Chief Research Scientist. This committee includes stakeholder partners who are national experts in their fields. Broad representation consistent with a complex disease state will safeguard scientific rigor and trial integrity and included groups who are critical to dissemination and implementation of C3FIT results.
- C3FIT's Central Stakeholder Engagement Committee (SEC) will ensure that patient partner and stakeholder partner priorities are reflected in the study design, data analysis, and dissemination of study findings. It will include patient and caregiver/family partners along with care providers from multiple disciplines and representatives from two national patient advocacy groups. The Committee will be facilitated by the Engagement Coordinator, who will report the Committee and Clinical Site Engagement Groups' recommendations to the Steering Committee.
- Selected ISPU and CSC/PSC Sites will develop Clinical Site Stakeholder Engagement Groups, which will identify specific supplemental recruitment strategies, study implementation issues, and provide practical tips to support study subjects and care providers at their clinical sites. Each will include patients and caregivers/family along with care providers from multiple disciplines. The group will meet in-person two times per year

at their respective sites and will be facilitated by the clinical site personnel. Group input will be directed to the central study Stakeholder Engagement Committee.

4. STUDY DESIGN

C3FIT is a randomized comparative effectiveness trial (CET) of two care delivery methodologies at approximately 18 clinical sites. Primary and secondary outcomes are described in Section 1.

A. Disease-specific Enrollment Criteria

Clinical Indicators. Definitive stroke will be defined by ICD-10 code criteria. Definitions will be based on ICD-10 criteria (see Table 4). Investigators will use tests and assessments deemed appropriate for an individual patient to determine the appropriate diagnosis. Additional stroke subtype categorization will occur using the TOAST Criteria as performed by C3FIT clinical site investigators.

Prior Therapy. There is no exclusion for prior therapy.

Demographic Characteristics. The clinical sites have been carefully selected with the goal of providing nationwide representation, urban and rural representation, inclusion of both men/women and all race/ethnic groups affected by. Patients aged 18 and older are eligible with no upper age exclusion criterion.

Contraindications. Since no drugs or experimental devices are utilized in this trial there are no specific contraindications.

Pregnancy Exclusions. There is no exclusion for pregnancy or planned lactation and no inherent risk from the proposed intervention.

B. Randomization

C3FIT is randomized at the facility (clinical site) level rather than the individual patient level. Randomization at the facility level is appropriate, as the proposed comparator arms could not be reasonably instituted at the patient level for a system change design. Clinical sites were stratified by geography, balanced by patient volume, and randomized to the CSC/PSC or ISPU model.

C. Site Selection

C3FIT clinical site eligibility for inclusion is the JC CSC/PSC certification (or operating as such), which ensures that all sites will have well-established in-hospital care delivery programs and documented success in guideline-driven delivery of care that introduces a level of homogeneity among clinical sites. Sites with sufficient volume of stroke admissions were identified with selection was made with special consideration given to sites with populations that include diverse race/ethnic groups. At the patient level, all stroke patients with a stroke diagnosis who reside in a defined geographic region are potential candidates. Though JC CSC/PSC clinical sites tend to be located in largely urban areas, we will include geography in the target population that encompasses the index county and contiguous counties to include both a more diverse and more rural population.

D. Patient Eligibility

Inclusion and Exclusion Criteria are detailed below.

Inclusion Criteria:

- Age 18+.
- Clinical diagnosis of acute stroke with or without brain imaging compatible with intracerebral hemorrhage or ischemic stroke; see ICD 10 codes in Table 4.
- English or Spanish speaking subjects.
- Patient admitted within 7 days of their index stroke event.
- Patient is discharged alive and not to hospice care.
- Patient living at discharge within the geography of recruitment for that C3FIT site.
- Pre-morbid mRS/smRS of 0-1.
- Patient and/or surrogate give consent to participate after an informed consent process.
- Patients who go to rehabilitation inpatient therapy or other care facilities are eligible, as long as they reside in the geographic are of recruitment and do not go to hospice care.

Exclusion Criteria:

- Clinical transient ischemic attack (TIA)[38-41] is ***excluded*** even if there is a computerized tomography (CT) or magnetic resonance imaging (MRI) lesion corresponding to the clinical syndrome at presentation.
- Already enrolled or planned enrollment in another clinical trial for which participation in C3FIT would be compromised with regard to follow-up assessment of outcomes or continuation in C3FIT.
- Patients with a planned admission to hospice care prior to consent.
- Patients not anticipated to survive for 1 year due to neurological or other medical status (i.e., advanced cancer, hospice care, heart disease, etc.).
- Patients who in the opinion of the site investigator cannot be involved in follow up care.
- Inability or unwillingness of subject or legal guardian/representative to understand and cooperate with study procedures or provide informed consent.

Table 4. ICD 10 Codes for Stroke Included and Excluded from C3FIT

ICD 10 Codes for Stroke Included in C3FIT[48]: • I 60; non-traumatic subarachnoid hemorrhage • I 61: Non-traumatic intracerebral hemorrhage • I 62: Other and un-specified non-traumatic intracerebral hemorrhage • I 63: Cerebral infarction: • I 64: Stroke, not specified as hemorrhage or infarction
ICD 10 Codes Excluded from C3FIT[48]: • I 65: Occlusion and stenosis of pre-cerebral arteries, not resulting in cerebral infarction Cerebral artery stenosis without cerebral infarction • I 66: Occlusion and stenosis of cerebral arteries, not associated with cerebral infarction. (Cerebral artery stenosis without cerebral infarction) • I 67: Other cerebrovascular diseases (Cerebral arteries dissection, cerebral aneurysm non ruptured, hypertensive encephalopathy, Moya Moya disease, nonpyogenic thrombosis of intracranial venous system, cerebral arteritis, acute cerebrovascular insufficiency, posterior reversible encephalopathy syndrome, cerebral vasospasm and vasoconstriction, Reversible cerebrovascular vasoconstriction syndrome). • I 68: Cerebrovascular disorders in diseases classified elsewhere (cerebral amyloid angiopathy) • I 69: Sequelae of cerebrovascular disease (Multi infarct dementia) • G 45 (unless they meet criteria for I63) (Transient Ischemic attacks and related syndromes).

E. Study Arms

The proposed project will involve randomization to: (1) the ISPU model developed and tested in the CMS pilot, versus (2) the CSC/PSC model implemented as part of the program overseen by the JC. Specific differences between the two interventions are detailed in Table 5. During hospital stay, clinical care and risk factor management in the ISPU arm (and also the CSC/PSC arm) will continue to operate per existing JC and American Stroke Association (ASA) national guidelines.

Table 5. CSC/PSC Care compared to ISPU Care

Parameter	CSC/PSC	ISPU
Time Focus	Acute care hospital door-to-doorand follow-up over 1 year	Continuum of care for 1-year
Goals	Process compliance	• Patient-centered QOL • Patient centered functional outcome
Measurement	Performance measures	• Functional outcome
Geography of Care Delivery	• Hospital • Post-hospital clinic Home health	• Hospital • Home- and caregiver/family-based post-stroke care (Stroke Mobile)
Integration with Rehabilitation	• Discharge summary and clinic follow-up	• Stroke Connect active in in-patient rehab centers and extended care facilities thru Stroke Mobile
Focus of Modification	Providers	Patient and family
Post-hospital Follow-up	Clinic	Home
Patient/Caregiver/Family-centered Care	No	Yes
Patient-centered Outcome	No	Yes

F. Patient Enrollment Procedures

In both CSC/PSC and ISPU Sites, study personnel will be responsible for approaching suspected stroke patients, describing the study, and providing an IRB-approved informed consent process for the patient and caregiver. Admission records will be reviewed frequently by the site

personnel, and discharge diagnosis and zip code of residence of all patients admitted with stroke will be identified to determine inclusion.

During hospital discharge or within 5 business days post discharge ideally (to a maximum of 14 total days), patients meeting all inclusion/exclusion criteria for enrollment in C3FIT will be involved in an informed consent process, and once consent is obtained the subject will be given a unique identifier. After consent has been obtained, study personnel will obtain the location to which the patient will be discharged, discharge diagnosis by ICD code, primary and secondary outcomes and other baseline data. Caregivers may be consented at any time during the C3FIT study, but no data will be collected from them until consent is obtained.

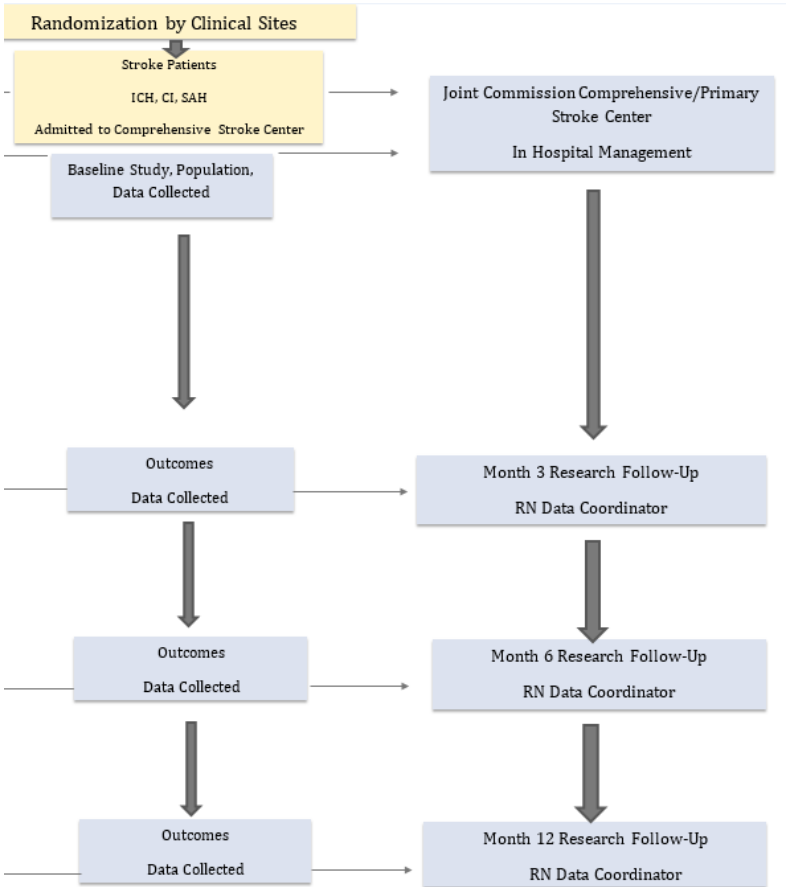
In conjunction with our patient and caregiver stakeholders, we will develop and utilize a protocol-driven approach for approaching patients and caregivers about the study and where possible, both patients and caregivers will participate in the consent process. Training on patient identification and a video on the informed consent process will be developed at the Clinical Coordinating Center (CCC) based on the pilot experience. If questions arise from an individual approached for recruitment, our patient/caregiver research partners at each C3FIT Site may be engaged to assist.

Screening for potential recruitment to C3FIT will progress during the hospital stay. Stroke patient admission logs will be checked frequently by the Coordinator for cases meeting the inclusion/exclusion criteria above. Data establishing eligibility will be obtained from the hospital admission sheet and progress notes. Functioning levels pre-stroke will be determined to establish a pre-stroke mRS/smRS of 0 or 1. Those deemed to fit the inclusion/exclusion criteria will be approached to initiate the informed consent process. Study personnel will obtain the location to which the patient will be discharged, for patients who consent, and baseline assessments will be obtained after consent is obtained. In addition, to data collected from the patient, the patient's caregiver and other contacts will be identified and collected to ensure recontact for future research visits and study goals and schedule will be reviewed. Informed consent will be obtained from both the patient and the caregiver or their legal surrogate."

Informed Consent Process. The patient and caregiver/family will not be enrolled until verbal discussion (in-person, by phone, or virtually) that describes the purpose of the study, study interventions, risks and benefits associated with study procedures, and other human subjects' protections (contained in the informed consent document) occur; consent forms can be sent by mail or email for signature, and virtual e-Consent can be used. Participation in the study will not affect patient or caregivers' in-hospital or post-discharge care, and, as such, discussions of alternatives to participating are not necessary. Potential patients will be informed that the alternative to participating in the C3FIT follow-up will be the standard post-discharge recovery care paradigm provided by the clinical site. Informed consent will be obtained by the PI or via their designated study personnel. Consent may be obtained from the patient if, in the opinion of the Site Investigator, the patient is capable of participating in the informed consent process or from the appropriate legal surrogate based on applicable law. Personnel obtaining consent will be appropriately certified by the University of Miami's Collaborative Institutional Training Initiative (CITI) certification or appropriate certification as deemed by the clinical site. The informed consent document will be reviewed periodically; changes will be approved by the Steering Committee, as well as the IRB and Data Safety

Monitoring Board (DSMB). Documentation of the signed informed consent will be maintained at the clinical site.

Figure 4. C3FIT Patient Flow Diagram – CSC/PSC Arm Only



Outcome visits = blue; Scheduled visits = gray.

Management of Patients. For patients in both arms of the trial, the study aims to utilize the standard in-hospital management of all stroke patients for the site, and all patients at the site will be treated using this standard management. This implies that participation in C3FIT does not directly affect the care and intervention provided to individual patients enrolled in the study at the site during the hospital stay, and that informed consent for follow-up by C3FIT can be obtained during discharge planning or within 5 business days post discharge ideally (to a maximum of 14 total days) for the subject.

Participant Retention. Monitoring of potential patient dropout and loss to follow up at each clinical site will be conducted at an early stage (in-person, by phone, or virtually using the Vivify Go App or other audio/video capabilities) to allow intervention. Both will be mitigated by having C3FIT's site personnel encourage and maintain participation and patient engagement, providing monthly feedback reports, having the Clinical Site PI contact patients/caregivers to discuss feelings about continuing participation, and utilizing other techniques identified in our demonstration project. Data from monitoring visits, GWTG, and the SDCC will be used by the CCC to monitor fidelity of the intervention during the period of enrollment and follow-up.

Participant Reimbursement. Research participants can be reimbursed for their time and effort in C3FIT at a rate of $25 for the collection of study outcomes at baseline, 3, 6, and 12 months by completing a SRU call and an intervention research visit for a total of $100. Sites that elect to provide reimbursement will do so in a method in alignment with their own site's institutional policies.

5. MODEL OF CARE – THE CSC/PSC ARM

Post-discharge, management and treatment of patients in the CSC/PSC arm will follow general clinical practice guidelines as is usually provided by the site in the management of all patients following a stroke, e.g. one-month clinic follow-up by a vascular neurologist. Patients will return to the CSC/PSC site per protocol for data collection research visits at 3, 6, and 12 months, and the University of Alabama Birmingham (UAB) SDCC Survey Research Unit (SRU) will contact them by phone at these times (see Figure 4). No C3FIT intervention management will be provided at these visits, however, usual standard of stroke care will occur. If there are emergent needs, the patient will be referred to that site's emergency department, patient's family physician, or the physician PI at the site.

6. BASELINE AND FOLLOW-UP ASSESSMENTS AND LABORATORY EVALUATIONS

The following outlines the Data Paradigms for the CSC/PSC arm based on obtained values for various scales and data points utilized. The guidelines establishing blood pressure and cholesterol goals are from the American Heart and Stroke Association.[8]

A. On-Study/On-Intervention Evaluations

The schedule of evaluations occurring after randomization while the subject is on-study and on (or about to start) intervention along with allowable time window in which evaluations may take place (±30 days with a target of ±14 days) is shown in Table 7. Primary and secondary outcomes are considered a mandatory part of the protocol; remaining measures will be collected if patient/caregiver are able and/or available.

Table 7. Data Collection Paradigm: CSC/PSC Arm

Item/Metric	In Hospital Prior to Discharge	Post Discharge Visit											
		Day 0-14	Month of Visit to Home/Facility										
		1	2	3	4	5	6	7	8	9	10	11	12
Informed Consent Confirmed	X			X			X						X
Demographics (Age, Gender, Race/Ethnicity, Marital Status, Zip Code of Residence, Income, and Education)*	X			X			X						X
Caregiver/Family identified*	X			X			X						X
Medical Record Number (MR #)*	X												
Get-With-The-Guidelines (GWTG) in-hospital data*	X												
Complications*[1]	X			X			X						X
Patient Medical History	X			X			X						X
National Institutes of Health Stroke Scale (NIHSS)*	X												X
Stroke Subtype*	X												
Prior stroke/Transient Ischemic Attack (TIA)*	X												
Risk factor profile*[2]	X												X
Cholesterol panel or LDL*	X			X			X						X
Hemoglobin A1C (HBA1C)*	X			X			X						X
Perceived Support				SRU			SRU						SRU

Stroke Impact Scale (SIS)				SRU			SRU						SRU
Simplified Modified Rankin Scale (smRS)	X			SRU			SRU						SRU
Blood Pressure (BP) Control: at target	X			X			X						X
Lipid Control: LDL, at target	X			X			X						X
Diabetes Control: HBA1C, at target	X			X			X						X
Smoking Status	X			X			X						X
Body Mass Index (BMI)	X			X			X						X
Diet Assessment	X			SRU			SRU						SRU
Exercise Assessment	X			SRU			SRU						SRU
Mortality surveillance				X			X						X
Recurrence surveillance				X			X						X
Readmission surveillance				X			X						X
Time at Home				X			X						X
Depression: Patient Health Questionnaire (PHQ-9)				X			X						X
Caregiver Strain Index (CSI)				X			X						X

RED=Primary and Secondary Outcomes, BLACK=Additional Assessments by Data Coordinator
SRU=UAB's Survey Research Unit
[1]Complications monitored: Urinary tract infection, pneumonia, aspiration, deep vein thrombosis, skin breakdown, fall, myocardial infarction, depression, fever/other infection, and Afib.
[2]Risk factor profile: hypertension, diabetes, hyperlipidemia, smoking status, BMI, Afib, family history.
*Will be collected if patient/caregiver are able and/or available.

Intervention Discontinuation Evaluations. If the patient or caregiver/family declines follow up in-person visits, we will offer follow-up phone or virtual evaluations for primary and secondary outcomes and other assessments. If consent not provided for this, no follow up will occur.

Special Instructions and Definitions of Evaluations. Evaluations to be performed include: SIS and smRS, PHQ-9 depression scale, Caregiver Strain Index, blood pressure, Cholesterol panel, Hemoglobin A1c, BMI, Smoking cessation, exercise assessment, diet assessment, readmission, and recurrence, and others (see Table 7).

Final On-Study Evaluations. On study evaluations will be completed by the Coordinator and the University of Alabama Birmingham (UAB) SDCC Survey Research Unit (SRU) to include SIS and smRS, and other assessments (see Table 5).

Concomitant Interventions. None.

Study Intervention Modifications. None.

Assessments. Table 7 identifies and defines the assessments and the timeframe for each measurement parameter.

Other Laboratory Studies. None.

7. MANAGEMENT OF ADVERSE EXPERIENCES

Adverse experiences are anticipated to be rare. This study does not involve agents or interventions that are likely to be associated with adverse experiences. This study will use the standardized JC and ASA national guidelines for stroke care management. As revisions occur to the national guidelines these will be made available to clinical sites to modify their clinical site stroke patient care management strategies.

8. INTERVENTION DISCONTINUATION

A. Data and Safety Monitoring Board (DSMB)

A formal Data and Safety Monitoring Board (DSMB) will be convened at regular intervals (for example, twice a year) to review recruitment, data security, and patient safety. We do not anticipate adverse events from this intervention, but the DSMB will monitor overall outcomes, including the following: death, recurrent stroke, rehospitalization, serious hemorrhage, recurrent or new ischemic event, serious adverse experiences, and premature withdrawal from the study. This study does not involve agents that likely will be associated with adverse experiences; as such, the DSMB will have a follow-up schedule and Significant Adverse Effects (SAE) reporting schedule that will include regular meetings with possible emergency meetings.

Data and Safety Monitoring Plan. The DSMB is tasked with mandating specific data required for independent analysis. A formal DSMB Plan will be developed by the DSMB Chair and the CCC and SDCC PIs that includes a framework for monitoring of study data and process, clinical and primary/secondary outcomes and will be submitted to the full DSMB. The frequency of data and safety monitoring will be determined in consultation with PCORI.

B. Adjudication Committee (AC)

In addition to the PI, two vascular neurologists will be charged with adjudicating stroke-related hospitalizations reported during the follow up period. This group (the Adjudication Committee) will review specific outcomes, including recurrent stroke, including subtype; and serious hemorrhage, including site.

C. Criteria for Intervention Discontinuation

- Revocation of informed consent.
- Subjects moving substantial distance from the original geographical location.
- Morbidity or mortality giving rise to insurmountable barriers to continued assessment.

9. STATISTICAL CONSIDERATIONS

C3FIT will compare the effectiveness of the *JC-certified CSC/PSC care system with the ISPU care system* in improving patient outcome and quality of life post-stroke. The primary outcome is the SIS-3.0 at 12 months, while assessment at 3 and 6 months are part of secondary outcomes. The primary analysis will focus on intervention differences in mean SIS score at 12 months. Mixed models will be used to assess the SIS outcome at 12 months, allowing the hierarchical nature of the data to be reflected (patients within Sites), and providing an accounting for data that are not missing completely at random. We anticipate (and trust) that randomization will balance potential confounding factors; however, secondary analysis will be performed with adjustment for baseline factors that could be imbalanced and potentially confound the estimated intervention differences, specifically adjusting for factors assessed at baseline that are known to be strongly associated with stroke outcomes (specifically age and stroke severity). Patients who die or cannot return due to morbid conditions will be assigned to "floor" score for poor outcome (and hence does not reduce the number of evaluable patients). With these patients not representing missing data, we anticipate there will be relatively little additional missing data and that these data will be generally missing at random (i.e., patients

not returning because of other conditions, like moving); however, missing data that is present will be addressed by including baseline, 3 and 6 month data in the model and allowing the mixed model to adjust estimates for the missing data at 12 months by incorporating information available through the correlation between measurements.

A. Sample Size

The total sample size for the primary outcome for this study will be approximately 1,800 patients (each arm anticipated to have approximately 900 patients with approximately 100 patients, at each clinical site), although some sites will enroll up to 140 consented participants due to limited enrollment by other sites due to institutional COVID PANDEMIC issue. We have intentionally restricted clinical site participation to those Sites certified as a TJC CSC/PSC (or acting as such). This restriction is important not only to provide CSC/PSC intervention "state of the art" comparator group, but also to increase the homogeneity of Sites and, thereby, reduce intraclass correlation coefficient in the hierarchical models. We do not have information on the intraclass correlation coefficient of the SIS, but given this restriction, we would suggest it is quite small (0.01); however, for power calculations, we have conservatively assumed it is of modest size (0.05) and also provide estimates should it be large (0.10). These larger intraclass correlations would arise if there is larger than anticipated heterogeneity of intervention effect, and that there is adequate power for these larger intraclass correlation coefficients shows that we are well-positioned to detect intervention even in the presence substantial heterogeneity of the effect. Under this assumption and with the standard deviation of the SIS being approximately 8[49], if the interclass correlation is 0.05 then mean intervention differences of 2.7 and 3.2 can be detected with 80% and 90% power respectively (power calculations by PASS, NCSS, Kayville, UT); 2.7 was chosen based on evidence from Lin et al[30]. Even if the intraclass correlation is 0.10, differences of 3.7 and 4.3 can be detected with 80% and 90% power. As such, we have quite good power to detect clinically significant differences generally smaller than half of a standard deviation of the outcome scale.

B. Analyses

Analysis of the primary analysis will focus on intervention differences in mean SIS and smRS scores at 12 months. In addition, the mixed models will be used to assess the SIS and smRS outcomes at 12 months, allowing the hierarchical nature of the data to be reflected (patients within Sites), and providing an accounting for data that are not missing completely at random. Analyses of the secondary outcomes of time either rehospitalization or subsequent stroke will be assessed using proportional hazards analysis. In order to incorporate the hierarchical nature of these data, this analysis will be implemented using packages such as the SURVIVAL procedure from the SUDAAN package (Research Triangle Institute, Research Triangle Park, NC).

Analysis of the QOL secondary outcome will follow the analysis approach as the primary analysis and will have similar power (i.e., ability to detect intervention differences of magnitude of a half-standard-deviation). The study will also focus on identifying specific subgroups who are particularly responsive or resilient to intervention differences.

10. HUMAN SUBJECTS PROTECTIONS

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the Steering Committee, IRB, and DSMB responsible for oversight of the study. A signed consent form will be obtained from the subjects.

The total sample size for the primary outcome for this study will be approximately 1262 patients who have consented to participate. The original sample size approximated 100 patients at each clinical site, although some sites will enroll up to 140 consented participants due to limited enrollment by other sites resulting from institutional COVID pandemic issues..

- Participating patients at a clinical site randomized to CSC/PSC arm will be followed by the Coordinator to collect the same acute in-hospital metrics to measure care quality, health status, and outcomes and will also be contacted via telephone by the blinded personnel at the UAB SDCC SRU to assess primary outcomes.
- The patient and their caregiver (or their legally authorized representative, if patients are unable to provide consent) will be approached to participate in the study ideally during hospitalization or within 5 business days of hospital discharge ideally (to a maximum of 14 total days) to allow for data collection of specific acute in-hospital metrics). Caregivers may be consented at any time during the C3FIT study, but no data will be collected until consent is obtained. At research visits, the following will be obtained: (1) demographic and other data collection; (2) follow-up data collection specific to the CSC/PSC arm; and (3) contact via telephone survey to collect SIS and smRS outcome data.
- C3FIT's population will include patients with all stroke subtypes and levels of severity, regardless of gender, race, ethnicity, or socioeconomic status. Each Site will recruit from their geographically eligible patients (who have a discharge diagnosis of stroke according to their ICD-10 code) until approximately 100 patients are consented, although some sites will enroll up to 140 consented participants due to limited enrollment by other sites due to institutional COVID PANDEMIC issue.

B. Adequacy of Protection Against Risks

Recruitment and Informed Consent. The acute in-hospital study sample will include patients admitted to the hospital with suspected stroke symptoms. Potential participants (both patient and caregiver if available) will be approached for recruitment ideally within 5 business days post discharge ideally (to a maximum of 14 total days) for the participant. In the event that the patient is unable to provide consent, their surrogate can be consented. Patients will be identified by study personnel from ED and stroke service admission logs; pilot data suggests nearly complete case ascertainment. To assure that acute in-hospital recruitment and informed consent procedures are followed consistently across Sites, a guidance document will be prepared in consultation with Site PI's and other patient, caregiver and organizational stakeholders, and Site personnel will be trained consistently by CCC staff.

The post-hospital discharge study sample will include patients and caregivers who have a discharge diagnosis of stroke and who reside in each clinical site's defined geographic area. Potential participants will be approached prior to hospital discharge regarding their interest in

participating in the study, and every effort will be made to consent both patient and caregiver at that time.

Patients and caregivers at a CSC/PSC site will be managed according to a traditional post-acute JC-certified CSC/PSC design, including a phlebotomy (draw blood) for cholesterol and HBA1C according to the study time schedule in Figure 7.

The consent process will begin at hospital admission at a C3FIT clinical site. The PI at the site or his/her Co-I designee will provide information to the patient and/or caregiver about the nature of the trial, the two arm comparator groups and the randomization of the site. The fact that the C3FIT study does not involve an investigational drug or device will be discussed with the patient and caregiver. Potential participants will be made aware of the scientific basis for the comparison of methods of care delivery, and the clinical equipoise of the investigators. Information on the requirements of the participants will be discussed: (1) to allow appropriate outcome scales to be obtained, (2) the approximate time involved in obtaining these scales based on or pilot experience, (3) that some of the outcome scales will be obtained by phone by blinded interviewers at the UAB SDCC SRU, (4) and that common laboratory tests will be obtained that would be appropriate for monitoring any person who suffered a stroke.

Potential and enrolled participants will: (1) be assured that they may withdraw consent at any time and do not have to provide a reason for their withdrawal; (2) have the right to speak with a member of our patient/stakeholder advisory group if they so choose to obtain additional information; and (3) be provided access to study personnel at their C3FIT clinical site (including the PI) to answer any questions or address concerns. In addition, the C3FIT personnel at the CCC are available for any questions or issues they identify. Potential participants will be assured that study personnel will be well trained, are familiar with guidelines for human subject's protection, and will have completed appropriate human subject's protection training as required by their site and the C3FIT Central IRB. A member of the Stakeholder Committee for C3FIT is a medical ethicist who has assisted in the design of the pilot study and, as such, will be available as a resource to C3FIT study personnel if specific ethical issues arise.

B. Potential Risks to Subjects and Protections

Potential risks for C3FIT participants and proposed methods to reduce these risks are described below. A member of the Stakeholder Committee for C3FIT is a medical ethicist who has assisted in the design of the pilot study and, as such, will be available as a resource to C3FIT study personnel if specific ethical issues arise.

5) *Breach of confidentiality of medical information in the acute in-hospital or outpatient setting – minimal risk.* All data will be stored in encrypted, password-protected databases that meet mandated IT security standards and will include subject identifiers (name, address, date of birth, and medical record numbers) necessary to maintain contact during the study.
6) *Anxiety/discomfort – minimal risk.* Participants will be assured that all study-related data and information (including both outcome assessment and monitoring data) will be kept confidential by the PI and study personnel, any questions and concerns can be addressed at any time, and participants can refuse to answer any question or not participate at any time during the study.

7) *Harm from physical and clinical assessments or measurements conducted as part of the outpatient CSC/PSC program – minimal risk.* Physical assessments like the NIHSS (measured prior to hospital discharge), the SIS, and smRS are standard assessment scales utilized in clinical practice. C3FIT study personnel will undergo training and certification in these scales, which have no recognized physical harm. Other scales used, including the primary outcome scale (SIS), have been used in many clinical situations/studies with no recognized harm.
8) *Discomfort and/or harm from blood draws to assess cholesterol level and HbgA1c – minimal risk.* Standard phlebotomy techniques will be used as in typical care. The minimal pain and risk of fainting will be acknowledged to potential participants, and participants may decline some or all of the blood draws.

Since no investigational device is involved in the C3FIT study, we anticipate few adverse events. However, our conservative approach is to provide several layers of protection for our study participants: (1) the informed consent process itself; (2) access to the C3FIT personnel, including the C3FIT nurses and physician Site PI; (3) access to the CCC staff, including the C3FIT PI; (4) a Central IRB at Vanderbilt to provide consistency across 18 C3FIT Sites; and (5) a Data and Safety Monitoring Board (DSMB) that will review patient outcome data; and (6) human subjects research protections using the CITI certification as required by the Central IRB.

Adverse events (physical, behavioral, or psychological) will be reported to the Clinical Site PI or the SDCC; they will report these adverse events per guidelines in a timely fashion to the CCC, where they will be reviewed by the PI, Project Manager and forwarded to the DSMB.

C. Potential Benefits of the Proposed Research

Benefits for Patients. The major benefit to patients will accrue to future patients who benefit from the information gained from this study to design a patient-centered stroke healthcare delivery system that is comprehensive, integrated, and caregiver/family-focused. Many of the current issues faced by stroke patients involve lack of defect free stroke care in the in-hospital phase of care, leading to longer lengths of stay and in-hospital complications. These complications can lead to loss of QOL over many years. Lack of defect free care also plagues the post-hospital phase of care where stroke recurrence leads to readmissions and less Time at Home. Patients can also benefit by access to results of C3FIT to inform their choices in health care based on data that identifies the most effective and efficient care.

Based on positive results of C3FIT, patients could also benefit by having the potential for home care management, avoiding time and travel costs for outpatient clinic visits. Patients will have screening for HbgA1C and cholesterol to measure risk factor control at-target which may help identify targets of therapy. Patients could also benefit by having their caregivers supported by study personnel reducing caregiver strain. Because patients are involved in the design, implementation and dissemination of C3FIT outcomes that matter to them will be foremost in the study design.

Benefits for Caregivers. The major benefit to caregivers will accrue to future caregivers where the information gained from this study can be used to design a patient-centered stroke healthcare delivery system that is comprehensive, integrated, and caregiver/family-focused. Such a system may encourage recovery in their associated patient and limit stroke recurrences and readmissions.

If results from C3FIT are positive, caregivers could have the potential advantage of home visits, avoiding the stress, time commitment, and travel costs of clinic visits. Caregivers could potentially benefit by having a team that monitors their stress level and offers support.

Benefits for Organizational Stakeholders and Society. Organizational stakeholders will benefit by having access to high quality data to inform decisions regarding design and implementation of the most efficient and effective stroke delivery system.

D. Risk-to-Benefit Ratio

C3FIT risks to participants are reasonable. C3FIT does not involve any investigational drug or device, so the risks of unknown or unrecognized side effects of investigational drugs and devices are not an issue. C3FIT involves several blood specimen collections (HbgA1C and cholesterol) with associated pain from the needle stick. This discomfort is transient and considered minimal. These tests would be considered standard of care in a stroke patient. The collections themselves are to obtain lab values that will be used to document control at target of risk factors and inform decisions about best medication or other therapy based on nationally accepted guidelines. Testing procedures involve only grading scales often used in practice (i.e., NIH Stroke Scale, Simplified Modified Rankin Scale (smRS), or scales that are commonly used in stroke clinical trials for outcome). The information requested will include some information about sexual, urinary, and bowel function but will be obtained by trained medical personnel with a minimum of patient distress. The time involved in obtaining information from patients and caregivers is carefully considered. Only those scales determined critical to patient management and documentation of key functional and QOL outcomes are utilized. The timing of administration of these scales is also carefully chosen to not provide undue time commitment or stress at any visit. Given the minimal risks and significant potential benefits the risk benefit ratio seems reasonable and quite acceptable.

Importance of the Knowledge to be Gained. We have discussed the opportunity to improve stroke care delivery given the lack of defect free care, complications, recurrences, and lack of risk factor control documented for stroke patients. In addition, the opportunity to focus on stroke outcomes that are patient-centered will significantly improve patient and caregiver engagement in their intervention and recovery journey resulting from stroke. Organizational stakeholders such as the JC and the ASA, who are tasked with offering improvement programs that are informed by high quality scientific evidence, will find data from C3FIT invaluable, as Level 1 evidence to assist in identifying the appropriate focus for resources and effort does not currently exist. Vascular neurologists (VNs) and rehabilitation and internal medicine physicians will find that the results of this trial will help design care delivery approaches that provide the most appropriate patient centered functional and QOL outcomes rather than depending on compliance with process measures that may not contribute to these more important outcomes.

As in any research effort, much of the time, stress, and risk of the project is born by participants. It is hoped that including them as Research Partners may help to ally some of this burden. In any event, they are to be honored for their involvement.

Data and Safety Monitoring Plan. A formal Data and Safety Monitoring Board (DSMB) will be convened at regular intervals (for example, twice a year) to review and monitor recruitment, data security, and patient safety. The DSMB and development of the formal DSMB Plan is described in Section 8.

ClinicalTrials.gov. This randomized trial has been registered, and results will be reported in ClinicalTrials.gov as encouraged by NIH and required by Public Law 110-85.

E. Inclusion of Women and Minorities

This study has no exclusion criteria based on gender, race, or ethnicity. We anticipate that patients recruited to our study will reflect the demographic profile of the general stroke population, which proportionally includes more older adults than younger and good representation of minorities. While the age-adjusted incidence of stroke (primarily ischemic stroke) in men is approximately 30% higher than in women, more women have strokes because women live longer than men. However, because they are older at time of stroke, women have more co-morbidities so they may be less likely to meet some of inclusion/criteria.

F. Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, PCORI, or the DSMB.

G. Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, PCORI, or the DSMB as part of their duties to ensure that research subjects are protected.

12. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Publication Subcommittee of the Steering Committee. Presentations, abstracts, or manuscripts will be submitted to PCORI within 30 days of acceptance.

13. REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive Summary: Heart Disease and Stroke Statistics-2016 Update: A report from the American Heart Association. Circulation. 2016 Jan 26;133(4):447-54. doi: 10.1161/CIR.0000000000000366.
2. Bakas T, Clark P, Kelly-Hayes M, et al. AHA/ASA scientific statement. Evidence for stroke family caregiver and dyad interventions. A statement for healthcare professionals from the American Heart Association and American Stroke Association. Stroke. 2014;45:2836-52.
3. Rosamund W, Flegal K, Furie K, et al. Heart Disease and Stroke Statistics – 2008 Update: A report from the American Heart Association Statistics Committee and Stroke Statistics Committee. Circulation. 2008;117:e25-146.
4. Coull A, Lovett J, Rothwell P. Population based study of early risk of stroke after transient ischemic attack or minor stroke: Implications for public education and organization of services. BMJ. 2004;328:326-8.
5. Petty G, Brown R, Sicks J. Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975-1989. Neurology. 1998;50:208-16.

6. Samsa G, Brian J, Lipscomb J, et al. Epidemiology of recurrent cerebral infarction: A Medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. Stroke. 1999;30:338-49.
7. Tooth L, McKenna K, Barnett A, Prescott C, Murphy S. Caregiver burden, time spent, caring and health status in the first 12 months following stroke. Brain Injury. 2005;19:963-74.
8. Persson J, Holmegaard L, Kerlberg I, et al. Spouses of stroke survivors report reduced health-related quality of life even in long-term follow-up. Results from Shalgrenska Academy Study on Ischemic Stroke. Stroke. 2015;46:2584-90.
9. Gaines K, Commiskey P. Stroke: The critical neglected first year post-stroke. J Integr Care. 2018; https://doi.org/10.1108/JICA-09-2017-0030.
10. Emberson J, Lees KR, Lyden P, et al. Effect of intervention delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischemic stroke: A meta-analysis of individual patient data. Lancet. 2014 Nov 29;384(9958):1929-35. doi: 10.1016/S0140-6736(14)60584-5.
11. Choi JC, Jang MU, Kang K, et al. Comparative effectiveness of standard care with IV thrombolysis versus without IV thrombolysis for mild ischemic stroke. J Am Heart Assoc. 2015;4:e001306.
12. Wardlow JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, et al. Recombinant tissue plasminogen activator for acute ischemic stroke: An updated systematic review and meta-analysis. Lancet. 2012;379:2364-72.
13. Boudreau D, Guzauskas G, Chen E, Lalla D, Tayama D, Fagan S, et al. Cost-effectiveness of recombinant tissue-type plasminogen activator within 3 hours of acute ischemic stroke. Current evidence. Stroke. 2014;45:3032-9.
14. Tung C, Win S, Lansberg M. Cost-effectiveness of tissue-type plasminogen activator in the 3- to 4.5-hour time window for acute ischemic stroke. Stroke. 2011;42:2257-62.
15. The Joint Commission. 2016. http://www.jointcommission.org/.
16. Lakshminarayan K, Schissel C, Anderson D, et al. Five-year re-hospitalization outcomes in a cohort of patients with acute ischemic stroke. Medicare Linkage Study. Stroke. 2011;42:1556-62.
17. Roberts CS, Gorelick PB, Ye X, Harley C, Goldberg GA. Additional stroke-related and non-stroke-related cardiovascular costs and hospitalizations in managed-care patients after ischemic stroke. Stroke. 2009;40:1425-32.
18. Joubert J, Reid C, Barton D, et al. Integrated care improves risk-factor modification after stroke: Initial results of the Integrated Care for the Reduction of Secondary Stroke model. J Neurol Neurosurg Psychiatry. 2009;80:279-84.
19. Chaturvedi S, Turan TN, Lynn MJ, Kasner SE, Romano J, Cotsonis G, et al., for the WASID Study Group. Risk factor status and vascular events in patients with symptomatic intracranial stenosis. Neurology. 2007;69:2063-68.
20. McAlister FA, Majumdar SR, Padwal RS, Fradetta M, Thompson A, Buck B, et al. Case management for blood pressure and lipid level control after min or stroke: PREVENTION randomized control trial. Canadian Medical Association Journal. 2014;186:577-84.
21. Billinger S, Arena R, Bernhardt J, et al. AHA/ASA Scientific Statement. Physical activity and exercise recommendations for stroke survivors. A statement for healthcare professionals

from the American Heart Association and American Stroke Association. Stroke. 2014;45:2532-53.
22. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis S, et al., for the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical intervention with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): The final results of a randomised trial.Lancet. 2014;383:333-41.
23. Chimowitz MI, Lynn MJ, Turan TN, Fiorella D, Lane BF, Janis S, et al., for the SAMMPRIS Investigators. Design of the stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis trial. J Stroke Cerebrovascular Dis. 2011;20:357-68b.
24. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, et al., for the SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. NEJM. 2011;365:993-1003a.
25. Carter BL, Rogers, M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension. Arch Int Med. 2009;169:1748-55.
26. Porter M, Lee T. The strategy that will fix health care. Harvard Business Review. 2013 Oct.
27. Wu RC, Lo V, Rossos P, et al. Improving hospital care and collaborative communications for the 21st century: key recommendations for general internal medicine. Interact J Med Res. 2012;1:e9.
28. Porter M, Teisberg E. Redefining healthcare: Creating value based competition on results. Boston. Harvard Business School Press. 2006.
29. Porter M. Value-based healthcare delivery part II: Integrated practice units, outcome and cost measurement. Medical Leadership Institute. Dec 2010. http://www.medicaidleaders.org/sites/default/files/integrated%20practice%20units.pdf.
30. Lin KC, Fu T, Wu CY, et al. Psychometric comparisons of the Stroke Impact Scale 3.0 and Stroke-Specific Quality of Life Scale. Qual Life Res. 2010;19:435-443.
31. Sacco R, Boden-Albala B, Gan R, et al. Stroke incidence among whites, blacks, and Hispanics from the same community of Northern Manhattan. Am J Epidemiol. 1998;147:260.
32. Ramirez L, Kim-Tenser M, Sanossian N, et al. Trends in acute ischemic stroke hospitalizations in the United States. J Am Heart Assoc. 2016;5:e003233. doi:10.1161/JAHA.116.003233.
33. The Joint Commission. Quality Check. 2016. http://qualitycheck.org/StrokeCertificationList.aspx.
34. American Heart Association Get With The Guidelines. Focus on quality: The more healthcare quality improves the more patient outcomes do too. 2018. www.heart.org/HEARTORG/Professional/GetWithTheGuidelines/Get-With-The-Guidelines--HFStroke_UCM_001099_SubHomePage.jsp.
35. Centers for Medicare and Medicaid Services. Putting patients first. 2018. https://www.cms.gov/.
36. Duncan P, Bushnell C, Rosamond W, et al. The Comprehensive Post-Acute Stroke Services Study (COMPASS): Design and methods for cluster randomized pragmatic trial. BMC Neurology. 2017;17:133.
37. Powers WJ, Rabinstein AA, Ackerson T, et al. on behalf of the American Heart Association Stroke Council. Acute ischemic stroke: A guideline for healthcare professionals from the

American Heart Association/American Stroke Association. Stroke. 2018; STR.0000000000000158, originally published January 24, 2018. https://doi.org/10.1161/STR.0000000000000158.
38. Bogousslavsky J and Regli F. Cerebral infarct in apparent transient ischemic attack. Neurology. 1985; 35: 1501-1503.
39. Albers G, Caplan L, Easton J, et al. Transient ischemic attack: Proposal for a new definition. NEJM. 2002; 347: 1713-1716.
40. Alubacher J, Martel P, Mas J. Clinical practice guidelines: Diagnosis and immediate management of transient ischemic attacks in adults. Cerebrovascular Dis. 2005; 20: 220-225.
41. Easton J, Saver J, Albers G, et al. Definition and evaluation of transient ischemic attack. AHA/ASA Scientific Statement. Stroke. 2009; 40: 2276-2293.
42. ACOG Committee Opinion. Guidelines for diagnostic imaging during pregnancy and lactation. Obstetrics & Gynecology. 2017; 130 (4): e210-e216.
43. Toppenberg K, Hill D, Miller D. Safety of radiographic imaging during pregnancy. Am Fam Physician. 1999; 59 (7): 1813-1818.
44. Ovbiagele B, Saver JL, Fredieu A, et al. PROTECT: A coordinated stroke intervention program to prevent recurrent thromboembolic events. Neurology. 2004 Oct 12;63(7):1217-22.
45. Wolfe CD, Redfern J, Rudd AG, et al. Cluster randomized controlled trial of a patient and general practitioner intervention to improve the management of multiple risk factors after stroke: Stop Stroke. Stroke. 2010 Nov;41(11):2470-6. doi: 10.1161/STROKEAHA.110.588046. Epub 2010 Sep 23.
46. Gaines K. Centers for Medicare & Medicaid Services (CMS). Health Care Innovation Award (HCIA) #1C1CMS331043. Jul 2012-Dec 2015.
47. Gaines K. NIH Office of Minority Health. #CPIMP071044.
48. 2019 ICD-10-CM Codes 160-169: Cerebrovascular disease. Retrieved from: https://www.icd10data.com/ICD10CM/Codes/I00-I99/I60-I69/I63-/I63.9.
49. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S, Laster LJ. The Stroke Impact Scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. Stroke. 1999 Oct;30(10):2131-40.