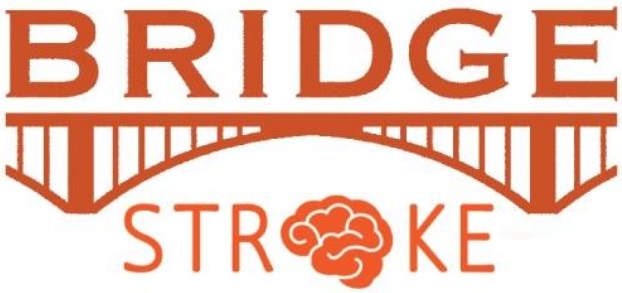

Brazilian inteRvention to Increase eviDence usaGe in practicE - Stroke

A Cluster randomized trial to evaluate the increase in usage of evidence-based practices using a multifaceted strategy

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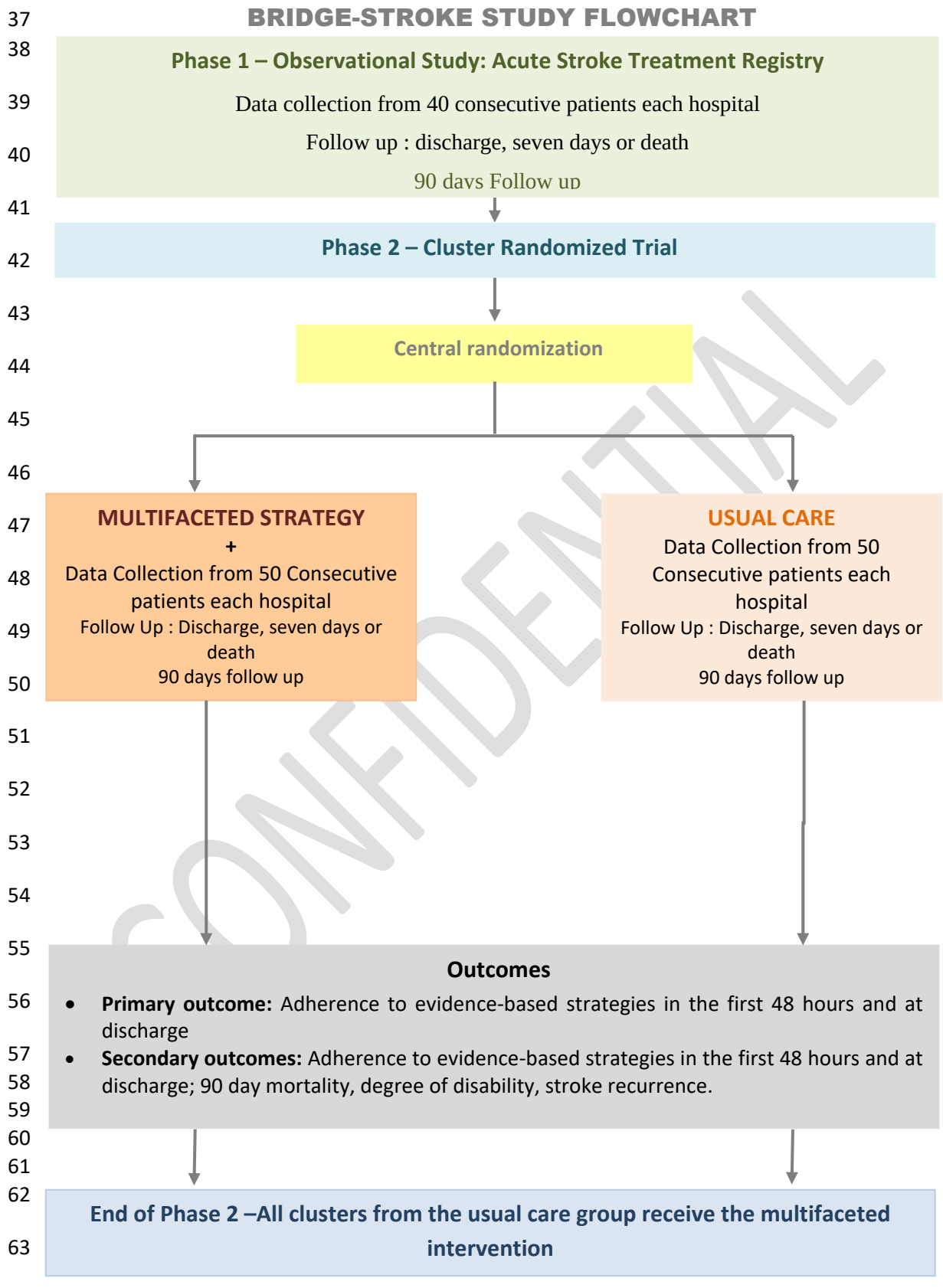

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Title	BRIDGE-STROKE - Brazilian inteRvention to Increase eviDence usaGe in practicE – Stroke - Cluster randomized trial to evaluate the increased use of evidence-based practices using a multifaceted strategy
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Study Design	The BRIDGE_STROKE study will be conducted in two phases: Phase 1: Prospective observational study (registry) aimed at recording the clinical practice of acute management of stroke in patients seen at public and private hospitals. In addition, there will be a longitudinal follow-up of these patients up to hospital discharge or the seventh day of hospitalization. After 90 days data on mortality, disability and stroke recurrence will be collected by a phone call interview. Phase 2: Cluster randomized trial to investigate the effectiveness of a program to improve in-hospital care processes at these hospitals, with a 90 day follow up to verify mortality, stroke recurrence and disability.
Methodological Quality	Web-based central randomization and allocation concealment; Blinded and independent committee for assessment and validation of the stroke diagnosis and outcomes; Intention-to-treat analysis;
Objectives of the Study	**Objectives of the First Phase** • To assess use of evidence-based interventions /Antithrombotics, rt-PA in eligible patients, Door-to-Needle Time < 60 min for rt-PA, prophylaxis for DVT) in acute treatment and at hospital discharge (anticoagulants in patients with atrial fibrillation or flutter, antithrombotic agents, statins (LDL < 100 or not documented).

	• To detect the main barriers to the acceptance of interventions. • To prepare a registry of stroke patients in Brazilian hospitals to assess data related to demographic characteristics, morbidity, mortality, and standard practice in the treatment of stroke. **Phase 2 Primary Objective:** • To assess whether a multifaceted intervention to improve clinical practice is more effective than usual treatment regarding the prescription of evidence-based therapies for acute stroke treatment in the first 48 hours and prior to discharge including (Early Antithrombotic, RTPA within therapeutic window, DTNT < 60 min, DVT Prophylaxis, Dysphagia Screening, Antrombotic prior to discharge, anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation, LDL < 100 or not documented, smoke cessation education). **Phase 2 Secondary Objectives** • To assess whether a multifaceted intervention to improve clinical practice is more effective than usual treatment regarding the prescription of evidence-based therapies for acute stroke treatment in the first 48 hours and prior to discharge in an "all or none" model • To assess whether a multifaceted intervention to improve clinical practice is more effective than usual treatment regarding in reducing stroke recurrence, disability and mortality in 90 days.
Eligibility Criterion	**Hospitals:** The hospitals eligible for the BRIDGE study will consist of public and private hospitals offering 24/7 emergency care, with at least one routine physician in the unit for 24 hours and one on-call neurologist. These hospitals must complete the screening form for appropriate initial assessment of basic conditions for inclusion and adherence to the project. **Patients:** Patients over 18 years old, diagnosed with ischemic stroke (including transient ischemic attack) with symptoms lasting up to 24 hours. We will exclude patients with signs of hemorrhagic stroke, expansive lesions, central nervous system infections, and those coming from institutions that did not provide institutional approval form signed by the patients' guardians.
Study Intervention	**Intervention Group:** Multifaceted strategy to improve clinical practices including case manager, reminders, staff training, checklists, and educational materials **Control Group:** usual management of stroke patients
Follow-up	Patients will be evaluated within the first 48 hours and at

	discharge, and 90 days after discharge, data on mortality, disability and stroke recurrence.
Outcomes	**Primary Outcome of the First Phase** • Proportion of prescription of evidence-based strategies. in the first 48 hours and prior to discharge • Barriers to implementation of methodologies. **Primary Outcome of the Second Phase** • Proportion of prescription of evidence-based strategies in the first 48 hours and prior to discharge (composite adherence score), inlcluding Rt-PA within therapeutic window, DTNT < 60 min, DVT Prophylaxis, Early antithrombotic, Antithrombotic at discharge, Anticoagulants for Atrial fibrillation or flutter, LDL < 100 or not documented agents, Assessment for rehabilitation, Smoke cessation education) **Secondary Outcomes of the Second Phase** • Proportion of prescription of evidence-based strategies in the first 48 hours and at discharge "All or none" measures including: Rt-PA, DTNT < 60 min, DVT Prophyilaxis, Early antithrombotic, Antithrombotic at discharge, Anticoagulants for Atrial fibrillation or flutter, LDL < 100 or not documented, Assessment for rehabilitation, Smoked cessation education • Proportion of usage of the additional strategies: global Rt-PA rate, anti-hipertensive agents, and door to needle time< 45 min) • In hospital and 90 days mortality • Degree of disability (measured by the Modified Rankin Scale) at discharge and in 90 days. • Stroke recurrence in 90 days.
Sample Size	Phase 1 : Considering possible losses between phase 1 and 2 , it will be included up to 42 clusters. Phase 2: Considering approximately 50 patients per clusters and from 30 to 36 clusters included, we estimate that it will be needed to collect data from 1500 to 1800.

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Acronyms and Abbreviations

ASA - Acetylsalicylic Acid

TIA - Transient Ischemic Attack

GCP - Good Clinical Practice

CEC - Clinical Endpoint Committee

EDC - Electronic Data Capture

CRF - Case Report Form

CVD - Cardiovascular Disease

DNT - Door-to-Needle Time

GCP - Good Clinical Practice

AMI - Acute Myocardial Infarction

OR - Odds Ratio

Rt-PA - Recombinant thromboplastin/Alteplase

RRR - Relative Risk Reduction

ACS - Acute Coronary Syndrome

AIS – Acute Ischemic Stroke

1. Introduction and Rationale

1.1. Relevance of the Problem - The impact of cardiovascular diseases

Due to the epidemiological transition experienced by most countries in recent decades, chronic diseases, especially cardiovascular diseases (CVDs), including stroke and acute coronary syndrome (ACS) became the most important public health issue. According to the World Health Organization, cardiovascular diseases currently represent the primary cause of death and disability worldwide(1).

Regarding stroke, the estimated prevalence in the United States was 2.8% of the population in 2010, with an estimated increase of 4 million people with a diagnosis of stroke in 2030, representing an increase of 21.9% in the prevalence starting in 2013. Every 40 seconds someone in the U.S. has a stroke and every 4 minutes someone dies from stroke

In South America stroke has been poorly studied. A systematic review of incidence, prevalence and stroke subtypes, shows that overall stroke prevalence rates range from 1.74 to 6.51 per 1000, and annual incidence rates from 0.35 to 1.83 per 1000. In Peru, crude prevalence rate is 6.2 per 1000(2). In Brazil there is no accurate appreciation on stroke incidence. In Argentina, data from an ongoing study in Tandil are awaited (3). Regarding stroke mortality, data from a Brazilian study showed that in 1990, the mortality rate from cerebrovascular diseases was 54.3 deaths/100,000 inhabitants(4) and, in 2011, the estimated mortality rate was 52.4 deaths/100,000 inhabitants(5). Thus, there has not been a significant change in recent years.

The increased incidence and burden of stroke in South America is particularly important. Indeed, there has been a substantial global variation in the impact of stroke when compared with ACS; the mortality rate and impact of these diseases do not evolve smoothly. On a global basis, ACS typically exceeds stroke in terms of mortality and disability. However, in 39% of countries, stroke exceeds ACS in terms of mortality and, in 32% of the countries, stroke exceeds ACS in terms of disability.(6) . In fact, in

developing countries, stroke is responsible for greater overall burden, which may be related in part to development profiles and risk factors.

1.2. Stroke Acute Treatment in South America- Where do we stand in 2014

The available knowledge about the epidemiology of stroke in South America, as well as its standard management, comes from few and limited prospective studies often conducted in a single hospital or a single city, thus inserted in different socioeconomic contexts. Such differences are evident in the data presented in **Table 1** which refers to studies conducted in Brazil**.** There is a significant variation in the rate of use of thrombolytic therapy in these studies: from 1.1% in the study by Carvalho et al.(7) to 4.6, 5.8% and 6.0% in the studies by Carvalho et al, Conforto et al and Moro et al respectively (8-10). The first study was conducted in the region of the city of Fortaleza, comprising 31 hospitals showing distinct profiles. The second study shows data from a private hospital located in São Paulo after the implementation of the U.S. quality improvement program "Get with the Guidelines" ; whereas the third study shows the experience of the Hospital das Clínicas de São Paulo and the forth is restricted to the city of Joinville where the first Brazilian stroke unit was developed. A national profile of stroke management can only be defined after conducting a study covering all regions of the country, based on systematic data collection, and using standardized variables and outcome measures. This step is critical to the understanding of our reality and the development of improvement strategies.

Table 1 - Standards for management of ischemic stroke in Brazilian studies

Study	Use of thrombolytic therapy	Prescription of antithrombotic agents within the first 48 hours	Statin prescription
Carvalho et al. 2011(7)	1.1%	78.6%	52.0%
Carvalho et al. 2012(8)	4.6%	98.2%	56.1%
Conforto et al. 2008(9)	5.8%	Not applicable	Not applicable
Moro et al.2013(10)	6.0%	Not applicable	Not applicable

In Argentina however, data from a national registry (ReNACer), from 2004 till 2006, including 1991 patients from 74 institutions provided important information on the quality of stroke care. This study showed that only 1.05% of patients received thrombolytic therapy and 78.9% were treated with aspirin in the first 48 hours after the acute ischemic stroke(11). This is similar to Brazilian studies mentioned above.

1.3. Quality improvement programs

1.3.1. International Quality Indicators and Development of Improvement Programs

In order to reduce the burden of stroke in the United States, several organizations begun to develop and implement registries with the purpose of measuring the quality of care provided to stroke patients and encouraging improvements(12, 13). The "Get with the Guidelines" (GWTG) Program was developed by the American Heart Association/American Stroke Association (AHA/ASA) as a national registry linked to a performance improvement program with the primary goal of improving the quality of care and outcomes of stroke patients(14, 15).

In 2007, the AHA/ASA joined efforts with the Joint Commission's Primary Stroke Center Certification Program and the Center for Disease Control Coverdell Registry and developed a series of quality indicators used by these three programs. Such indicators made it possible to evaluate the performance of hospitals in terms of stroke management(15, 16). These indicators were developed taking into account the evidence-based therapeutic measures (and with class IA indication) included in the international guidelines of the AHA/ASA(17) and endorsed by the National Quality Forum. Thus, the following performance measures began to be used(15).

Acute Performance Measures:

- IV tPA (intravenous recombinant tissue plasminogen activator) in patients who arrive at the hospital with less than two hours of symptoms and are treated within three hours.
- Early Antithrombotic Medication
- Prophylaxis for Deep Venous Thrombosis.

Performance Measures upon Discharge:

- Antithrombotic Medication
- Anticoagulation in Patients with Atrial Fibrillation.
- Lipid-lowering medication prescribed upon discharge if LDL > 100 mg/dL, if the patient was previously treated with lipid-lowering medication, or if LDL has not been documented.
- Counseling or smoking cessation medication.
- Assessed for rehabilitation needs/services

The GWTG Program is an initiative that has demonstrated interesting results since its implementation in 2003. After the inclusion of more than one million patients in over one thousand hospitals in the United States by 2009, there was a change in the proportion of prescription of "all or nothing" measures from 44% to 84.3%. Furthermore, a multivariate analysis showed that the cumulative odds for all or nothing measures was 9.7% (CI 8.0 to 11.8, $p < 0.0001$) regardless of the characteristics of the patient or the hospital(15) However, an important limitation of this study is that it does

not include a comparison group (e.g., hospitals that are not participating in the program), thus it is not possible to quantify and compare the trends of improvements that may occur outside the GWTG (18). That is, the major limitation of this study is that it is not a randomized clinical trial.

In fact, important data regarding the management of stroke outside the GWTG Program in the United States have been presented. Such data draw attention to an alarming situation. Although 81% of the population can get to the hospital capable of administering rt-PA within one hour, only 4% of patients receive this intervention(19). This shows the continuous need to implement and expand quality improvement programs, even in developed countries.

Because of the deep economic and social impact of stroke in Brazil, in 2008, the General Coordination of Emergency of the Ministry of Health began to organize the National Network of Stroke Management. Currently, the Brazilian Stroke Network includes more than 40 hospitals nationwide(20). The objective of this initiative is to implement a program for the management of stroke patients, aiming to address all levels of care: recognition of the population, pre hospital care, hospital care, rehabilitation, and prevention(21). This certainly was an important step to improve stroke management in Brazil because, in the participating hospitals, the patients not only started to be treated faster but also to be seen by a more qualified health care team with better therapeutic options. However, there are no published data on the performance of the program over the past years.

1.4. Quality improvement based on clinical research - The Experience of Cluster Studies

1.4.1. What are cluster randomized trials and what is the advantage?

Most studies evaluating quality improvement strategies were "before and after" studies. Although interesting considering the logistics and low cost, this type of design is unable to provide a definitive answer as to the effectiveness and efficiency of interventions. This is because some patients' characteristics that are not considered in

the analyses may change the results (confounding variables), or may even be responsible for improving the outcomes of interest, thus causing confounding bias.

The only method capable of controlling known and unknown factors that may have an influence on the outcomes is central randomization with allocation concealment.

The randomization of patients conducted in traditional clinical trials is not effective to test educational interventions aimed at changing behaviors or clinical practices. There might be inter-group contamination, i.e., patients allocated to the control group may also receive the intervention under study. Therefore, there is an increase in random type II error because inter-group contamination tends to dilute the effect of the intervention.

In this sense, there should be cluster randomization (i.e., cluster randomized study) instead of individual patient randomization.

In this type of study, clusters or groups of individuals are randomly allocated to one of the groups, being especially useful to evaluate public health or health care quality improvement programs.

Patients generally choose the hospital where they will be treated based on geographical issues or because it is a center of excellence. Thus, disease severity is randomly distributed within the cluster (health care unit), i.e., there are seriously ill individuals and low-risk patients within the same cluster. Hence, there is an interaction between the individuals of the same cluster, making them similar as to the way they respond to interventions. The factors tend to influence individuals within the same cluster in a similar manner.

1.4.2. The example of studies about stroke

Cluster randomized clinical trial is a study design that has been increasingly used in studies focused on prevention and evaluation of the management of certain diseases. This method is especially relevant for studies on stroke and has been used by some researchers to evaluate various parameters of management improvement,

particularly in support areas such as rehabilitation, speech therapy, and nursing care(22-24). There are also some initiatives seeking to obtain better results in terms of prescription of therapeutic measures such as use of antithrombotic agents, use of fibrinolytic agents, discharge prescription(25-27). **Table 2** shows a summary of the cluster studies for stroke treatment performed so far.

Table 2 - Randomized cluster studies conducted at hospitals - Examples of studies about Stroke

Study	Intervention	Sample (no. of clusters/patients per cluster)	Primary Outcome
PRISM Group 2003**(25)**	Computer-based decision support system to aid in the selection of antithrombotic agents	16/39	Change in relative risk of ischemic and hemorrhagic events
Jones et al. 2005 **(23)**	Training package for nurses and assistants to improve their understanding of stroke patient care	10/8	Rivermead Mobility Index in 6 months
Pennington et al. 2005**(22)**	Training in evaluation and use of guidelines for speech and language departments	15/47	Extent of the compliance to the guidelines by language departments.
Strasser et al. 2008**(24)**	Multimodal training program for health care team in the care of patients in rehabilitation	27/21	Change in motor skill upon discharge compared to admission.
De Luca et al. 2009**(28)**	Training of health care teams in prehospital care	18/42	Proportion of eligible stroke patients referred to a stroke unit

Johnston et al. 2010**(27)**	Quality Improvement through a platform for discharge prescription.	12/114	Binary composite endpoint including: prescription of statins, blood pressure control, prescription of anticoagulants to patients with atrial fibrillation
PRACTISE**(26)**	Training of teams and formation of local teams to increase the rates of prescription of thrombolytic agents	12/459	rt-PA treatment in patients admitted within four hours of symptom onset.
QASC**(29)**	Training of a multidisciplinary team to identify the barriers and adaptations for identification and management of fever, hyperglycemia, and swallowing difficulties.	19/89	Improvement in the control of fever, hyperglycinemia, and swallowing disorders
CLOQS**(30)** Ongoing	Placement of timers in patients admitted with ischemic stroke	1,500 patients with stroke/200 patients undergoing thrombolysis	Percentage of patients who achieve the parameters of best practices (door-to-needle time < 60 minutes)

The PRACTISE study evaluated the rate of prescription of fibrinolytic agents in patients with up to 4 hours of symptom onset in clusters that received training of their teams of stroke treatment compared to clusters that did not receive training. This study showed a thrombolysis rate of 44.5% in the intervention group vs. 39.5% in the control group(26). Although statistically significant, such rate has clinically limited results. The QUISP study, in turn, evaluated the use of a platform for discharge prescription. The

difference in the use of best practices between the intervention and control groups was statistically significant (45% and 37%, respectively) when considering the patients (and the clinical significance was not much significant), but the difference was not statistically significant when considering the hospitals (40% vs. 39%)(27).

1.5. Rationale of the BRIDGE-STROKE Study

As mentioned before, "before and after" studies have the limitation of being long and not providing conclusive answers about the comparison between the new intervention and the well-established interventions. Thus, cluster studies are certainly interesting, but provide greater methodological difficulty. In addition to assessing isolated interventions, the cluster studies on stroke performed to date have methodological limitations that can certainly influence their limited results(31). Therefore, there is need for a study using appropriate methodology and robust intervention strategy.

The Coordinating Center of the Study is an institution of excellence in conducting large clinical trials in Brazil. The studies conducted at the Research Institute at Hospital do Coração (IEP-HCor) are meant to answer important research questions in the context of public health. Likewise, the IEP-HCor is one of the few research centers in the world with proven experience in conducting studies to improve clinical practice based on cluster studies. Such experience has already been demonstrated in the BRIDGE-ACS project, which implemented a multifaceted strategy for the use of evidence-based therapies to treat coronary syndrome. This strategy allowed for an increase from 49.5% to 67.5% in the prescription of best practices(32). This project was presented at the "Late Breaking Trials - 2012" session of the American College of Cardiology, with an important international impact, especially because it was a project supported and funded by the Brazilian Ministry of Health. Recently, this project also received the Incentive Award in Science and Technology for SUS-2012 as the Best Published Study.

The Steering Committee of the BRIDGE-STROKE study consists of researchers with extensive experience in clinical studies on internal medicine,

emergency medicine, cardiology, neurology, vascular diseases, and rehabilitation who have articles published in high impact journals.

2. OBJECTIVES

2.1. Objectives of the First Phase

- To assess the prescription pattern of evidence-based interventions (Aspirin/Antithrombotic, Rt-PA within the therapeutic window, Door-to-Needle Time < 60 min, prophylaxis for DVT, dysphagia screening) in acute treatment and at hospital discharge (anticoagulants in patients with atrial fibrillation or flutter, antithrombotic agents, LDL < 100 or not documented, assessment for rehabilitation and smoke cessation education).
- To detect the main barriers to the acceptance of interventions.
- To prepare a registry of the patients with stroke seen in Brazilian hospitals to assess data related to demographic characteristics, morbidity, mortality, and standard practice in the treatment of stroke.

2.2. Objectives of the Second Phase

2.2.1. Primary Objective

- To assess whether a multifaceted strategy to improve clinical practice is more effective than usual treatment regarding the prescription of evidence-based therapies in the first 48 hours and at discharge (Early Antithrombotic, Rt-PA within the therapeutic window, Door-to-Needle Time < 60 min, prophylaxis for DVT, dysphagia screening, antithromobotic at discharge, statins (LDL < 100 or not documented), anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation, patient education or medication for smoke cessation, **(Composite Adherence Score)**

2.2.2. Secondary Objectives

- To assess whether a multifaceted strategy to improve clinical practice is more effective than usual treatment regarding the prescription of evidence-based therapies in the first 48 hours and at discharge (including : Early

Antithrombotic, rt-PA within therapeutic window, Door-to-Needle Time < 60 min, prophylaxis for DVT, dysphagia screening, antithrombotic at discharge, statins[LDL 100 or not reported], anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation, education or medication for smoke cessation in an "All or None" Model.

- To assess whether a multifaceted intervention to improve clinical practice is more effective than usual care for adherence to additional therapies such as door to needle time < 45 minutes and antihypertensive usage.
- To assess whether a multifaceted intervention is more effective than usual care to decrease mortality, stroke recurrence and disability.

3. STUDY PLANNING

3.1. Project Description and Planning

The BRIDGE-STROKE study is a project focused on improving health care quality based on the implementation of evidence-based interventions in public tertiary hospitals and private hospitals in Brazil, Argentina and Peru. Stroke has been chosen as the focus of the study because it is the most important cause of mortality and disability in Latin America.

The BRIDGE-STROKE study will consist of two phases. In the first phase (Phase 1), we will conduct an observational registry study aimed at documenting the clinical practice of acute management of stroke and detecting the main barriers in incorporating evidence-based interventions into practice.

In the second phase (Phase 2), we will conduct a randomized cluster trial where participating hospitals will be randomized to receive or not a multifaceted intervention. This second phase is aimed at investigating if this package of clinical practice improvement (multifaceted intervention) is able to increase the prescription and recommendation of interventions with proven benefit in the first 48 hours of admission and at discharge).

In addition, the study will include a follow-up until discharge or until the seventh day of admission (whichever comes first) to evaluate whether the multifaceted intervention is able to increase the prescription of Aspirin/Antithrombotic, anticoagulants for atrial fibrillation, lipid lowering agents, assessment for rehabilitation, education or medication for smoke cessation, and to reduce mortality and degree of disability. as well as to assess mortality rate, stroke recurrence and disability at 90 days of follow-up. If this is the case, this package may be offered as a tool for improving clinical practice in hospitals in Latin America.

At the end of phase 2 we will offer the multifaceted strategy toolkit for all centers.

3.2. Design of the Study Phases

Phase 1: Prospective observational study (registry) aimed at recording the clinical practice of acute management of stroke in patients seen at public and private hospitals. In addition, there will be a longitudinal follow-up of these patients up to hospital discharge or the seventh day of hospitalization as well as a telephone call in 90 days.

Phase 2: Cluster randomized trial aimed at testing the effectiveness of a program to improve clinical practice at these hospitals.

3.3. Eligibility

3.3.1. Eligibility Criteria for Participating Hospitals

The hospitals eligible for the BRIDGE-Stroke study will consist of public and private hospitals offering 24/7 emergency care, with at least one routine physician in the unit for 24 hours and one on-call neurologist. These hospitals should have availability of a CNS imaging (cranial computed tomography/ MRI). They should also have alteplase for performing intravenous reperfusion therapy. These hospitals will complete

the screening form for appropriate initial assessment of basic conditions for inclusion and adherence to the project.

3.3.2. Eligibility Criteria for Participants

Patients diagnosed with ischemic stroke (including transient ischemic attack and ischemic stroke with hemorrhagic transformation) with symptoms lasting up to 24 hours. We will exclude patients with signs of hemorrhagic stroke, expansive lesions and central nervous system infections.

Definitions:

Ischemic stroke is defined as a sudden onset of acute focal neurological deficit of ischemic vascular origin:

a) that is not reversible in 24 hours or resulting in death (in <24 hours) and is not due to an identifiable cause of death (e.g., tumor or trauma) **OR**

b) that resolves in <24 hours and is accompanied by clear evidence of stroke on the brain imaging study.

Transient ischemic attack (TIA) is defined as:

a. focal neurological deficit lasting <24 hours and not due to identifiable non-vascular cause (e.g., brain tumor, trauma), **AND**
b. no new infarction on brain imaging study (if available).

Hemorrhagic transformation of ischemic stroke is cerebral infarction with blood that seems to represent hemorrhagic transformation instead of primary hemorrhage. Hemorrhagic conversion usually occurs in the cortical surface. Deeper hemorrhagic transformation requires evidence of non-hemorrhagic infarction in the same vascular territory. Apparent microbleeds on nuclear magnetic resonance (NMR), both in the cortex and in the deeper cerebral structures, will not be considered consistent with the outcome of hemorrhagic transformation.

3.3.3. Criteria for cluster maintenance

By the end of phase 1 all included hospitals will be evaluated in relation to data collection quality and effectiveness, as well as effective in the operational procedures. For phase 2 hospitals will be maintained according to a ranking based on the primary outcome observed during phase 1 until the needed number of clusters is reached.

3.3.4. Sample Characteristics

3.3.4.1. Hospitals

The centers will be selected using the following sources: Record of the research centers of the Hospital do Coração, records of the research centers from the ReNaCer study and recommendation of the Brazilian Stroke Network.

Those centers invited to participate should complete the screening form to confirm the possibility of using the tools available for the BRIDGE-STROKE study.

3.3.4.2. Patients

In phase 1 and 2, consecutive patients seen in the hospitals participating in the study and who meet the inclusion criteria will be enrolled. The enrollment in the study will be conducted 7 days a week, regardless of the time the patient arrives at the emergency department. Data will be collected from the medical records

3.4. Method of randomization and concealment allocation

In phase 2, the hospitals will be stratified in percentiles (tertiles or quartiles) according to the performance verified during phase 1. Once the hospital is allocated to one of the groups, all patients seen at that hospital will be treated following the same procedure. All hospitals will be randomized simultaneously.

The list of hospital randomization will be generated considering a random function with equal probability of allocation to one of the groups. Each center will be numbered and only the numbers will be used for randomization, which will be performed by a statistician of the HCor, thus ensuring allocation concealment. The study coordinator will inform the center which measures should be taken without informing the statistician about the hospitals that will receive evidence-based training.

At the end of phase 2, the centers that were randomized not to receive the intervention will receive all the tools to improve clinical practice after the end of phase 2.

3.5. Masking

This is an open study, and thus the investigators and patients will not be blinded to the allocation of treatment. Information regarding 03 month follow up outcomes will be obtained through standard forms and procedures applied in a telephone interview by a trained and blinded health care professional from the coordinating office. All stroke recurrence diagnosis will also be validated by a blinded Committee.

3.6. Study Procedures

The centers invited to participate must complete the hospital screening form. The Research Institute at Hospital do Coração (IEP-HCor) will receive the data on the cluster and confirm the participation of the cluster in the study.

In Phase 1 and Phase 2, an independent data collector (a person that is not involved in the patient assistance) must collect patient data, completing the "Registry CRF" and "Discharge CRF" and “90 Day Follow Up CRF”. During phase 2, data collection for the 90 day Follow up will be collected by a trained healthcare professional from the central office

In phase 2, the clusters randomized to the control group will keep their usual practice standards, while the clusters allocated to the intervention group will receive the toolkit described above to be used by the health professionals involved in stroke patients' assistance. Both groups must complete the following forms: "Admission", "Registry", "Discharge". In this phase will be included information regarding adherence to the multifaceted intervention. Furthermore, study coordinator and data collectors from the sites, when asked, must provide appropriate documents for adjudication purposes.

Patient screening will be performed at the Emergency Department in a consecutive model.

3.7. Description per visit

Baseline Visit

The team should check the following patient information:

- Inclusion/exclusion criteria
- Contraindication to pre specified evidence-based therapies.
- Demographic data
- Clinical history
- Physical examination
- Stroke severity (NIHSS)
- Vital signs
- Cranial Computed Tomography (CT) /
- Additional laboratory tests
- Use of tools

Discharge

- Hospital complications
- Medication at discharge or on the seventh day of admission, and contraindications to the use of evidence-based therapies.
- Assessment and delivery of any rehabilitation/physical therapy.
- Education provided to the patient.
- Disability.

Follow-up visit, Day 90 + 7 days

- Mortality data, degree of disability and stroke recurrence.
- During phase 1 these data will be collected by each cluster team, during phase 2 these data will be collected by a phone call from a healthcare professional form the central office blinded to site allocation.

It is important to highlight that data collection will be performed by an independent data collector, in order to prevent contamination. Thus the health team delivering treatment to the patients will not be involved in data collection.

3.8. Quality Improvement Tools

Based on the results of previous evidence testing the efficacy and/or effectiveness of a series of improvement tools of clinical practice, we will develop a multifaceted strategy including various tools that will provide the health professionals responsible for stroke patients in each center with:

- Knowledge of effective therapies;
- Clinical decision support;
- Updated and critically evaluated information on therapeutic interventions for stroke patients.

These tools will be applied in a pre-determined date after an investigators' meeting and health care team training

3.8.1.1. Case Manager

Health care professionals from each institution, including physicians and leader nurses, will be responsible for the timely delivery of the material and for checking the implementation of effective management, supporting the management when it is needed and also acting as quality monitors

The case manager is key to improving clinical practice. Using charisma and persuasion, the case manager should motivate, in a polite manner, the use of the proven effective therapies described herein.

3.8.1.2. Reminders

to facilitate the visualization of important interventions and their relation to the time of care. Different types of reminders may be used: patient wristband, "stroke" label on the admission record, and a therapeutic plan (algorithm checklist) to be attached to the admission form or medical record.

The "stroke" label will be placed in the patient's admission record at the time of screening for all patients with suspected ischemic stroke or TIA. If the diagnosis is not confirmed, the wristband should be taken off and the therapeutic plan will no longer be followed. If the diagnosis is confirmed, then the wristband and the therapeutic plan should be kept and followed together with the patient medical record.

Checklists including the optimal treatment recommendations for stroke patients will be made available. Such checklists will be attached to the local prescription as a therapeutic suggestion to be individually adjusted.

3.8.1.3. Interactive Training Workshops

Interactive training workshops may happen as follows;

- During an investigators' meeting where the principal investigator and case manager from each site allocated to the intervention group will receive a simulation-based training developed in small groups and will have access to the tools.
- During individualized training sessions developed in each hospital. It will also be stimulated that each participating site disseminates the intervention to other professionals from the institution. Additionally, this training session has the objective of reviewing the clinical pathway

within each hospital allocated to intervention, thus facilitating the assimilation of the quality improvement tools

3.8.1.4. Educational Material

3.8.1.4.1. Algorithm for the Treatment of Stroke Patients (Therapeutic Plan/Checklist)

Printed versions of these algorithms will be available, and will be distributed to centers as pocket books for quick reference.

3.8.1.4.2. Educational Posters

These posters will be distributed by the emergency department in order to draw the attention and help the teams regarding techniques that can support better practices.

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3.8.1.4.3. Educational Material

- For each hospital we will provide printed, physical or electronic material containing fundamental concepts of acute stroke treatment.
- The BRIDGE Stroke training techniques will also be available in a video that will be used during the training sessions. This video will also be available for the hospitals so that they can use it as a continuous improvement tool.

3.8.1.4.4. Feedback Reports

To each hospital allocated to the intervention group, periodical reports on performance will be provided. This strategy will stimulate the teams to seek continuous improvement. Additionally, periodic conference calls will be schedule whith each intervention site in order to explain about the quality measure and discuss which aspects needs improvement.

3.9. Outcomes

3.9.1. Primary Outcome of the First Phase

- Proportion of prescription of evidence-based therapies (see Table 3).
- Barriers to implementation of methodologies.

3.9.2. Secondary Outcomes of the First Phase

- Disability (mRankin) in 90 days
- Mortality, in hospital and 90 days.
- Stroke recurrence in 90 days.

3.9.3. Primary Outcome of the Second Phase

- Composite Adherence Score: defined as the sum of usage of evidence-based therapies in the first 48 hours and at discharge among the patients' total eligible opportunities. For this purpose, patients with contraindications (which are specific for each endpoint) were excluded from the denominators. Evidence based therapies in the first 48 hours include: early antithrombotic, RT-PA within therapeutic window, dysphagia screening, DVT Prophylaxis, Door to Needle Time < 60 minutes, dysphagia screening). Discharge Therapies include: antithrombotic, statins (LDL 100 or not documented), anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation and smoke cessation education or education),

3.9.4. Secondary Outcomes of the Second Phase

- Proportion of prescription of evidence-based strategies in the first 48 hours and at discharge ("All or None" Measures), including: early antithrombotic, RT-PA within therapeutic window, DVT Prophylaxis, Door to Needle Time < 60 minutes, dysphagia screening, antithrombotic at discharge, statins (LDL 100 or not documented), anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation and smoke cessation education or medication.
- Additional Strategies Usage:
    - Global Rt-PA rate
    - Anti Hipertensive agents at discharge.
    - Door to needle time < 45 minutos

- Mortality at 90 days.
- Disability (mRankin) in 90 days.
- Stroke Recurrence in 90 days.

3.10. Variables of Interest

The following quality indicators will be assessed:

Table 3 - Quality Indicators

Name of Variable	Description	Inclusion	Exclusion	Numerator
Global Rt-PA Rate	Rt-PA Usage	All stroke patients admitted within 24 hours of symptoms	Not applicable	Patients that receive Rt-PA
Rt-PA	Recombinant Plasminogen Activator used within therapeutic window	Eligible patients diagnosed with stroke who arrive at the hospital within 3.5 hours of symptom onset and who are treated within 4.5 hours of symptom onset. *The subgroup of	Patients with medical contraindications or other documented reasons	Patients who received Rt-PA within 3.5 hours of symptom onset. *The subgroup of patients who arrive at the hospital within 02 hours of symptom onset and who are treated within 03 hours of symptom onset will also be evaluated.

		patients who arrive at the hospital within 02 hours of symptom onset and who are treated within 03 hours of symptom onset will also be evaluated.		
Early Antithrombotic Agents	Antithrombotic therapy prescribed within 48 hours of admission (includes antiplatelet agents or anticoagulants).	Eligible patients diagnosed with stroke or TIA	Patient with any documented medical contraindication as a reason for no treatment.	Patients treated with antithrombotic agents until the end of the 2nd day of admission (including ASA, ASA+dipyridamole, ticlopidine, clopidogrel, unfractionated heparin, low molecular weight heparin, and warfarin, but does not include SC heparin at prophylactic doses for DVT.
Prophylaxis for DVT	Patients at risk for DVT (unable to walk) who received DVT prophylaxis until the end of the second day.	Patients eligible for DVT prophylaxis with a diagnosis of stroke.	Patients who can walk at the end of the 2nd day. Excluding patients with any documented medical contraindication.	Patients treated with DVT prophylaxis until the end of the 2nd day of admission (including heparins, heparinoids, other anticoagulants or pneumatic compression devices.

Dysphagia Screening	Dysphagia Screening prior to any oral intake	Patients with a diagnosis of acute ischemic stroke	Not Applicable	Patients who are screened for dysphagia with validated tests before being given any food or fluids by mouth
Door-to-Needle Time < 60 minutes	Time since the patient's arrival to the hospital until the start of rt-PA infusion	Patients eligible for treatment with rt-PA	Patients with documented medical contraindication.	Patients treated with reperfusion therapy within 60 minutes of admission.
Door to needle < 45 minutes	Time since the patient's arrival to the hospital until the start of rt-PA infusion	Patients eligible for treatment with rt-PA	Patients with documented medical contraindication.	Patients treated with reperfusion therapy within 45 minutes of admission.
Oral Anticoagulation for Atrial Fibrillation or Flutter	Anticoagulation prescribed at discharge for patients with documented atrial fibrillation or flutter during hospitalization	Eligible patients with diagnosis of stroke and a history of paroxysmal or persistent atrial fibrillation or atrial flutter during this hospitalization period.	Patients with any documented medical contraindication as a reason for no treatment.	Patients who received anticoagulation at discharge (including therapeutic doses of heparin, heparinoids, warfarin, or other anticoagulants such as direct thrombin inhibitors.
LDL = 100 or not documented	Statins prescribed upon discharge if LDL >= 100 mg/dL, if the patient was previously treated with lipid-lowering medication before the admission, and if	Eligible patients with a diagnosis of stroke or TIA if LDL >= 100mg/dL, if the patient was previously treated with lipid-lowering	Patient with any documented medical contraindication as a reason for no treatment.	Patients who received statins upon discharge (including statins, fibrates, niacin, binding resins, or selective cholesterol absorption inhibitors)

	LDL has not been documented.	medication before the admission, and if LDL has not been documented.		
Smoking Cessation	Intervention for smoking cessation (education or medication) prior to discharge for smokers.	Eligible patients with a diagnosis of stroke or TIA and smokers (defined as having initiated or maintained the habit of smoking in the last year).	Patient with any documented medical contraindication as a reason for no treatment.	Patients or their caregivers who received smoking cessation education or medication for smoking cessation before discharge.
Anti hypertensives	Anti Hypertensives prescribed prior to discharge for patients with diagnoses Hypertension	Eligible patientes diagnosed with stroke and documented history of hypertension	Patients with any documented contra indication for antihypertensive usage.	Patients who receive anti hipertensive agents at discharge
Assessed for Rehabilitation	Patients assessed by or treated by rehabilitation professional	All patients diagnosed with stroke	Not Applicable	Patients who are assessed by or who receive rehabilitation services

*See attached the table containing the main contraindications to the above mentioned therapies.

- Stroke recurrence will be checked in the medical forms or by a brief telephone call from the data collector of each site (during phase 1), using an adaptation of the Stroke and TIA Verification Questionnaire (Appendix 1) (33). During phase 2 this outcome will be assessed by the central office nurse.

- The degree of disability will be measured using the modified Rankin Scale (mRankin) (see Appendix 2).During phase 2 this assessment will be performed by the central office health care professional blinded to site allocation.
- Deaths will be classified as Cardiovascular, Non Cardiovascular, and Unknown. The cause of death is determined by the main condition that caused the death, not by the immediate mode of death. All causes of death will be deemed to be cardiovascular, unless there is a clearly defined non cardiovascular death, except for death without any additional information, which will be classified as Unknown cause. Cardiovascular death includes, but is not limited to, atherosclerotic coronary heart disease (acute myocardial infarction, sudden cardiac death, sudden death not associated with cardiac symptoms with gradual worsening, unwitnessed death without defined alternative cause, death related to cardiac surgery or coronary angiography), atherosclerotic vascular disease (cerebrovascular disease, including ischemic and hemorrhagic stroke, aortic, mesenteric, vascular, and renal disease, or peripheral artery disease, death related to non-coronary vascular procedure), and other cardiovascular diseases (pulmonary embolism, endocarditis, congestive heart failure, valve heart disease, arrhythmias). Example of non-cardiovascular death includes the primary cause of death as being infectious, related to malignancy, pulmonary, gastrointestinal, accidental, renal, and suicide.

Cardiovascular death will be classified as sudden, not sudden, and unwitnessed.

1) Sudden Cardiovascular Death: It is defined as unexpected and also classified as:

   a. Witnessed: occurring within 60 minutes since symptom onset in the absence of another clearly non-cardiovascular cause **OR**

   b. Unwitnessed: within 24 hours of having been seen alive in the absence of pre-existing conditions of circulatory failure or other cause of non-cardiovascular death.

All sudden deaths will be classified according to criteria (a) or (b).

2) Not Sudden Cardiovascular Death: This category is related to patients with cardiovascular symptoms with progressive worsening before death. It includes all patients with cardiovascular death who did not meet the criteria for sudden cardiac death or unwitnessed cardiovascular death.

3) Unwitnessed cardiovascular death: Unexpected death occurring when the patient has been seen in the previous 24 hours and with the absence of other identified major causes of death.

3.11. Follow-up

Data from patients included in the study referring to in-hospital stay will be collected from medical records. Data referring to 90 day follow up will be collected by the local data collectors during phase 1 from medical records (in case the patient is still in the hospital or has attended a medical meeting) or by phone call (in case there are no medical records available). In phase 2, data will be assessed by the Central Office health care professional, through a telephone interview.

3.12. Endpoint Definition

For the primary endpoint definition (adherence to all eligible evidence-based therapies in the first 48 hours and at discharge) we are using a Composite Adherence Score. This score is determined by the number of opportunities for receiving therapies (range, 0 to 10 for both acute and discharge medications) and number of therapies received (range, 0 to 10 for both acute and discharge medications) for each eligible patient. If a specific therapy was contraindicated, it was excluded from the opportunities to receive therapy (denominator). Each patient will have a composite percent rate of adherence calculated as: received/opportunities) x 100.

For the secondary endpoint definition we used the “All or None” approach. According to these criteria, to be classified as “yes”, a patient must have received all eligible therapies, otherwise the patient is classified as a “no answer in the database.

3.13. Statistical Analysis Plan

Quantitative variables will be described by mean and standard deviation whenever there is a normal distribution, or median and/or interquartile amplitude median and interquartile ranges in case of non-parametric distribution. Qualitative variables will be presented as absolute frequencies (number of patients) and relative frequencies (percentages).

Phase 1 (Registry)

This phase serves as baseline for the cluster randomized trial. Outcomes estimates from this phase will be used for a new sample size calculation and for defining the strata to be used in the randomization.

The main purpose of the phase 1 analysis is identifying the variability of the primary outcomes between clusters. Therefore, results will be presented as with the correspondent estimates of the standard deviation (or variance) within cluster and between clusters, This estimated will be generated by a mixed linear regression model with random effects between clusters. These estimates are enough to express the intracluster correlation coefficient (ICC) that will be used for the purpose of estimating the sample size. The ICC (ρ) is defined as:

$$\rho = \frac{\sigma_a^2}{\sigma_a^2 + \sigma_e^2}$$

where σ_a^2 refers to the random effect variance of the clusters (*clusters)* and σ_e^2 to the variance of the measure. In practical manners we can assume the o ICC shows how much from the total variablity is atributable to the clusters.

ICC estimates to each one of the outcomes' components will also be presented. Further details on ICC calculation and variations on the calculation for binary outcomes are described in Hayes e Moulton (2009)(34)

Phase 2 (Cluster Randomized Trial)

Results will be separated per group (intervention vs control). Results will be presented by groups (intervention vs. control) presenting first the clusters characteristics folowed by the patients characteristics.

Initially, will be demonstrated the adherence to the quality improvement intervention will be reported, as will be the time from training until intervention onset. Descriptive statistics on time from site activation until first patient inclusion will also be reported.

Inclusion Flowchart will be presented according to the CONSORT guidelines for cluster randomized trials.

All analysis will follow the intention to treat principle. Different interpretations for the intention to treat principle (regarding the analysis of missing data are used by different authors. To avoid misinterpretation, we define the intention to treat principle to be used in our analysis as follows:

1- The cluster allocated to the intervention group that don't follow or don't adhere to the intervention will be instructed to proceed with data collection irrespectively and will be evaluated within the group that was originally allocated. The same holds true for the control group, irrespective of possible contamination.
2- Although one site receives and uses the intervention, the inclusion and exclusion criteria will be applied to the patients. Thus, in case there are patients that might be initially included in the sample, but for some reason is found not eligible to the study, one will be excluded from the analysis.
3- Missing data from the primary composite outcome will be treated as negative endpoints (worst case scenario).

The second criteria justifiable by its own definition. For example, if a patient initially suspected as stroke or TIA is included in the study but later the diagnosis is not confirmed, means that this patient is not eligible to the study on the first hand, and is not eligible to any of the components of the primary outcome.

The third criterium is conservative, although the data regarding the components of the primary outcome are easily obtained and it is expected (if any) a minimal missing data rate (probably < 0.1%). Thus, there will not be data imputation

The primary outcome will be analyzed using a mixed effects linear regression model with random effects to account for the correlation of observations within clusters. This model will consider residuals assuming a normal distribution. We intend to perform a sensitivity analysis considering a mixed effect linear model that better suits the real distribution of the data (beta distribution models, binomial distribution using the sum of each component, for example) in case we don't observe a normal distribution.

The choice for the simple model (with possible failure on the assumptions) over a most complex one was made due to lack of background in the literature supporting other methods for better sample size estimation assuming the same type of outcome used in our study. However, we understand that this choice would estimate a more conservative (larger) sample size.

The components of the primary outcome will be individually evaluated using mixed effects general linear models considering binomial distribution (logistic regression with random effect at the intercept (cluster adjusted)).

All models will be adjusted for the cluster baseline value (obtained during phase 1) and for the group effect (intervention vs control).

Treatment effects will be expressed as absolute mean difference or the composite outcome and odds ratio with the respective 95% confidence intervals for the individual components.

As a sensitivity analysis we will perform: an adjusted analysis for hospital status (teaching vs non-teaching), and presence of a stroke unit; an analysis considering only the sample that was included following the proposed intervention protocol (*per protocol analysis*).

Pre-specified subgroup analysis, for which interaction by group (intervention vs control) will be assessed as follows: teaching hospital (or not), presence of a stroke unit,

presence of a neurologist in the emergency department, final diagnosis (AIS vs TIA), and country.

Disability will be assessed by the mRankin scale primarily in a dicothomous model (proportio of patients with mRankin < 2) and secondarily by a shift analysis.

Anticipated sub-analysis for subsequent sub-studies include: cross country analysis, stroke unit sub-population.

The analysis will be perfomed using R *software* in its most updated version. The level of stastitical significance is set as two-sided 5%.

3.14. Sample Size

Phase 1

Because of the reduced availability of resources compared to the centers evaluated in these studies, it is expected that the prescription of evidence-based interventions in the first 48 hours and at discharge is even lower in public hospitals (estimate of 40%). Thus, in Phase 1, the objective will be to include 40 stroke patients per participant hospital This sample size is sufficient to detect all the expected percentages (between 1.0% and 95%, depending on the type of evidence-based intervention) for indicators of health care quality, considering an absolute sampling error of 10% and a significance level of 5%.

Phase 2

Ideally, it is expected that after the implementation of a program to improve clinical practice, evidence-based interventions are prescribed to most patients (about 90%). However, programs of clinical practice improvement have moderate effect (absolute increase of 10%) on the prescription of treatments with proven benefit. There is no clear definition of the effect size expected for interventions of clinical practice improvement in the literature because of the wide heterogeneity in terms of the design

of the available evidence, statistical power and methodological quality. Additionally, the efficacy of different tools may vary according to the clinical setting.

Unlike individual patient randomization where it is expected each patient being independent from another, in cluster randomization patients treated in the same hospital are expected to be similarly treated. In such situations it is necessary to consider this dependence when estimating sample size. This is called intra-cluster correlation. As previously observed in studies evaluating patient care, the ICC is approximately 0.05. (31).

Thus, considering fixed sized clusters of approximately 50 patients, a 0.086 mean difference in the Composite Adherence Score, with 5% statistical significance we estimated the following scenarios differing according to standard deviation (SD), power and intracluster coefficient (ICC):

Mean difference	Standard Deviation	ICC	Power	Sample (number of clusters per arm)	Total sample size (number of Patients)
0.086	**0.25**	**0.05**	**90%**	**15**	**1500**
0.086	**0.25**	**0.10**	**80%**	**18**	**1800**
0.086	**0.20**	**0.10**	**90%**	**16**	**1600**
0.086	**0.20**	**0.15**	**80%**	**17**	**1700**

Overall

Considering approximately 50 patients per cluster in phase 2 and between 30 and 36 sites, it will be necessary to collect data from 1500 to 1800 patients.

Considering possible losses from phase 1 to phase 2 we will include up to 42 sites during phase 1. Thus, it will be collected data from up to 1680 patients.

In case a high variability between hospitals is observed, or the pattern of prescription is much different from expected, a new sample size calculation will be performed for phase 2.

3.15. Data Collection System

The IEP-HCor Data Management System is a web-based system developed by a team of programmers at IEP-HCor to run on a Microsoft SQL platform®. The system has the following functions: patient registry, 24-hour randomization with allocation concealment, data input, data cleansing, and data export for statistical analysis.

Data are collected by means of electronic case report forms via the Internet using the IEP-HCor Data Management System. Data are entered into the system by the team of each center. All forms are electronically signed by the principal investigator in each center or by other appointed persons. Instructions for using the system will be made available to investigators.

4. ETHICAL ASPECTS AND GOOD CLINICAL PRACTICES

The BRIDGE-STROKE study will be conducted in accordance with the Brazilian and international standards described in the documents below:

- Declaration of Helsinki
- Brazilian Resolution 466/12 and related documents of the Ministry of Health
- ICH Harmonized Tripartite Guidelines for Good Clinical Practice, 1996.
- Ottawa Statement for Design and Conduct of Cluster Randomized Trials(35)
- Local Applicable Regulatory requirements for sites in Argentina and Peru

4.1. Study Approval

Before starting the study, the investigator must forward a copy of the protocol, a copy of the informed consent form, and of other required documents to the Research Ethics Committee of the institution. The approval letter from the REC must be sent to the Coordinating Center. Any changes to the original protocol must also be approved by the REC of each center.

4.2. Informed Consent and Institutional Authorization Form

The BRIDGE Stroke study is a cluster randomized trial evaluating clinical practice improvement. The particularities and ethical issues of this study design are contemplated in the Ottawa Statement(35).

Since the study interventions are not oriented to the patients but to the health care providers (the research team has no direct contact with the patient) there will not be any direct intervention oriented to the patient or procedure evaluation that is not established practice. Only data on acute stroke treatment will be collected from each institution. Thus, patients will not provide individual informed consent for this purpose.

The individual informed consent will be provided only for the purpose of 90 day follow up data collection, since this is the only moment where the research team establishes direct contact to the patient.

However, each responsible party (the clinical director, the emergency department coordinator or any other responsible authority) must consent with the center participation. Each institution will be asked to provide an authorization form. This authorization form must be properly evaluated and approved by local Ethical Committees. This form also guarantees data confidentiality regarding the identity of the patients as well as health care providers.

4.3. Study Approval

Before initiating the study, the protocol and the consent form used in the research center, as well as other documents, must be submitted to and approved by the

Research Ethics Committee (REC) of Hospital do Coração according to local regulatory requirements. The investigator must submit brief written descriptions of the trial status to the REC annually, or more frequently, if requested by such institutions.

4.4. Study Registration

The BRIDGE-STROKE study will be registered on the Platform Brazil, on the platform of the Brazilian Clinical Trials Registration (ReBEC), and on ClinicalTrials.gov.

4.5. Data Confidentiality

No patient data will be disclosed. The data capture system will use numbers to identify the patients and centers. The data on printed medical records will be kept as confidential by all participating centers, being stored in locked cabinets. The confidentiality of patients will be preserved in all reports and at any time of the study.

4.6. Reports

The investigator must submit reports on the evolution of the study to the REC of the institution every six months and a final report upon completion of the study.

5. STUDY COORDINATION

5.1. Coordinating Center

The Coordinating Center of the BRIDGE-STROKE study will be the Research Institute at Hospital do Coração (IP-HCor). The institution is widely experienced in conducting large randomized clinical trials. The qualified teams will provide the participating centers with guidance and support to ensure adherence to the study protocol. The teams have the necessary experience and level of expertise in research methods and biostatistics, in addition to being aided by awarded researchers.

Considering patients with cardiovascular diseases, the studies coordinated by the IEP-HCor over the last 5 years recruited more than 25 000 patients.

Equipe de trabalho no centro coordenador:

- Otávio Berwanger – Senior Investigator – Co-Chair – Steering Committee
- Maria Julia Machline Carrion – Principal Investigator, Co-Chair – Steering Committee.
- Alexandre Biasi Cavalcanti – Senior Trialist – Clinical Trials Unit Manager
- Eliana Vieira Santucci – Data Manager
- Helio Penna Guimarães – Senior Trialist

- Karina Normilio – Site Manager.
- Juliana Yamashita – Regulatory Affairs.
- Ligia Nasi Laranjeira – Site Manager (Coordinator)
- Lucas Petri Damiani – Statistician.
- Nanci Valeis – Regulatory Affairs (Coordinator)
- Pedro Gabriel Melo de Barros e Silva – Trialist (CEC)
- Rafael Marques Soares – Site Manager Especialista em Gerenciamento de Centros. Instituto de Pesquisa HCor.
- Renato Hideo – Statistician.
- Viviane Bezerra Campos – Data Manager.

5.2. Steering Committee

The members of the BRIDGE-STROKE Steering Committee will be responsible for overseeing the clinical trial, including decisions to discontinue or modify the study procedures, if necessary, deal with the challenges involved in implementing the protocol, review and interpret the data, and prepare the final manuscript. This Committee is directed by two co-chairs. Such coordinating work will be conducted in person or through meetings over the phone held at least quarterly. All other commissions of the BRIDGE-STROKE study will report directly to the Committee.

5.3. Executive Committee

This Committee is composed by members of the Steering Committee that operate at the Coordinating Center. This Committee acts as an administrative and executive arm of the Steering Committee, being responsible for operational decisions on behalf of the Steering Committee.

5.4. Publication Committee

Members of the Executive Committee will be selected to join a Publication Committee that will be responsible for writing the final manuscript and submit it for publication. This committee will also manage the database and will be responsible for assessing publication proposals based on data from the BRIDGE-STROKE study.

5.5. Adjudication Process

The Clinical Events Committee (CEC) is responsible for assessing all patients included in the study in order to adjudicate the stroke diagnosis. All potential events will be entered into the tracking database of the CEC. Next, there will be an administrative review of each outcome to see if all required documents are available. For the adjudication process, we will consider the following original documents: official medical reports about the event, tests signed by physicians, and other tests considered relevant to the related outcome. Electronic records or DVD on imaging studies will not be required, but may be requested if the official reports are not available or in case of disagreement between adjudicators or between clinical presentation and test results.

The IEP-HCor will print the necessary documents of the eCRF and include additional supporting information in a CEC package. The HCor will forward two copies of each package of outcomes to the CEC, where the packages will be randomly assigned to two independent medical reviewers. The reviewers will independently review the cases assigned to them, document and provide supporting information for analysis of each case directly in the outcome package. If both adjudicators agree, the adjudications of the event will be considered complete. If there is disagreement between the medical reviewers, or at the discretion of a reviewer, the case will be submitted for review by at least one additional reviewer to establish the final adjudication. The result of the final

adjudication will be entered into the database by the coordinator of CEC. A copy of all signed adjudications will be presented in each respective folder and stored in the CEC. Additional details of specific processes for each one of the two branches of the CEC will be detailed in the documentation maintained separately from standard procedures in HCor.

All adjudications must be documented in the review package of the event with regard to the endpoint criteria. In any case that defines the precedence, the chair of the CEC will document the details of the adjudication, and the case will be registered in a log that will serve as a guide for reviewers as to ensure consistency in relation to the use of endpoint definitions.

5.6. Data Quality Management

The procedures to ensure data quality include:

1) All investigators will attend a training session before the start of the study to standardize procedures, including data collection;
2) The investigators will be able to contact the Study Coordinating Center to solve issues or problems that may arise;
3) Data entry into the IEP-HCor Data Management System is subject to various checks for missing data, plausible, possible or non-permitted value ranges, and logic checks. Problems are informed by the system at the time of data entry;
4) Statistical techniques to identify inconsistencies will be applied periodically (about every two weeks). The centers will be notified of the inconsistencies and asked to correct them;
5) Statistical routines to identify fraud will be conducted periodically (every 90 days);
6) All centers will be monitored throughout the study;
7) The Coordinating Center will conduct a monthly review of detailed reports on screening, inclusion, follow-up, and data consistency and completeness. The Coordinating Center will take immediate action to solve any problems.

5.7. Responsibilities of the Study Sponsor

This is a relevant clinical trial, designed and sponsored by the IEP-HCor. The objective is solely to obtain the best scientific knowledge in daily clinical practice, free from any conflict of interest. If necessary, the source of financial support will be acknowledged in presentations and publications. The results of the BRIDGE-STROKE study will be published regardless of the positive or negative nature of the data.

5.8. Responsibilities of Investigators and Sub-investigators at Participating Centers.

The principal investigator of each center will conduct and/or oversee the daily operations of the study in his/her respective center, assisted by the sub-investigator and the research coordinators. Most tasks can be assigned by the principal investigator to team members of each research center, provided that these individuals are qualified for the tasks and appropriately listed in the form of task assignment. However, the principal investigator will continue to be legally responsible for the tasks. In addition, the investigators are responsible for initiating the study at its center, maintaining the study procedures, ensuring improvements in the protocol, and also ensuring data quality and accuracy.

5.9. Monitoring

Representatives of the Project Office of the BRIDGE-STROKE must be allowed to visit all the participating centers periodically to evaluate data, quality, and integrity of the study. At the center, they will review the records of the study and compare them directly with the source documents, and discuss the conduct of the study with the investigator, and check if the facilities remain acceptable.

Additionaly, to monitor possible selection bias, all sites are asked to complete a screening log in a weekly basis, Recruitment evolution during phase 2 in each site will

be weekly controlled and compared to the performance observed in phase 1. In case sites don't perform as in phase 1 or in case they don't provide an appropriate and sistematic screening log, they will ve asked to review all admission of possible ischemic strokes and TIAs during the same period.

5.10. Publication of Results

The success of the BRIDGE-STROKE study will depend on the teams involved, on the efforts and collaboration of all investigators, research coordinators, and patients. Therefore, the main results will be published, and the authors will be the Steering Committee on behalf of the BRIDGE Stroke Investigators who will be cited at the end of the manuscript. Will be considered up to three members from each site (according to the principal investigators' criteria). Other inclusions will be evaluated by the Publication Committee.

6. AMENDMENTS TO THE PROTOCOL

Any protocol alterations will be registered in writing by an amendment signed by the Principal Investigator.

Approval and recommendation of changes provided by the REC is required before its implementation, unless there are safety reasons that override approval or recommendation.

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Protocol Amendments Description

Protocol Version	Descritption and Reason for Change	Date
2.2	First Approved Version	June 2014
2.3	1) Cluster retention criteria for phase 2 is better explained. 2) Better description of data collection procedures. 3) 90 days follow up visit is included.	September 2014
2.6	1) Four different sample size scenarios were presented (ranging from 1500 to 1800 patients. This was made because we anticipated that not all sites included in the pre-randomization phase would be able to participate in the trial, so as a precaution we decided to have an idea of different scenarios that could answer the research question. Nevertheless, a new sample size calculation after phase 1 was anticipated since the first protocol version. 2) Generalized Estimation Equation was presented as the main analytical method, in order to better account for the cluster effect. 3) Primary and Seconday Objectives are better explained. 4) Clarification on the eligibility criteria for patients. Eligible patients are eligible if they present to the emergency department within 24 hours form symptoms onset. 5) Stratification in tertiles is added. 6) Better description on the variables of interest. 7) Clusters' size including approximately a mean of 40 patients.	May 2015
3.0	1) A more detailed description of the statistical analysis plan is added to the protocol into serve as the basis for the first version of the SAP as a separate document. 2) Description of how the intention to treat principle will be applied in the trial. This is especially important for the handling of missing data considerations (also added in this version). 3) The linear regression mixed effect model was preferred as the main statistical method. 4) Assumptions on the distribution and possible adjustments in the analysis considering a non-normal distribution are also stated.	December 2017

Statistical Analysis Plan (SAP) for the Brazilian inteRvention to Increase eviDence usaGe in practicE – Stroke (BRIDGE Stroke) - A Cluster randomized trial to evaluate the increase in usage of evidence-based practices using a multifaceted strategy

Trial Registration: NCT02223273

Protocol Version 3.0 – November, 2017.

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1) Administrative information

Statistical Analysis Plan (SAP) for the Brazilian inteRvention to Increase eviDence usaGe in practicE – Stroke (BRIDGE Stroke) - A Cluster randomized trial to evaluate the increase in usage of evidence-based practices using a multifaceted strategy

a) ClinicalTrials.org Registration: NCT02223273
b) Protocol Version 3.0 – November, 2017.
c) SAP Revision

Protocol Version	SAP version	Descritption and Reason for Change	Date
2.2	Not Applicable*	Not Applicable	June 2014
2.3	Not Applicable*	No Changes made	September 2014
2.6	Not Applicable*	8) Four different sample size scenarios were presented (ranging from 1500 to 1800 patients. This was made because we anticipated that not all sites included in the pre-randomization phase would be able to participate in the trial, so as a precaution we decided to have an idea of different scenarios that could answer the research question. Nevertheless, a new sample size calculation after phase 1 was anticipated since the first protocol version. 9) Generalized Estimation Equation was presented as the main analytical method, in order to better account for the cluster effect.	May 2015
3.0	1.0	1) A more detailed description is added to the protocol in order to serve as the basis for the first version of the SAP as a separate document. 2) Description of how the intention to treat principle will be applied in the trial. This is especially important for the handling of missing data considerations (also added in this version). 3) The linear regression mixed effect model was preferred as the main statistical method. 4) Assumptions on the distribution and possible adjustments in the analysis considering a non-normal distribution are also stated.	December 2017

*The first version of the SAP as a separate document is the present version (1.0) based on the Protocol version 3.0. Previously, the statistical considerations were exclusively summarized in the Protocol body. Therefore, between version 2.2 and 2,6, no changes were made in the Protocol.

2) Background and rationale

The full rationale for undertaken the trial is explained in detail in the Protocol. Briefly, stroke is the second cause of death worldwide and a major public health issue especially in middle, low middle and low-income countries (that is the case for Latin America Countries). Despite the widespread availability of best practices guidelines as well as quality indicators. However, the adherence to evidence-based therapies remains suboptimal.

Most studies evaluating quality improvement strategies were "before and after" studies. Although interesting considering the logistics and low cost, this type of design is unable to provide a definitive answer as to the effectiveness and efficiency of interventions. This is because some patients' characteristics that are not considered in the analyses may change the results (confounding variables), or may even be responsible for improving the outcomes of interest, thus causing confounding bias.

The only method capable of controlling known and unknown factors that may have an influence on the outcomes is central randomization with allocation concealment.

The randomization of patients conducted in traditional clinical trials is not effective to test educational interventions aimed at changing behaviors or clinical practices. There might be inter-group contamination, i.e., patients allocated to the control group may also receive the intervention under study. Therefore, there is an increase in random type II error because inter-group contamination tends to dilute the effect of the intervention.

As mentioned before, "before and after" studies have the limitation of being long and not providing conclusive answers about the comparison between the new intervention and the well-established interventions. Thus, cluster studies are certainly interesting, but provide greater methodological difficulty. In addition to assessing isolated interventions, the cluster studies on stroke performed to date have

methodological limitations that can certainly influence their limited results[31]. Therefore, there is need for a study using appropriate methodology and robust intervention strategy.

3) Objectives

7.1. Objectives of the first phase

- To assess the prescription pattern of evidence-based interventions (Aspirin/Antithrombotics, Rt-PA, Door-to-Needle Time < 60 min, prophylaxis for DVT, dysphagia screening) in acute treatment and at hospital discharge (anticoagulants in patients with atrial fibrillation or flutter, antithrombotic agents, statins for patients with LDL ≥ 100 or not documented, assessment for rehabilitation and smoke cessation education).
- To detect the main barriers to the acceptance of interventions.
- To prepare a registry of the patients with stroke seen in Brazilian hospitals to assess data related to demographic characteristics, morbidity, mortality, and standard practice in the treatment of stroke.

7.2. Objectives of the second phase

7.2.1. Primary objective

To assess whether a multifaceted strategy to improve clinical practice is more effective than usual treatment regarding the prescription of evidence-based therapies in the first 48 hours and at discharge (Early Antithrombotics, Rt-PA, Door-to-Needle Time < 60 min, prophylaxis for DVT, dysphagia screening, antithromobotics at discharge, statins for patients with LDL ≥ 100 or not documented, anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation, patient education or medication for smoke cessation.

7.2.2. Secondary objectives

- To assess whether a multifaceted strategy to improve clinical practice is more effective than usual treatment regarding **individually** the prescription

of evidence-based therapies in the first 48 hours and at discharge and in an "All or None" model; that is:

$$W_i = \begin{cases} 1, & if \sum_{j=1}^{10} y_{ij} = \sum_{j=1}^{10} x_{ij} \\ 0, & otherwise \end{cases}$$

- To assess whether a multifaceted intervention to improve clinical practice is more effective than usual care for adherence to additional therapies such as door to needle time < 45 minutes and antihypertensive usage.
- To assess whether a multifaceted intervention is more effective than usual care to decrease mortality, stroke recurrence and disability.

4) Study methods

a) Trial design

Cluster randomized trial aimed at testing the effectiveness of a program to improve clinical practice at these hospitals.

b) Method of randomization and concealment allocation

The hospitals will be stratified in tertiles according to the performance verified during the observational phase (Phase 1). Once the hospital is allocated to one of the groups all patients seen at that hospital will be treated following the same procedure.

The list of hospital randomization will be generated considering a random function with equal probability of allocation to one of the groups. Each center will be numbered and only the numbers will be used for randomization, which will be performed by a statistician of the HCor, thus ensuring allocation concealment. The study coordinator will inform the center which measures should be taken without informing the statistician about the hospitals that will receive evidence-based training.

c) Eligibility criteria

i) Eligibility criteria for participating hospitals

The hospitals eligible for the BRIDGE-Stroke study consists of public and private hospitals offering 24/7 emergency care, with at least one routine physician in the unit for 24 hours and one on-call neurologist. These hospitals should have availability of a CNS imaging (cranial computed tomography/ MRI). They should also have alteplase for performing intravenous reperfusion therapy. These hospitals completed the screening form for appropriate initial assessment of basic conditions for inclusion and adherence to the project.

ii) Eligibility criteria for participants

Patients diagnosed with ischemic stroke (including transient ischemic attack and ischemic stroke with hemorrhagic transformation) with symptoms lasting up to 24 hours. We will exclude patients with signs of hemorrhagic stroke, expansive lesions and central nervous system infections. Definitions are discriminated in the Protocol.

d) Withdrawal

i) Criteria for cluster maintenance

By the end of Phase 1 all included hospitals will be evaluated in relation to data collection quality and effectiveness, as well as effective in the operational procedures. For phase 2 hospitals will be maintained according to a ranking based on the primary outcome observed during phase 1 until the needed number of clusters is reached.

This strategy will minimize possible post-randomization drop-outs.

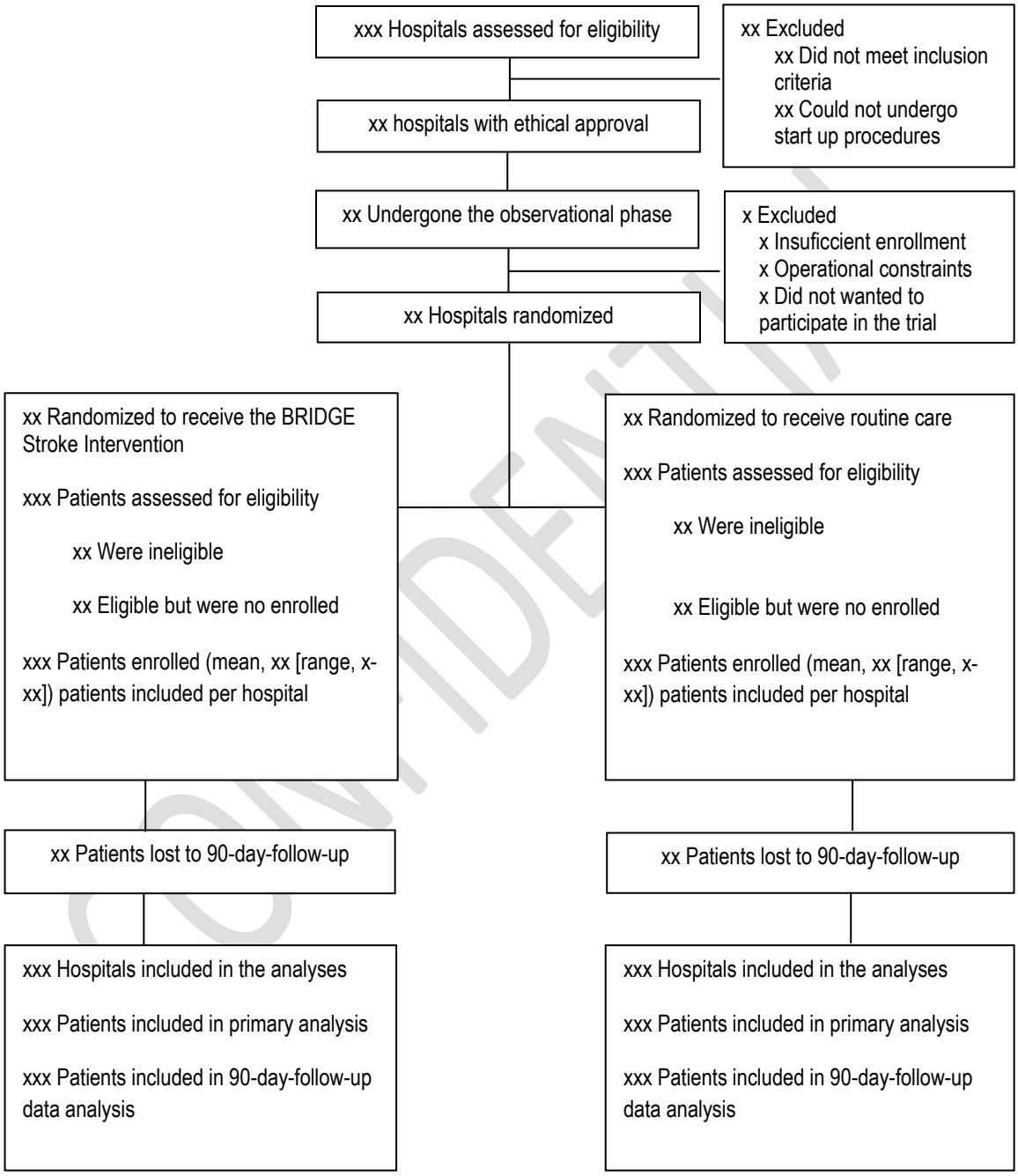
ii) Follow-up

Data from patients included in the study referring to in-hospital stay will be collected from medical records. Data referring to 90 day follow up will be collected by the Central Office health care professional in a telephone interview.

The informed consent at the patient level for this trial is obtained only for the purpose of the 90-day follow up. Therefore, since the admission information is retrieved from the medical records, we will have data from all patients included in the trial.

Withdrawal may occur only at the 90-day follow up. Any withdrawal at this level will be stated in the CONSORT diagram (Figure 1).

Figure 1. Recruitment (Cluster/Patients) – CONSORT Flow Chart



e) Sample size

i) Phase 1

Because of the reduced availability of resources compared to the sites evaluated in these studies, it is expected that the prescription of evidence-based interventions in the first 48 hours and at discharge is even lower in public hospitals (estimate of 40%). Thus, in Phase 1, the goal was to include 40 stroke patients per participant hospital. This sample size was sufficient to detect all the expected percentages (between 1.0% and 95%, depending on the type of evidence-based intervention) for indicators of health care quality, considering an absolute sampling error of 10% and a significance level of 5%.

This phase serves as baseline for the cluster randomized trial (Phase 2). Outcomes estimates from this phase will be used for a new sample size calculation and for defining the strata to be used in the randomization.

The main purpose of the phase 1 analysis is identifying the variability of the primary outcomes between clusters. Therefore, results will be presented as with the correspondent estimates of the standard deviation (or variance) within cluster and between clusters. These estimates will be generated by a mixed linear regression model with random effects between clusters. These estimates are sufficient to express the intra-cluster correlation coefficient (ICC) that will be used for the purpose of estimating the sample size. The ICC (ρ) is defined as:

$$\rho = \frac{\sigma_a^2}{\sigma_a^2 + \sigma_e^2},$$

where σ_a^2 refers to the random effect variance of the clusters (*clusters)* and σ_e^2 to the variance of the measure. In practical manners we can assume the ICC show how much from the total variability is attributable to the clusters.

Further details on ICC calculation and variations on the calculation for binary outcomes (which will be used for secondary outcomes) are described in Hayes e Moulton (2009)[(34)].

ii) Simulations for Phase 2

Ideally, it is expected that after the implementation of a program to improve clinical practice, evidence-based interventions are prescribed to most patients (about 90%). However, programs of clinical practice improvement have moderate effect

(absolute increase of 10%) on the prescription of treatments with proven benefit. There is no clear definition of the effect size expected for interventions of clinical practice improvement in the literature because of the wide heterogeneity in terms of the design of the available evidence, statistical power and methodological quality. Additionally, the efficacy of different tools may vary according to the clinical setting.

Unlike individual patient randomization where it is expected each patient being independent from another, in cluster randomization patients treated in the same hospital are expected to be similarly treated. In such situations it is necessary to consider this dependence when estimating sample size. This is called intra-cluster correlation. As previously observed in studies evaluating patient care, the ICC is approximately 0.05. (31).

Thus, considering fixed sized clusters of approximately 50 patients, a 0.086 mean difference in the Composite Adherence Score, with 5% statistical significance we estimated the following scenarios differing according to standard deviation (SD), power and intra-cluster coefficient (ICC):

Table 1. Estimated sample size scenarios prior to Phase 1.

Mean difference	Standard Deviation	ICC	Power	Sample (number of clusters per arm)	Total sample size (number of Patients)
0.086	0.25	0.05	90%	15	1500
0.086	0.25	0.10	80%	18	1800
0.086	0.20	0.10	90%	16	1600
0.086	0.20	0.15	80%	17	1700

In case a high variability between hospitals is observed, or the pattern of prescription is much different from expected, or more sites needed to be dropped after Phase 1, a new sample size calculation was anticipated before starting Phase 2.

iii) Sample size in Phase 2

The previous statement about sample size was done before acquiring data in Phase 1. Our expectations were accurate regarding the standard deviations; however the observed ICC was higher (around 0.25). Consequently, assuming these findings and a

significance level of 5%, a sample of 36 clusters, with mean inclusion of 40 patients per cluster (around 1440 patients), the trial will have 80% power to detect a 0.125 difference in mean **Composite Adherence Score**.

f) Framework – Hypothesis

The null hypothesis is that there is no difference in adherence to evidence-based therapies for acute ischemic stroke or transient ischemic attack patients between the usual care and the intervention group. The alternative hypothesis is that there is a difference between the groups.

g) Interim analysis and stopping guidance

No interim analysis is planned for this trial.

h) Timing of final analysis

The final analysis for the BRIDGE Stroke trial is planned to take place after patient recruitment, patient follow up, and events adjudication are completed**.**

i) Timing of outcomes assessment

The schedule of study procedures is given in the item 3.0 of the protocol. A description of variables of interest is also given in item 3.10 as it is in the present document.

5) Statistical principles

All analysis will follow the intention-to-treat principle. Different interpretations for the intention to treat principle regarding the analysis of missing data are used by

different authors. In order to avoid misinterpretation, we define the intention-to-treat principle to be used in our analysis as follows:

4- The cluster allocated to the intervention group that don't follow or don't adhere to the intervention will be instructed to proceed with data collection irrespectively, and will be evaluated as the group that was originally allocated. The same holds true for the control group, irrespective of possible contamination.
5- Patients who were not eligible for the study will be ignored in the analyses.
6- Missing data from the primary composite outcome will be treated as negative endpoints (worst case scenario imputation).

The second criterion is justifiable by the outcomes definitions. For example, if a patient initially suspected as stroke or TIA is included in the study but later the diagnosis is not confirmed, means that this patient is not eligible to the study on the first hand, and is not eligible to any of the components of the composite score.

The third criteria is conservative, although the data regarding the components of the primary outcome are easily obtained and it is expected (if any) a minimal missing data rate (probably < 0.1%). Thus, data imputation shawl be minimum and other forms of imputation will be considered as sensitivity analysis.

a) Confidence intervals and P values

Statistical tests and confidence intervals will be two-sided with 5% significance level.

b) Adherence and protocol deviations

All sites are required to include consecutive patients that meet the inclusion criteria. In order to monitor possible screening failures, the coordinating center will track the accrual speed according to the observed rates during Phase 1. Additionally, the investigators sites are asked to send a detailed screening log on a weekly basis. Failure to one of the above mentioned assumptions will raise the suspicion of screening failure.

If this is the case, the sites will be asked to provide the hospitals' complete admission list of suspected stroke (using ICD 10 codes) during the recruitment period and perform another screening. Data from patients that failed the initial screening but are identified in the second screening turn will be included in the analysis.

Compliance to the Intervention is assessed by attendance in the investigators meeting, outreach visits (local training), web conferences, and by the identification of clear evidence that, for each patient, the materials were used by the local team.

Descriptive statistics on the percentage compliance to the intervention per cluster/site (N, mean, maximum, minimum) will be presented.

6) Analysis

a) Baseline characteristics

Continuous variables will be described by mean and standard deviation whenever there is a normal distribution, or median and/or interquartile amplitude median and interquartile ranges in case of non-parametric distribution. Qualitative variables will be presented as absolute frequencies (numbers) and relative frequencies (percentages), as described in mock Table 2. Tests of statistical significance will not be undertaken for baseline characteristics.

1632

1633

1634 **Table 2.** Clusters and Patients Baseline Characteristics

Characteristics **Patient baseline characteristics**	Intervention **(xx clusters; xxx patients)**	Control **(xx clusters; xxx patients)**
Men	xx (xx%)	xx (xx%)
Age, mean (SD), y	xx (xx)	xx (xx)
Diabetes	xx (xx%)	xx (xx%)
Hypertension	xx (xx%)	xx (xx%)
Dyslipidemia	xx (xx%)	xx (xx%)
Current Smoking	xx (xx%)	xx (xx%)
Family history of stroke	xx (xx%)	xx (xx%)
Family history of CAD	xx (xx%)	xx (xx%)
Stroke	xx (xx%)	xx (xx%)
CAD	xx (xx%)	xx (xx%)
Atrial fibrillation	xx (xx%)	xx (xx%)
Renal failure	xx (xx%)	xx (xx%)
Use of aspirin in the last month	xx (xx%)	xx (xx%)
Use of anticoagulants in the last month	xx (xx%)	xx (xx%)
Use of statins in the last month	xx (xx%)	xx (xx%)
Final Diagnosis		
AIS	xx (xx%)	xx (xx%)
TIA	xx (xx%)	xx (xx%)
Cluster Baseline Characteristics		
Neurologist Available at ED	xx (xx%)	xx (xx%)
Mechanical Thrombolysis/Thrombectomy Capabilities	xx (xx%)	xx (xx%)
Stroke Unit	xx (xx%)	xx (xx%)
Stroke Protocol Available at ED	xx (xx%)	xx (xx%)
Stroke Protocol available at the Hospital	xx (xx%)	xx (xx%)
JCI Accreditation	xx (xx%)	xx (xx%)
Teaching Hospital	xx (xx%)	xx (xx%)
Prior participation in multicenter clinical trial	xx (xx%)	xx (xx%)
Volume of patients seen in ED per mo, median [IQR]	xx [xx - xx]	xx [xx - xx]
Baseline rate of primary outcome	xx [xx - xx]	xx [xx - xx]

Abbreviations: SD, standard deviation; CAD, coronary artery disease; AIS, acute ischemic stroke; TIA, transient ischemic attack, ED, emergency department; JCI, Joint Commission International; IQR, interquartile range.

b) Outcomes

i) Primary outcome of the first phase

- Proportion of prescription of evidence-based therapies
- Barriers to implementation of methodologies.

ii) Secondary outcomes of the first phase

- Disability (mRankin) in 90 days.
- Mortality, in 90 days.
- Stroke recurrence in 90 days.

iii) Primary outcome of the second phase

Composite Adherence Score is the primary outcome defined for each individual (i) as:

$$Z_i = \frac{\sum_{j=1}^{10} x_{ij}}{\sum_{j=1}^{10} y_{ij}},$$

where $j = \{1, \dots, 10\}$ represents each component (procedure) and

$$y_{ij} = \begin{cases} 0, & if\ patient\ i\ isn't\ eligible\ for\ procedure\ j \\ 1, & if\ patient\ i\ is\ eligible\ for\ procedure\ j \end{cases}, \text{ and}$$

$$x_{ij} = \begin{cases} 0, & if\ the\ site\ didn't\ successfully\ performed\ the\ procedure\ j\ on\ patient\ i \\ 1, & if\ the\ site\ successfully\ performed\ the\ procedure\ j\ on\ patient\ i \end{cases}.$$

For this purpose, patients with contraindications (which are specific for each endpoint) were excluded from the denominators. The 10 components used in

the score are the evidence based therapies in the first 48 hours that includes: early antithrombotics, RT-PA, dysphagia screening, DVT Prophylaxis, Door to Needle Time < 60 minutes, dysphagia screening. And Discharge Therapies that includes: antithrombotics, lipid lowering agents for patients with LDL ≥ 100 or not documented, anticoagulants for atrial fibrillation or flutter, assessment for rehabilitation and smoke cessation education or education. All the definitions of the procedures considered in the composite score are described in Table 3.

iv) Secondary outcomes of the second phase

- Proportion of prescription of evidence-based strategies in the first 48 hours and at discharge cited in the primary outcome **individually** and in an "All or None" model.
- Additional strategies usage (also with definition presented in Table 3):
    - Global Rt-PA rate, defined as the number of stroke patients treated with alteplase over the number of stroke patients admitted within 24 hours of symptoms onset.
    - Anti Hipertensive agents at discharge.
    - Door to needle time < 45 minuts
- Mortality at 90 days.
- Disability (mRankin) in 90 days.
- Stroke Recurrence in 90 days.

1688 **Table 3.** Quality indicators

Name of Variable	Description	Inclusion	Exclusion	Numerator
Global Rt-PA Rate	Rt-PA Usage	All stroke patients admitted within 24 hours of symptoms	Not applicable	Patients that receive Rt-PA
Rt-PA	Recombinant Plasminogen Activator used within therapeutic window	Eligible patients diagnosed with stroke who arrive at the hospital within 3.5 hours of symptom onset and who are treated within 4.5 hours of symptom onset. *The subgroup of patients who arrive at the hospital within 02 hours of symptom onset and who are treated within 03 hours of symptom onset will also be evaluated.	Patients with medical contraindications or other documented reasons	Patients who received Rt-PA within 3.5 hours of symptom onset. *The subgroup of patients who arrive at the hospital within 02 hours of symptom onset and who are treated within 03 hours of symptom onset will also be evaluated.
Early Antithrombotic	Antithrombotic therapy	Eligible patients	Patient with any documented	Patients treated with antithrombotic

Agents	prescribed within 48 hours of admission (includes antiplatelet agents or anticoagulants).	diagnosed with stroke or TIA	medical contraindication as a reason for no treatment.	agents until the end of the 2nd day of admission (including ASA, ASA+dipyridamole, ticlopidine, clopidogrel, unfractionated heparin, low molecular weight heparin, and warfarin, but does not include SC heparin at prophylactic doses for DVT.
Prophylaxis for DVT	Patients at risk for DVT (unable to walk) who received DVT prophylaxis until the end of the second day.	Patients eligible for DVT prophylaxis with a diagnosis of stroke.	Patients who can walk at the end of the 2nd day. Excluding patients with any documented medical contraindication.	Patients treated with DVT prophylaxis until the end of the 2nd day of admission (including heparins, heparinoids, other anticoagulants or pneumatic compression devices.
Dysphagia Screening	Dysphagia Screening prior to any oral intake	Patients with a diagnosis of stroke	Not Applicable	Patients who are screened for dysphagia with validated tests before being given any food or fluids by mouth
Door-to-Needle Time < 60 minutes	Time since the patient's arrival to the hospital until the start of rt-PA infusion	Patients eligible for treatment with rt-PA	Patients with documented medical contraindication.	Patients treated with reperfusion therapy within 60 minutes of admission.
Door to needle < 45 minutes	Time since the patient's arrival	Patients eligible for	Patients with documented	Patients treated with reperfusion

	to the hospital until the start of rt-PA infusion	treatment with rt-PA	medical contraindication.	therapy within 45 minutes of admission.
Oral Anticoagulation for Atrial Fibrillation or Flutter	Anticoagulation prescribed at discharge for patients with documented atrial fibrillation or flutter during hospitalization	Eligible patients with diagnosis of stroke and a history of paroxysmal or persistent atrial fibrillation or atrial flutter during this hospitalization period.	Patients with any documented medical contraindication as a reason for no treatment.	Patients who received anticoagulation at discharge (including therapeutic doses of heparin, heparinoids, warfarin, or other anticoagulants such as direct thrombin inhibitors.
LDL ≥ 100 or not documented	Statins prescribed upon discharge if LDL ≥ 100 mg/dL, if the patient was previously treated with lipid-lowering medication before the admission, and if LDL has not been documented.	Eligible patients with a diagnosis of stroke or TIA if LDL ≥ 100mg/dL, if the patient was previously treated with lipid-lowering medication before the admission, and if LDL has not been documented.	Patient with any documented medical contraindication as a reason for no treatment.	Patients who received statins upon discharge (including statins, fibrates, niacin, binding resins, or selective cholesterol absorption inhibitors)
Smoking Cessation	Intervention for smoking cessation (education or medication) prior to discharge for smokers.	Eligible patients with a diagnosis of stroke or TIA and smokers (defined as having initiated or maintained	Patient with any documented medical contraindication as a reason for no treatment.	Patients or their caregivers who received smoking cessation education or medication for smoking cessation before discharge.

		the habit of smoking in the last year).		
Anti-hypertensive	Anti-Hypertensive prescribed prior to discharge for patients with diagnoses Hypertension	Eligible patients diagnosed with stroke and documented history of hypertension	Patients with any documented contra indication for antihypertensive usage.	Patients who receive anti-hypertensive agents at discharge
Assessed for Rehabilitation	Patients assessed by or treated by rehabilitation professional	All patients diagnosed with stroke	Not Applicable	Patients who are assessed by or who receive rehabilitation services

- *See attached the table containing the main contraindications to the above mentioned therapies.

Stroke Recurrence, mRankin and Mortality definitions and quality control procedures to access those outcomes are described in detail in the Protocol.

c) Analysis methods

Results will be separated per group (intervention vs control). Clusters characteristics will be presented first, followed by the patient's characteristics. As described in mock Table 1. Adherence to the quality improvement intervention will be reported, as the time from training until intervention onset. Descriptive statistics on time from site activation until first patient inclusion will also be reported.

The primary outcome will be analyzed using a mixed effects linear regression model with random effects to account for the correlation of observations within clusters. This model will consider residuals assuming a normal distribution. We intend to perform a sensitivity analysis considering a mixed effect linear model that better suits the real distribution of the data (beta distribution models, binomial distribution using the sum of each component, for example).

The choice for the most simple model (with possible failure on the assumptions) over a most complex one was made due to lack of background in the literature supporting other methods for better sample size estimation assuming the same type of outcome used in our study. However, we understand that this choice estimates a more conservative (larger) sample size.

The components of the primary outcome will be individually evaluated using mixed effects general linear models considering binomial distribution (logistic regression with random effect at the intercept (cluster adjusted)).

All models (including the primary outcome) will be adjusted for the cluster's baseline value.

Treatment effects will be expressed as absolute mean difference or the composite outcome and odds ratio with the respective 95% confidence intervals for the individual components. Preferentially following the mock Table 4.

Table 4. Adherence to individual performance measures and primary outcome assessment between groups.

Outcome	Intervention (xx clusters; xxx patients)	Control (xx clusters; xxx patients)	Odds Ratio [95%CI]	P value	ICC
Primary Endpoint					
Composite adherence score (%) - mean (sd)[a]	xx.x ± xx.x	xx.x ± xx.x	x.x [-x.x; x.x][d]	x.xx	x.xx
Secondary Endpoints					
Acute Interventions during first 48 hours					
IV Rt-PA within therapeutic window[b]	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Door-to-needle time < 60 min	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Early Antithrombotics	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
DVT Prophilaxy	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Discharge therapies					
Antithrombotics	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Anticoagulants for AF or Flutter	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
LDL >-100 or not documented	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Smoking Cessation Education	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Assessed for Rehabilitation	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx
Dysphagia Evaluation	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx

Complete adherence to all acute and specified discharge therapies)[c]	xx (xx.x%)	xx (xx.x%)	x.x [-x.x; x.x]	x.xx	x.xx

ICC denotes intracluster correlation coefficient. IV Rt-PA denotes intravenous recombinant plasminogen activator. DVT denotes deep venous thrombosis.

[a]Composite adherence score: early antithrombotics, Rt-PA < 3.5h, DVT prophylaxis, door-to-needle time < 60 min, dysphagia screening, assessed for rehabilitation, antithrombotics at discharge, anticoagulants for atrial fibrilation or flutter, LDL >= 100 or not documented (statins), smoke cessation educationb.

[b]RtPA in eligible patients (who arrive at the hospital within 3.5hours of symptom onset).

[c]Patients who received all the therapies: Rt-PA within therapeutic window (patients who arrived within 3.5 hours of sympton and treated within 4.5h of symptom onset), antithrombotic in 48h, antithrombotic in 7 days, prophylaxis for DVT, door-to-needle time < 60, oral anticoagulantion for AF or Flutter, statins in LDL ≥ 100 or undocumented, intervention for smoking cessation, assessed for rehabilitation, dysphagia evaluation.

[d]Mean difference in 95% CI

We intend to perform at least two sensitivity analyses: an adjusted analysis for hospital status (teaching vs non-teaching) and presence of a stroke unit. And a second sensitivity analysis considering only those sites that followed the protocol, in which patients were consecutively included without loss, and those sites that actually implement the proposed interventions (*per protocol analysis*).

Pre-specified subgroup analysis, for which interaction by group will be assessed as follows: teaching hospital (or not), presence of a stroke unit, presence of a neurologist in the emergency department, final diagnosis (AIS vs TIA), and country.

Disability will be assessed by the mRankin scale primarily in a dicothomous model (proportion of patients with mRankin < 2) in patients with AIS using logistic mixed regression models considering the cluster and time (patient longitudinal measure) dependencies, and secondarily by a shift analysis.

Secondary outcomes clinical outcomes in hospital will be evaluated similar to other dichotomous comparisons using mixed logistic regression models. Events evaluated in the 90 days follow up will be compared using proportional hazards frailty models[(3)] with random intercept according to cluster (site), and effects estimates will be presented as Hazard Ratios. Results will be adjusted by site's Phase 1 events rates and will be presented as suggested in mock Table 5.

Table 5. Clinical outcomes comparisons between groups

Clinical Outcomes	Intervention (xx clusters; xxx patients)	Control (xx clusters; xxx patients)	Odds Ratio 95%CI	P value	ICC
Events (in hospital)					
Stroke Recurrence	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Hemorrhagic Transformation	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Non fatal cardiac arrest	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Major Bleeding	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Acute Coronary Syndrome	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Total Mortality	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Cardiovascular Mortality	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]	x.xx	x.xx
Events (within 90 days)					
Stroke Recurrence	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]*	x.xx	x.xx
Total Mortality	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]*	x.xx	x.xx
Cardiovascular Mortality	xx.x (xx.x%)	xx.x (xx.x%)	x.x [x.x; x.x]*	x.xx	x.xx

Abbrevations: ICC denotes intracluster correlation coefficient.
* Effects in 90 days expressed as Harazd Ratios

d) Additional analysis

Other models regarding the peculiar distribution of the primary outcome may be explored. Results as it is pre-specified should be enough to report the study results, however alternatives models such as mixed effects logistic regressions models considering the eligible procedure for the composite score as sample unit and Bayesian hypothesis tests using site's Phase 1 information as *prior* distribution to the randomized phase, and other proposals of primary outcome definition giving different weights for the procedures are some pre-specified alternatives.

Anticipated sub-analysis for subsequent sub-studies include: cross country analysis, stroke unit sub-population.

e) Statistical software

Analyses will be done using R software [4]

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