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### 1.ABBREVIATIONS AND GLOSSARY

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<td>BI</td>
<td>Barthel Index</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<td>EuroQOL, EQ-5D</td>
<td>European Quality of Life scale</td>
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<td>GWTG, GWTG-S</td>
<td>Get With The Guidelines-Stroke registry</td>
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<tr>
<td>IV rtPA</td>
<td>Intravenous recombinant tissue plasminogen activator (Alteplase)</td>
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<tr>
<td>LAR</td>
<td>Legally authorized representative</td>
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<tr>
<td>MaRISS</td>
<td>Mild and Rapidly Improving Stroke Study</td>
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<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
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<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<td>PRO</td>
<td>Patient reported outcome</td>
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<td>RIS</td>
<td>Rapidly improving stroke</td>
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<td>RISS</td>
<td>Rapidly improving stroke symptoms</td>
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<td>TOAST</td>
<td>Trial of Org 10172 in Acute Stroke Treatment stroke classification, a classification of ischemic stroke mechanism</td>
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2. STUDY SUMMARY

**Title:** Mild and Rapidly Improving Stroke Study

**Objective:** To elucidate long-term outcomes of patients with mild and rapidly improving stroke and examine the association with tPA treatment.

**Design:** Investigator-initiated prospective observational study.

**Primary Outcome Measure:** Proportion of patients with a mRS = or > 2 at 90 days

**Secondary Outcome Measures:**
Barthel Index (BI), Stroke Impact Scale-16 (SIS), EuroQOL, at 90 days, mRS at 30 days, mortality at 30 and 90 days.
In those who received IV rtPA, also: symptomatic hemorrhagic transformation, endovascular acute stroke rescue therapy within 24 hours.

**Exploratory Outcome Measure:**
In a subgroup of 100 patients with internet access, test the reliability of a web-based patient reported outcome instrument compared to a structured telephone interview.

**Eligibility:** mild ischemic stroke (NIHSS = or < 5) or rapidly improving stroke symptoms within 4.5 hours from onset; provide informed consent; speak English or Spanish.

**Sample Size:** 2650.

**Sites:** 100 preselected hospitals currently participating in GWTG-S.

**Study duration:** 2 years
Site subcontracting and IRB approval: 4 months
Patient recruitment: 18 months
Completion of follow-up: 3 months

**Narrative:** To understand the long-term outcomes of patients with mild and rapidly improving stroke symptoms, this prospective observational study will leverage the current information in the Get With The Guidelines-Stroke registry and collect 90-day outcomes. A total of 2650 patients with mild and/or rapidly improving stroke symptoms will be enrolled in 100 hospitals participating in GWTG-S. The primary outcome is the proportion of patients with a modified Rankin Scale ≥2 assessed through a structured telephone interview of stroke outcomes. The feasibility of using an automated web-based patient reported outcome will be tested in a group of 100 patients. Predictive models and risk scores of poor outcomes will be created. The efficacy and safety outcomes of patients with mild and improving strokes treated with thrombolitics will be explored.
3. GOAL, HYPOTHESIS AND SPECIFIC AIMS

The overall goal of this study is to elucidate long-term outcomes of patients with mild and rapidly improving stroke and examine the association with tPA treatment. In order to accomplish this goal, we will pursue the following specific aims:

Specific Aim 1. Determine the 90-day outcomes for patients with mild stroke symptoms or rapidly improving stroke symptoms. We hypothesize that a subgroup of patients with mild stroke symptoms defined by the NIHSS, or with rapidly improving symptoms, will have poor outcomes. The population to be studied is a prospective cohort of 2650 patients at 100 GWTG-S preselected hospitals with mild ischemic stroke (NIHSS = or < 5) or rapidly improving stroke symptoms within 4.5 hours from onset, which provide informed consent, and speak English or Spanish. Outcomes will be obtained through a structured telephone interview with the patient or proxy. The primary outcome is the proportion of patients with a modified Rankin Score (mRS) = or > 2 at 90 days. Secondary outcomes include: Barthel Index (BI), Stroke Impact Scale (SIS), EuroQOL, at 90 days, mRS at 30 days, mortality at 30 and 90 days.

Specific Aim 1b. Determine the reliability of an automated patient reported outcome (PRO). We hypothesize that an automated PRO is feasible and reliable. A subset of 100 patients with internet access will be invited to complete a web-based PRO that includes the mRS, BI, SIS-16, and EuroQOL, which will be compared to the telephone interview.

Specific Aim 2. Determine the predictors for worse 90-day outcomes in patients with mild stroke symptoms or rapidly improving stroke symptoms. We hypothesize that certain variables can predict poor outcomes. Prediction models will use current GWTG-S demographic, risk factor, and clinical presentation variables, as well as newly collected in-hospital variables (individual components of the baseline NIHSS, serial in-hospital NIHSS, and stroke mechanism).

Specific Aim 3. Among patients with mild or rapidly improving stroke symptoms, compare the safety and efficacy outcomes of intravenous thrombolysis compared to non-thrombolized patients after adjusting for treatment predictors. The hypothesis is that analysis of the interaction between predictors of poor outcome and IV rtPA treatment can identify a subgroup of patients with mild and rapidly improving stroke symptoms that can potentially benefit from thrombolytic therapy. We anticipate that about 10% of the population studied will be treated with IV rtPA. The primary efficacy outcome: mRS 0-1 at 90-days. The primary safety outcome is symptomatic hemorrhagic transformation. Secondary outcomes include: 90-day BI, EuroQOL, and SIS-16, endovascular acute stroke rescue treatment within 24 hours.
4. BACKGROUND AND RATIONALE

Stroke is the 5th cause of death in the US and 3rd cause of death worldwide, as well as a leading cause of disability (1). Population based studies reveal that about half of all strokes have low NIHSS on presentation (2,3). Mild and rapidly improving strokes are a common reason to not administer thrombolytics, although up to one third of patients with mild and rapidly improving strokes are unable to return home. Nonetheless, detailed long-term outcomes in those with mild and or rapidly improving stroke are lacking. This is essential to determine whether more aggressive treatment is reasonable for some these patients.

How are mild and rapidly improving symptoms defined? Traditionally, the NIHSS has been used to describe a severity of a stroke. Most recent clinical studies of intervention for acute ischemic stroke have excluded those with an NIHSS ≤5 or ≤6. However, in clinical practice, the determination of mild stroke as a reason not to administer IV rtPA is left up to the clinician. Amongst 10,295 GWTG-S patients not treated with IV rtPA solely because of a mild stroke, 94% had a NIHSS of 5 or less (4). However, it is clear that an isolated aphasic syndrome, even though it would accrue a low NIHSS, would be quite disabling and would not be considered mild.

The situation of rapidly improving symptoms is more complicated. Different studies and reports have defined improvement by the absolute change in NIHSS points from baseline, the final NIHSS score, or the percent improvement in the NIHSS (5-10). A recent consensus statement recommended defining rapidly improving stroke symptoms as those that improve to an NIHSS ≤5 and are non-disabling (11). However, a large proportion of the improvement may occur prior to hospital arrival. Although a number of EMS scales of severity are available, they have not been carefully analyzed to include pre-hospital fluctuations in the definition of rapidly improving stroke. Therefore, in practice, the physician ascertains if symptoms have rapidly improved or not. In GWTG-S, amongst those not treated due to only rapidly improving symptoms, 26% had an NIHSS >5 suggesting persistent disabling symptomatology (4).

Are mild stroke and rapidly improving stroke similar? Although there may be overlap between mild and rapidly improving stroke, with as many as 1 in 4 patients rapidly improving to a mild level, these conditions have clearly different causes, presentations and outcomes. Rapid improvement would suggest rapid recanalization and reperfusion of ischemic tissue, while mild strokes are probably caused by persistent occlusion of a vessel. In a retrospective analysis of GWTG-S, rapidly improving stroke patients tended to be older, have more cardiac and carotid disease, and have a higher NIHSS at baseline. After adjustment for multiple variables, rapidly improving strokes that improve to mild had the best outcomes. Therefore, each category (mild, rapidly improving, and rapidly improving to mild) has distinct characteristics.

How common are mild and rapidly improving stroke symptoms? About 31-46% of patients that present to the Emergency Department within 3 hours of onset with an acute ischemic stroke have mild or rapidly improving stroke symptoms (12-15). The largest available series include the large GWTG-S registry where 31.2% of 93,517 patients that arrived within 2 hours of onset were not treated with intravenous thrombolytics (IV rtPA) because of mild or improving stroke (14), and the 4-state Paul Coverdell registry, in which mild or rapidly improving stroke symptoms were the main causes (46.6%) for being considered ineligible for IV rtPA in those
arriving within 2 hours from symptom onset (15).

**What are the outcomes of mild and rapidly improving stroke symptoms that do not receive thrombolytic therapy?** Most data comes from registries or retrospective analysis that vary in the definition of mild and rapidly improving stroke. In GWTG-S, amongst 29,200 patients with mild and rapidly improving stroke not treated with IV rtPA, 27% were unable to return home, and 29% could not ambulate independently at discharge. Small series have shown that at 3 months, a mRS of 2-6 was present in 15% (16) to 32% (17). Therefore, as many as one third have suboptimal outcomes. However, detailed long term outcomes are lacking for this cohort of patients.

**How many mild and rapidly improving stroke patients receive IV rtPA?** Alteplase labeling and prior stroke guidelines (18) recommend against IV rtPA administration when neurological signs are clearing spontaneously and when neurological signs are minor and isolated. However, newer guidelines recognize that some of these patients may have poor outcomes and therefore recommend treatment of mild but disabling stroke within 3 hours of symptom onset (19). This coincided with a revision of the alteplase prescribing information in 2015 that does not include these exclusions. Although treatment at academic or high volumes centers report that as many as 21% of mild strokes receive IV rtPA treatment (4,20), national registries show more modest rates of 10% to 12% (21,22).

**Do those that receive IV rtPA do better than those that are untreated?** This is an open question and the subject of ongoing research. It is difficult to compare outcomes outside of a randomized controlled trial as there is the potential for bias (confounding by indication); that is, specific higher severity markers may guide the clinician to administer IV rtPA to one patient but not to another. The largest report suggests that although the risk of symptomatic hemorrhage is <2%, outcomes at discharge were poor, with 29% not discharged home and 31% unable to ambulate independently at discharge (4). Delayed 3-month outcomes are available only from small series showing mRS 2-6 in 17% (23) to 42% (24).

**What underlies poor outcomes in mild and rapidly improving stroke?** Poor outcomes may be due to an isolated but disabling symptom such as aphasia that may not translate into a high NIHSS score (25). Also, early progression of mild symptoms is not uncommon. A single center study reported that 8.3% of 229 patients with a mild stroke or TIA (NIHSS <5) had progression of symptoms within 72 hours, similar to those with more severe strokes (26). Similarly, in an MRI based study, 10% of those excluded from thrombolytic therapy for mild or improving symptoms had early neurologic deterioration and infarct expansion and 20% had poor discharge outcome (27). Rapidly improving symptoms may subsequently deteriorate. Smith and colleagues (28) reported that 11/41 patients with mild/improving symptoms not treated with tPA were not discharged home; 6 of them had early worsening. Early worsening is thought to be due to hemodynamic failure, or re-occlusion of a spontaneously reanalyzed vessel, which may occur in 12% of all tPA-treated patients and 27% of those with initial recanalization (29). An OR of 4.1 for subsequent deterioration was described in those with rapidly improving symptoms compared to those without rapid improvement (28).

**Is the modified Rankin Scale a good measure of outcome in mild and rapidly improving stroke?**
The mRS measures functional disability in stroke and is the most commonly employed stroke functional outcome scale in stroke studies. Although it has good validity and reliability (30), it is unidimensional with important ceiling effects and poor assessment of health-related quality of life (31). More detailed outcome measures are needed to better understand functional outcomes after mild and rapidly improving stroke. Other measures also employed in MaRISS as secondary outcomes include the Barthel Index (BI), the Stroke Impact Scale-16 (SIS-16), and EuroQOL (EQ-5D). The BI measures activities of daily living; a score of ≥85 corresponds to independence with minimal assistance, while a score ≥95 to minimal or no disability (32-34). The SIS-16 concentrates on the physical domains rather than cognitive or emotional domains (31,35,26). The EQ-5D measures health outcomes and explores non-physical domains (37,38).

Can poor outcomes be predicted at baseline evaluation? We have assessed predictors of poor outcome in mild and rapidly improving stroke in GWTG-S, and found that older age, Africa Americans, the greater burden of stroke risk factors such as hypertension, diabetes, prior stroke, atrial fibrillation, heart failure and peripheral vascular disease, as well as delayed arrival and higher NIHSS are associated with worse discharge outcomes, while the baseline use of antiplatelet, antihypertensive and antilipidemic medication was associated with better outcomes. Others have found that large vessel occlusion and distal hypoperfusion predicted stroke progression (27,39). However, the influence of stroke mechanism and early in-hospital fluctuations on outcomes is not currently known.

Summary of background for MaRISS. Mild and rapidly improving stroke symptoms are common presentations of acute ischemic stroke. The great majority of patients are not treated with thrombolytics. The outcomes of mild and rapidly improving stroke are suboptimal with almost 1 in 3 unable to return home or ambulate independently at discharge. Nevertheless, continuous improvement may occur in the first 3 months after discharge (40), but 3-month outcomes are available from only small series, include only the mRS, and vary extensively. Therefore, the long-term outcomes and predictors of poor outcome are not well characterized. MaRISS will describe the long-term outcomes with a battery of sensitive outcome measures, and will elucidate predictors of poor outcome by carefully analyzing stroke baseline characteristics and early fluctuations.
5. STUDY DESIGN AND METHODS

STUDY DESCRIPTION

MaRISS is a prospective observational study that will enroll 2650 patients from 100 GWTG-S hospital in order to define the 90-day outcomes of patients with mild and/or rapidly improving stroke by a telephone-based assessment of stroke outcomes based on established and validated measures including the mRS, BI, SIS-16 and EuroQOL. In addition, we will test the feasibility of using an automated web-based patient reported outcome. Based on detailed baseline and early hospitalization demographic and clinical data, assessment of early fluctuations by serial NIHSS examinations, and evaluation of and stroke mechanisms through the TOAST classification, we will create predictive models of poor outcomes. The efficacy and safety outcomes of patients with mild and improving strokes treated with thrombolytics will be explored by comparing them to those treated conservatively without thrombolytics.

5.1 RESEARCH PLAN

Aim 1. Determine the 90-day outcomes for patients with mild stroke symptoms or rapidly improving stroke symptoms. Based on the available data, we hypothesize that a subgroup of patients with mild stroke symptoms defined by the NIHSS, or with rapidly improving symptoms, will have poor outcomes. In order to test this hypothesis, a prospective cohort of patients with mild or rapidly improving stroke evaluated within 4.5 hours from onset will be followed after discharge from hospital to determine the 90-day independence and disability.

The primary outcome for this aim is the proportion of patients with a mRS ≥ 2 at 90 days; secondary outcomes include the BI, SIS-16, and EuroQOL at 90 days, mRS ≥ 2 at 30 days, and mortality at 30 and 90 days.

This aim will be attained by collecting outcome variables that are not currently included in the GWTG database, including 30 and 90-day mRS, and 90-day BI, SIS-16 and EuroQOL, obtained through a telephone interview with the patient or the proxy. The 30-day mRS will be used only when a 90-day outcome is not available.

A total of 2650 patients will be enrolled across the 100 sites over 2 years. Institutional Review Board will be obtained at each site, and patients will sign informed consent after the decision to treat or not is completed. The current GWTG data points will continue to be obtained, in addition to specific outcome measures. Eligible individuals include those with a mild or rapidly improving ischemic stroke, defined clinically, admitted within 4.5 hours from onset (41,42), that provide informed consent, and speak English or Spanish (outcome measures validated for these two languages). Those with a premorbid mRS >1 will be excluded.

Ischemic stroke is assessed clinically by the stroke team at the eligible hospital by the presence of focal neurological symptoms of sudden onset in the absence of hypoglycemia <50 mg/dl or brain CT evidence of intracerebral hemorrhage. Other clinical and imaging information may be used by the investigator to determine an ischemic etiology for the focal neurological symptoms.
Mild stroke is defined as an NIHSS of 5 or less, based on commonly accepted criteria (43).

Rapidly improving stroke is defined by the site neurologist or stroke team member. There is currently no standard definition for RIS. A variety of definitions have been employed, including: a) NIHSS improvement 4 points from baseline (5); b) NIHSS 0 or 1 on follow-up or improvement of 8 points from baseline (major neurological improvement) (6); c) NIHSS 3 on follow-up or improvement of 10 points from baseline (dramatic neurological improvement) (7,8); d) improvement by 20% (9); and e) improvement by 40% from baseline NIHSS score (10).

In this observational study, we will not mandate intervention or treatment, and will enroll patients after the decision has been made to treat or not treat with intravenous rtPA. We will record the change in NIHSS from arrival to ED to decision to treat (usually within 1 hour) and then, post-hoc, analyze the drivers of the decision to intervene based on the change in clinical status. The criteria employed by the treating physician to determine a rapidly improving stroke will also be recorded. In an attempt to incorporate pre-hospital improvement, there will be an estimation of the change in clinical status from onset to hospital arrival based on EMS, family or patient’s report.

The modified Rankin Scale measures disability or dependence in stroke patients and has become the most commonly employed stroke functional outcome measure, with good validity and reliability (30,44). A 30-day mRS will be used only when a 90-day mRS is unavailable (i.e. lost to follow-up). In order to standardize the collection of the mRS, MaRISS will employ the mRS-9Q survey (45): this validated method consists of 9 questions with a yes/no answer; the answers are entered into an online calculator that screens for inconsistent answers and produces a consistent score that excludes examiner variability. The analysis will adjust for pre-morbid historical mRS (0 or 1). There are some shortcomings with the mRS: it may not be sensitive to disabling symptoms that impact quality of life, as it captures disability but not health-related quality of life. For that reason, we will employ as secondary outcomes other measures of independence and quality of life:

The Barthel Index is the most commonly used scale to measure activities of daily living. It has good inter-rater reliability; a score of ≥85 corresponds to independence with minimal assistance, while a score ≥95 to minimal or no disability (32-34). For statistical purposes, the BI will be dichotomized with a score of 95-100 considered favorable. One of the shortcomings of the BI is that it suffers from a ceiling effect.

The Stroke Impact Scale-16 has less ceiling and floor effects than generic health-related quality of life instruments such as the SF-36 and is able to discriminate across low mRS levels (31, 35). The SIS-16 concentrates on the physical domains rather than cognitive or emotional, and is feasible to administer by telephone interview (36). For statistical purposes the SIS-16 will be treated as a continuous measure, and the distribution, mean, standard deviation, range, median, and interquartile range will be calculated.

The EQ-5D/EuroQOL is a standardized instrument that measures health outcomes, it is a brief and simple test, with good inter-rater reliability, and is comparable to the SF-36; it also explores non-physical domains, compared to the SIS-16 (37,38). For statistical purposes the EuroQOL
will be treated as a continuous measure, and the distribution, mean, standard deviation, range, median, and interquartile range will be calculated.

These outcome measure instruments are available in English and Spanish. Site coordinators will perform the outcome measures through a telephone interview. They will be certified in the performance of the outcome measures through an online training program. These outcomes are aligned with those planned in randomized trials of mild strokes (PRISMS Trial, P. Khatri (PI), Sponsor: Genentech). This will permit future data aggregation and interpretation.

**Aim 1b. Determine the reliability of an automated patient reported outcome (PRO).** In addition to the telephone-based interviews to assess outcomes, we will evaluate the feasibility of employing a self-accessed web-based, patient reported outcome measure (PRO). In order to do this, a subset of 100 random patients identified at baseline as having internet access from home will be invited to complete a web-based PRO that includes the mRS, BI, SIS-16, and EQ-5D. These will be compared for alternate form reliability with their own telephone-based responses, using a Kappa statistic for the mRS and correlation coefficients for the SIS-16 and EQ-5D. In this manner, we will determine if an automated web-based PRO can be standardized and scaled. If this proved to be the case, different formats of PRO can be envisioned, such as one accessed through a smart phone.

**Aim 2: Determine the predictors for worse 90-day outcomes in patients with mild stroke symptoms or rapidly improving stroke symptoms.** The working hypothesis is that certain demographic variables (i.e. age), clinical variables (rapid fluctuations in NIHSS), stroke mechanism (i.e. large artery disease), and type of symptoms (i.e. aphasia, hemiparesis and ataxia) will be strong predictors for poor outcomes. This aim will be accomplished by evaluating current GWTG demographic, risk factor, and clinical presentation variables, as well as newly collected in-hospital variables including individual components of the baseline NIHSS, serial in-hospital NIHSS, qualitative assessments of pre-hospital and in-hospital neurologic fluctuations, and the TOAST stroke classification.

The variables used in the prediction models include:

1. **Demographic:** age, gender, race/ethnicity. These are currently collected in the GWTG registry.
2. **Clinical:** traditional stroke risk factors, prior use of antithrombotic, antihypertensive and antilipidemic agents, time from onset to arrival. These are currently collected in the GWTG registry.
3. **Symptomatology:** evaluated by the National Institutes of Health Stroke Scale (NIHSS). This is a well-validated, reliable scale, available in various languages, and is used both in the research setting and in clinical practice as a way to estimate the magnitude of neurologic impairment by quantifying the neurologic examination. Its use is established for neurologists, non-neurologists and nurses. Although low NIHSS scores have been associated with good outcomes and used as criteria for excluding patients from thrombolytic treatment, only very low final NIHSS are correlated with very good functional recovery (46), and specific components of the NIHSS such as aphasia can be associated with a poor outcome. The NIHSS will be recorded on arrival, at the time of treatment decision.
(standard of care), at any time of clinical deterioration within 24 hours, at 24+/−4 hours from symptom onset, and at day 3 (or discharge if before day 3). We will test the global score, its change over the first days, and each individual component of the NIHSS as potential predictors of outcome. The individual components of the NIHSS and its serial collection are not currently encompassed in the GWTG registry. Site investigators will be certified in the performance of the NIHSS. In addition to the NIHSS, we will collect a new qualitative assessment of pre-hospital and in-hospital neurologic fluctuation to correlate with outcomes.

4. **Mechanism**: defined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) stroke classification; TOAST is widely used to classify the mechanisms that underlie ischemic stroke (47) with good inter-rater reliability (48). The potential for early deterioration after stroke is correlated with the stroke mechanism, and large artery disease can result in early recurrence.

Prediction models and risk scores for mild and rapidly improving stroke will be created and evaluated for the primary outcome (mRS at 90-days), secondary outcomes (90-day BI, SIS-16, EQ-5D), and 30 and 90-day mortality, based on demographic variables, stroke mechanism, presenting symptoms, and changes in neurologic status.

As mortality, the mRS and BI will be treated as dichotomous outcomes as defined previously and logistic regression prediction models will be created. The SIS-16 and EQ-5D will be treated as continuous measures and analyzed using linear models. We will first confirm variable and model assumptions regarding normality, and when necessary outcome variables will be transformed to achieve normality. Potential predictor variables will be examined both continuously and categorically in relation to the outcomes, and included in final prediction models appropriately. Initial models will include all potential predictors simultaneously, and more parsimonious models will be created using backwards selection keeping all variables associated with the outcomes at a very liberal criteria of p<0.20.

**Aim 3:** Among patients with mild or rapidly improving stroke symptoms, compare the safety and efficacy outcomes of intravenous thrombolysis compared to non-thrombolized patients after adjusting for treatment predictors. It is anticipated that the mild or rapidly improving stroke patients treated with thrombolysis will have a low rate of symptomatic hemorrhagic transformation, less subsequent worsening requiring endovascular rescue therapy, and better 90-day outcomes than those not treated with rtPA. We will compare the safety outcomes and efficacy in those treated with or without IV rtPA, accounting for potential confounders including important determinants of treatment.

The **main safety outcome measure** for this aim is symptomatic hemorrhagic transformation. This is defined as any neurological deterioration that, in the judgment of the site investigator, is related to intracranial hemorrhage confirmed by CT or MRI. It has traditionally been considered as deterioration by at least 4 NIHSS points within 36 hours of IV rtPA administration. **Secondary safety outcome measures** are the 30 and 90-day mortality.

The **main efficacy outcome measure** for this aim is a mRS 2-6. **Secondary efficacy outcome measures** include the 30-day mRS and the 90-day BI, EQ-5D, and SIS-16, as well as endovascular acute stroke rescue treatment within 24 hours.
5.2 STATISTICAL CONSIDERATIONS

A) ANALYSIS PLAN

By analyzing the interaction between predictors of poor outcomes and rtPA treatment in relation to the 90-day outcomes, it is possible that potential subgroups of patients with mild or rapidly improving symptoms can be identified by baseline presentation that may benefit from thrombolytic treatment.

As mentioned above, the dichotomous outcomes, symptomatic hemorrhagic transformation, mortality, the mRS and BI, will be analyzed using logistic regression prediction models. The SIS-16 and EQ-5D will be treated as continuous measures and analyzed using linear models and transformed if necessary to satisfy normality assumptions.

Confounding by indication is the greatest threat to the validity of this analysis. To overcome this potential important source of bias we will use a propensity score analysis to control for treatment predictors. First, we will create a logistic regression prediction model for treatment with IV rtPA using all available GWTG data at admission. We will use this model to control for treatment predictors in our final logistic regression models and generalized linear models to predict our outcomes of interest. We will separately and additionally control for all particularly relevant possible confounding variables, including risk factors for the outcomes in the GWTG database.

A sequence of final models will be created. First, we will examine the unadjusted association between IV rtPA treatment and the outcomes. Next, we will control for demographic variables only. Lastly, our full multivariate models will include the propensity score including clinical and symptomatology variables associated with IV rtPA treatment. In the final multivariate model we will explore potential effect modification between IV rtPA treatment and covariates in relation to the outcomes of interest using interaction terms. If effect modification is detected with a liberal p<0.10 stratified analyses will be performed.

B) SAMPLE SIZE CALCULATION

We estimate that a total of 2650 patients will need to be recruited to detect a significant difference in 90-day outcomes across treatment groups for aim 4, with 80% power and a two-sided alpha level of 0.05. This calculation is based on the following assumptions:

- Proportion of mild Stroke & RIS: 31% of those arriving within 2 hours (14), probably larger proportion of those arriving within 4.5 hours.
- Proportion of mild Stroke & RIS treated with IV rtPA: 10%. This is based on the SITS registry (21) and the US GWTG data: 3,139 patients with NIHSS≤5 received IV rtPA, while 29,200 with mild and rapidly improving stroke did not, for a 9.7% rate of mild stroke treated with IV rtPA (E. Smith, personal communication).
- Outcome in untreated mild Stroke & RIS: 62% will have a mRS 0-1. This is based on the PRISMS estimate. Also, in GWTG, 62% were not discharged home (Smith 2011); it is assumed that some of those discharged from rehabilitation (16%) will have good outcomes, while some of those discharged home will have poor outcomes at 90 days.
• Outcome in treated mild Stroke & RIS: 71% will have a good outcome. This is based on the SITS registry and our own data analysis of discharge outcomes in those treated with IV rtPA with baseline NIHSS ≤5 (4,21).

5.3 STUDY ORGANIZATION

A) STAFF ROSTER

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B) MaRISS Steering Committee

The MaRISS Steering Committee monitors the project’s overall direction, study performance metrics and data collection to assure that final results are accurate, as well as that the rights and welfare of human subjects are protected. The Steering Committee Members have quarterly conference calls and annual in-person meetings to review study progress and provide recommendations on study status, data collection, and data analysis. The Steering Committee provides UM with advice on the general conduct of the study, data collection practices and procedures, and proposed changes in study procedures. The MaRISS Steering Committee is composed by the following members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Email</th>
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<tbody>
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</table>
C) CORE CENTERS

University of Miami: Clinical Coordinating Center and Data Management Center

The University of Miami (UM) is the leader and coordinating center of this study. UM is responsible for protocol design and the development of the study manual in accordance with Good Clinical Practice (GCP) guidelines. UM will maintain overall supervision of the conduct of the study. UM is also the data management center and, through an agreement with Outcome Science, Inc. (the data management company for all GWTG programs), will receive MaRISS data in a limited data set to perform study analysis. UM will receive reports of serious adverse events and other significant adverse events related to IV rtPA and report them to the funding agency. It is responsible for principal manuscript generation. UM reports to the MaRISS Steering Committee.

American Heart Association

The American Heart Association (AHA) is the main collaborator in the MaRISS project. The AHA is responsible for coordinating with Outcome Sciences the modification of the GWTG-Stroke database to include MaRISS-specific research fields and providing detailed coding instructions to support these data fields; AHA personnel will review new data fields and coding instructions during their training of each recruiting site. As necessary, the AHA will host webinars to instruct recruiting sites on data abstraction. The AHA hosts the MaRISS website and web-based training tool, provides CE/CMEs for training completion, and monitors completion and maintenance of training and certification for recruiting site investigators and coordinators. It is also responsible for creating the web-based Patient Reported Outcome (PRO). The AHA will contact and complete subcontracts with recruiting sites, and have overall responsibility for issues related to participating site management. UM and AHA will have bimonthly conference calls to evaluate MaRISS progress including but not limited to subcontracting, IRB and certification status as well as enrollment goals.

D) PARTICIPATING SITES

1. Participating site characteristics
Prospective sites will have the following eligibility characteristics:

- Annual stroke discharges >300: these centers will have the ability to recruit sufficient number of patients, and are likely to have a dedicated stroke team and coordinator to ensure the successful completion of the added outcome measures proposed in this study.
- Baseline completion rate for NIHSS >60% in those patients treated with Alteplase that arrived within 4.5 hours from symptom onset: good GWTG performance measures will assure that the centers have adequate staffing, expertise, and quality in rapid stroke evaluation.

2. Participating site selection
One hundred eligible hospitals that currently participate in GWTG-S will be selected to ensure adequate recruitment and representation based on type of hospital and geographic location. Selection will be based on an initial stratification by geographic area (Northeast, Midwest,
South, West) and then by academic vs. non-academic status. Within each of these 8 sub-categories, each site will be ranked by annual discharges and baseline NIHSS completion performance. The top hospitals within each category will be selected in order to achieve similar proportions of large well-performing hospitals within each category.

3. Participating site responsibilities
1. Designation of site principal investigator and study coordinator.
   a. Site principal investigator is responsible for communicating and disseminating MaRISS eligibility criteria amongst the rest of the stroke group, will participate in patient enrollment and consent, and will complete the TOAST classification at discharge or designate an experienced practitioner to complete the TOAST classification.
   b. Study coordinator: it is suggested and anticipated that in most centers the stroke coordinator will serve as the MaRISS coordinator. However, the designation of the MaRISS coordinator is left to the discretion of each participating center. The study coordinator will participate in patient enrollment and consent, perform the MaRISS-required NIHSS at 1 and 3 days (or discharge if earlier), complete the 30 and 90-day telephone interviews, and enter the MaRISS specific data into the GWTG-S registry.
2. Obtain local IRB approval; when a local IRB is not required or available, MaRISS will facilitate IRB approval through a central commercial IRB.
3. Identifying, screening and recruiting participants. The average recruitment is anticipated to be 30 patients per hospital, or about 2 patients per months. Hospitals that recruit less than 6 patients in the first year will not be renewed for the second year.
4. Protecting participants’ rights.
5. Obtaining informed consent from each participant prior to performing any study-specific activity or assessment.
6. Collecting study data and following participants through study completion.
7. Entering study data in the research tab of GWTG-Stroke Registry.
8. Maintaining the study regulatory binder and the participant’s Clinical Research Forms up to date.
9. Retaining study regulatory and patient’s records for 10 years.
10. Providing AHA and Coordinating Center with IRB approval supporting documentation.
11. Reporting to UM serious adverse events and other adverse events of interest related to the use of IV rtPA.

4. Communication with sites
Prior to site activation, AHA personnel will communicate on a regular basis with participating sites to monitor progress with contracting, IRB approval and training completion. Once the study is operational, routine telephone calls with the clinical site coordinators to discuss protocol adherence, adequate enrollment and regulatory compliance monthly and as frequent as needed.
5.4 PARTICIPATING SITE TRAINING AND CERTIFICATION

The research team at each participating site is required to be trained in the study specifics, the outcome measures tools and the protection of human subjects prior to the site initiation. UM and the AHA research teams have developed a MaRISS training module to ensure that all study outcomes data are accurately collected and all study procedures are reliably performed. The MaRISS training module is located at: learn.heart.org, and requires a password provided by the AHA to each site research team. The training module components include:

MaRISS protocol and logistics: Brief outline of the study protocol, schedule of activities, CRF completion and data acquisition.

Outcome measures:
- Modified Rankin Scale (mRS): This scale measures the functional level after stroke. See attachment 1.
- Barthel Index (BI): This 10-item index measures the extent to which individuals can perform activities of daily living. See attachment 2.
- EuroQoL/EQ-5D: This instrument assess quality of life in five domains: mobility, selfcare, usual activities, pain/discomfort and anxiety/depression. See attachment 3.
- Stroke Impact Scale-16 (SIS-16): This scale measures stroke outcomes in activities of daily living, mobility, communication, memory and strength, with emphasis of motor impairment. See attachment 4.

Other scales:
- NIH Stroke Scale (NIHSS) measures the severity of the infarct by quantifying the neurological exam. See attachment 5.
- TOAST classification (see attachment 6) evaluates the stroke mechanism and includes five subtypes of ischemic stroke: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, stroke of undetermined etiology.

Human Subjects Protection: Site investigators and study coordinators must be knowledgeable of the essential elements of the human subjects protection. They must provide documentation of completing their institutional HS protection course, if they are certified. Otherwise, they must complete an abbreviated 3 module session developed by the Collaborative Institutional Training Initiative (CITI) Program.

Assessment of gained knowledge: a series of knowledge and case scenarios to evaluate proficiency in study procedures.

Once training has been successfully completed, study personnel will receive a certification of completion and CE/CME credits.

Figure 1 shows the MaRISS Training flowchart and required modules for the participating site principal investigator and study coordinator.
Figure 1. MaRISS training flowchart
5.5 STUDY PROCEDURES

A) Summary: This prospective observational registry will recruit a total of 2650 patients with mild and/or rapidly improving stroke symptoms. In addition to information currently collected in GWTG-S, after informed consent is obtained, participants will have the following MaRISS-specific interventions:

- NIHSS performed at 24 +/- 4 hours from onset of symptoms (or before if neurologic deterioration before 24 hours) and at 3 days (or discharge if earlier).
- Stroke mechanism determination through the TOAST classification at the time of discharge.
- Telephone call at 30 days to evaluate the mRS.
- Telephone call at 90 days to determine the mRS, BI, SIS-15, EQ-5D.
- A randomly selected subgroup of 100 patients will be asked to complete a web-based patient self-reported outcome measure.

The total study duration is 90 days

MaRISS-specific activities and their timing are outlined below:

<table>
<thead>
<tr>
<th>Activities</th>
<th>Study Visits</th>
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<tr>
<td></td>
<td>Visit 1 Baseline</td>
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<tr>
<td>Screening, informed consent and enrollment</td>
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<tr>
<td>Contact information</td>
<td>x</td>
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<tr>
<td>Initial physician assessment</td>
<td>x</td>
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<tr>
<td>Neurologic fluctuation assessment</td>
<td>x (pre-hospital)</td>
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<td>NIHSS</td>
<td>x*</td>
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<td>TOAST (Neurologist)</td>
<td>x**</td>
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<tr>
<td>Outcome assessment (telephone)</td>
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<tr>
<td>Select participants (N=100) complete Web-based PRO</td>
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<tr>
<td>GWTG-Research CRFs</td>
<td>x</td>
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(*) Both the baseline NIHSS recorded on arrival as well as the NIHSS performed just before treatment decision, if available, should be recorded.

(* *) Repeat NIHSS < 24h if clinical change
B) ELIGIBILITY CRITERIA

Patients will be invited to participate in this research registry study after the decision to treat stroke with IV rtPA or not has been already made by the attending physician and patients have received the recommended standard of care acute treatment.

**Inclusion criteria:**
1. Patients with mild or spontaneously rapidly improving acute ischemic stroke defined clinically. Mild stroke is defined as an NIHSS 0-5. MaRISS does not define Rapidly Improving Stroke Symptoms for purposes of enrollment. It enrolls patients after the determination to treat or not to treat has been made, in order not to influence treatment decisions.
2. Absence of non-ischemic conditions on neuro-imaging (i.e. absence of hemorrhage or a mass on non-contrast brain CT, or more advanced imaging obtained according to participating site’s imaging protocol).
3. Age 18 years or older.
4. Arrival to the hospital within 4.5 hours after the onset of stroke symptoms.
5. Patient or legally authorized representative provides consent within 24 hours of arrival. Obtaining consent beyond 24h will be allowed if the patient arrived to the hospital within 4.5 hours of the onset of symptoms and the NIHSS is performed as standard of care at 24 hours +/- 4 hours from onset of symptoms (or before if the patient has neurological deterioration) by a certified practitioner and provided that the NIHSS sub-scores information is readily available and can be recorded in the participant's study record.
6. Available by telephone and willing to receive two follow-up telephone calls over the next 3 months.

**Exclusion Criteria:**
1. Acute stroke patients arriving to the hospital beyond 4.5 hours from symptom onset.
2. Unable to obtain consent from either patient or legally authorized representative.
3. Pre-morbid modified Rankin scale greater than 1.
4. Not available by telephone.

C) SCREENING

The study team will actively search for patients that meet all the inclusion criteria and none of the exclusion criteria. The Participating Site will maintain a MaRISS Screening Log. This log will include documentation of all potential study participants that are reviewed for study eligibility. It will contain an identification number and individuals' initials, age, gender, screening date, and eligibility status:

- Eligible for study participation and date enrolled.
- Ineligible for study participation and reason.
- Consent refused and why.
D) RECRUITMENT

The average recruitment is anticipated to be 30 patients per hospital, or about 2 patients per months with an overall recruitment of 2650 participants at 100 participating sites. More sites may be included in the case of slow recruitment. Hospitals that recruit less than 6 patients in the first year will not be renewed for the second year. The recruitment of study participants at participating sites will begin after training is completed and the site study coordinators have been certified in the MaRISS study related activities.

Patients will be invited to participate in this research registry study by the site stroke coordinator/stroke nurse after the decision to treat stroke with tPA or not has been made by the attending physician and patients have received the standard of care acute treatment. The rationale for this is to avoid delays in acute treatment with IV rtPA in eligible patients. The stroke coordinator/stroke nurse will personally approach patient and will invite him/her to participate. A patient’s legally authorized representative or proxy will be approached if the patient is cognitively impaired as determined by the treating physician.

E) RETENTION

Avoidance of losses to follow-up or withdrawal of consent is a high priority in achieving study success. The study/stroke coordinator should make every effort to retain study participants without being coercive. Thus, it is important that several contacts are identified during the screening process. Specific strategies to ensure retention include:

a) At the time of conducting the informed consent process collect alternative contact information including:
   • Home, work, mobile telephone numbers.
   • Email address.
   • Mailing address.
   • Contact information for friends and family members who may be able to assist in locating participants.

b) At the time of hospital discharge:
   • Provide study participant with the proposed date/time in which the 30 and 90 days telephone calls will be performed.
   • Verify participant and alternative contact information.

c) At the time of the 30-day telephone call:
   • Remind participant that s/he will be called again in approximately 2 months.
   • Get in touch with alternative contact if unable to reach study participant.

d) At the time of the 90-day call:
   • Get in touch with alternative contact if unable to reach study participant.
F) INFORMED CONSENT PROCESS AND HIPAA FORM

Informed Consent Process
Once the site coordinator, investigator, or other site staff member identifies an individual that meets inclusion criteria, the informed consent process will be initiated and the express permission to participate must be obtained from patient. If the study candidate is determined to be cognitively impaired, informed consent to participate in the study will be obtained from a LAR. Those whose primary language is Spanish will be approached by a study team member that speaks Spanish or an institutional translator will be requested. The informed consent process will be conducted by a study team member who will:

- Provide potential participants with adequate information concerning the study objectives, procedures and duration of the study.
- Provide adequate opportunity for an individual to consider participation.
- Respond to individuals’ questions and concerns.
- Ensure that each individual understands all information provided.
- Clearly inform patient or legally appointed representative (LAR) that participation in the study is voluntary and that his/her decision of whether to participate or not will not affect patient’s care in any way. Specifically, the study investigator designee will inform participant/LAR that s/he is not obligated to participate in the study, stress that there are no consequences for not participating in the MaRISS research registry study, that his/her standard treatment will not be affected in any way, and that participant can withdraw the permission to participate at any time.
- Obtain the individual’s or LAR written voluntary consent to participate.
- A signed and dated informed consent form must be obtained prior to undergoing MaRISS specific interventions such as subsequent NIHSS and study data collection.

Informed Consent Documentation
The informed consent should be distributed in the following manner:
1. The investigator must maintain a signed original of the informed consent document for each participant in the study.
2. The study participant or legal representative will receive a copy of the signed and dated informed consent form.
3. A copy of the signed and dated document must be filed in the patient’s medical record and a note must be included in the medical record and in the participant CRF that consent for MaRISS was obtained. A suggested annotation is:

"Patient was invited to participate in the MaRISS Research Registry. The purpose, procedures, risks, benefits, and alternatives were explained to patient/proxy and all the questions answered to patient/proxy’s satisfaction. Freely given informed consent was obtained and a copy of the signed document has been filed in the patient's medical record. No study activities or assessments were done prior to obtaining consent from the participant and signature of the informed consent form by both the study participant (and legally authorized representative) and a member of the study team."
HIPAA Procedures
All the Recruiting Sites must comply with the HIPAA Privacy Rule, which protects the privacy of individually identifiable health information. A HIPAA form will be presented to a potential participant for signature in addition to the Informed Consent Form unless the institution’s privacy regulations allow that the necessary assurances are incorporated into the Informed Consent Form. The original signed and dated HIPAA form will be filed along with the original signed informed consent form in the participants’ CRFs.

6. SPECIFIC MEASUREMENTS AND OUTCOMES

6.1 DEFINING MILD STROKE

- Mild stroke is defined as NIHSS 0-5.

6.2 DEFINING RAPIDLY IMPROVING STROKE

Rapidly improving stroke (prior to thrombolysis) is determined by the treating team. The choices for classifying Rapidly Improving Stroke Symptoms in the MaRISS data collection forms are:

- NIHSS improvement in absolute points from baseline: for example, patient arrived aphasia and hemiplegic with an NIHSS of 17, now improved speech, only dysarthria and hemiparesis, NIHSS 7, for overall 10 point improvement.
- Proportion or percent improvement in NIHSS from baseline: For example, the NIHSS improved by 50% from 16 to 8.
- Final NIHSS value regardless of baseline NIHSS: for example, patient arrived with hemineglect, gaze deviation and left hemiplegia with a NIHSS was 18 and in the ED improved to only mild hemiparesis with a final NIHSS of 3.
- Improvement to a non-disabling condition: for example, patient improved from non dominant hemiplegia to minimal clumsiness of non-dominant hand.
- Other (need to specify).

More than one option may be used; all applicable reasons should be recorded. A copy of the initial physician assessment data collection form is included in attachment 7.

6.3 CODING PRE-HOSPITAL FLUCTUATIONS

Patient’s neurologic symptoms may fluctuate after symptom onset but prior to hospital arrival. As there are no validated methods to ascertain and quantify this change, it has to be a qualitative assessment. Research team will obtain information of significant changes, either improvement or deterioration, that occurred after symptom onset but prior to hospital arrival from patient, family or EMS reports.

A copy of the MaRISS Pre-hospital arrival fluctuation collection form is included in attachment 8.
6.4 CODING IN-HOSPITAL FLUCTUATIONS

Patient’s neurologic symptoms after hospital arrival will be recorded at Day 3 or at discharge if prior to day 3. As there are no validated methods to ascertain and quantify this change, it has to be a qualitative assessment. Research team will obtain information of significant changes, either improvement or deterioration, that occurred after hospital arrival from patient, family or medical record reports.

A copy of the MaRISS Post-hospital arrival (In-Hospital) fluctuation collection form is included in attachment 9.

6.5 ASSESSING THE NIHSS SCORE

The research team will collect information of the standard of care baseline NIHSS performed at hospital arrival as well as the NIHSS done by the treating physician at the time of acute treatment decision.

The NIHSS will be performed at 24 +/- 4 hours from onset of symptoms and at 3 days (or discharge if earlier) as well as at the time of neurological deterioration as MaRISS-specific assessments.

6.6 OBTAINING THE TOAST CLASIFICATION

The TOAST Classification of Subtypes of Acute Ischemic Stroke assessment must be done by the Neurologist (or by an experienced practitioner designated by the PI) at Day 3 or at the time of discharge if prior to Day 3. The following criteria will be used:

- **Large-artery atherosclerosis (embolus/thrombosis)** (Evidence by imaging of ≥ 50% stenosis of extra or intracranial artery in the distribution or the stroke)
  - a. Extracranial ICA/Vertebral artery
  - b. Intracranial Large Vessel Stenosis
  - c. Aortic Arch atherosclerotic disease
- **Cardioembolism** (high-risk/medium-risk):
  - a. Left atrial thrombus
  - b. Left ventricular thrombus
  - c. Atrial fibrillation
  - d. Paroxysmal Atrial Fibrillation
  - e. Sick Sinus Syndrome
  - f. Sustained Atrial Flutter
  - g. Recent Myocardial Infarction (within 1 month)
  - h. Rheumatoid mitral or aortic valve disease
  - i. Bioprosthetic and mechanical heart valve
  - j. Chronic myocardial infarction together with low ejection fraction < 28%
  - k. Symptomatic congestive heart failure with ejection fraction < 30%
  - l. Dilated cardiomyopathy
m. Nonbacterial thrombotic endocarditis
n. Infective endocarditis
o. Papillary fibroelastoma
p. Left atrial myoma
q. Other cardioembolic source

- Small-vessel occlusion (lacune)
- Stroke of undetermined etiology:
  a. Multiple etiologies seem likely
  b. Undetermined etiology despite thorough evaluation
  c. Evaluation incomplete
- Other determined etiology
  a. Hypercoagulable states:
     1. Malignancy
     2. Antiphospholipid antibody syndrome
     3. Inherited thrombophilia
  b. Iatrogenic
  c. Arterial dissection (carotid, vertebral)
  d. Other

A copy of the MaRISS TOAST Classification of Subtypes of Acute Ischemic Stroke data collection form is included in attachment 6.

6.7 THE MODIFIED RANKIN SCALE

The Modified Rankin Scale (mRS) is the MaRISS Primary Outcome Measure: proportion of patients with a mRS = or > 2 at 90 days.

The study coordinator/stroke coordinator will perform a 5-10 minutes telephone call at day 30 (+/- 7 days) to complete a modified Rankin Scale. At this time information about any new hospitalization or new ischemic event will be obtained as well.

The mRS will be completed over the phone during the MaRISS 90-day telephone call.


The Barthel Index (BI), the Stroke Impact Scale-16 (SIS-16) and the European Quality of Life EQ-5D scale are the MaRISS Secondary Outcome Measures.

The study coordinator/stroke coordinator will call study participant at 90 days (+/- 10 days) to complete the BI, SIS-16 and EQ-5D. At this time information about any new hospitalization or new ischemic event will be obtained as well. In this 25-30 minutes telephone call a modified Rankin Scale will be completed as well.
7. EVALUATIONS AND DATA COLLECTION

The study specific evaluations and data collection begin after screening enrollment and informed consent, and once the decision to use thrombolytics has been made in order not to delay or influence treatment decisions. Please note that MaRISS specific data needs to be collected in addition to GWTG-S data points. MaRISS CRFs are to be kept on file, sent to UM, and used as source documentation to complete the GWTG-S MaRISS fields. The flowchart in Figure 3 depicts the timing of MaRISS evaluations.

7.1 STUDY FLOW CHART

*Figure 3. MaRISS flow chart*

- **Performed as standard of care**
- **MaRISS-specific assessments**
(*) Consent should be obtained within 24 hours of arrival. Consent after 24 hours is allowed only if the following conditions are all met: a) the NIHSS is obtained at 24 hours +/- 4 hours as part of standard of care procedures; b) the NIHSS sub-scores are available to be entered into the MaRISS data collection forms; c) the NIHSS is performed by a certified practitioner.

(**) NIHSS performed at 24 hours +/- 4 hours from onset of symptoms.

7.2 MaRISS GWTG-S Required Items

Elements already required in the GWTG-S Registry:

- Age
- Gender
- Race
- Hispanic Ethnicity
- Symptom timeline
- Admission date and time
- Final stroke diagnosis (IS, TIA, non-stroke)
- Mode of arrival
- Previously known medical history
- Initial NIHSS
- IV thrombolytic therapy at this hospital
- Date/Time IV tPA initiated
- Contraindications thrombolytic 0-3hr
- Complications of Thrombolytic Therapy
- Discharge date
- Discharge disposition on day of discharge & mortality

Existing elements in the GWTG-S Registry required to be completed for MaRISS:

- Insurance
- Medications prior to admission (only cholesterol mandatory now)
- Ambulatory status prior to arrival
- Where was patient cared for and by whom
- Initial exam findings
- Contraindications thrombolytics 3-4.5 hr
- If no documented contraindications or warnings, Hospital-Related or Other Factors
- IA catheter based reperfusion in this hospital
- Ambulation status at discharge

7.3 MaRISS STUDY VISITS

VISIT 1: BASELINE VISIT
The baseline visit has various components:

1. **Confirm eligibility**: see section 5.5.B

2. **Obtain consent**: see section 5.5.F
3. **Collect contact information**: The Study Coordinator/Stroke Coordinator will collect the patient’s and alternative contact information, including:
- Telephone numbers home, work, mobile.
- Email address.
- Mailing address.
- Contact information for friends and family members who may be able to assist in locating participants.

4. **Initial physician assessment**: Determination of mild stroke and rapid improvement is discussed in section 6. In the baseline visit CRF and in the GWTG-S MaRISS fields, the definition that most closely approximates the reason to code Mild Stroke or Rapidly Improving Stroke should be given. In order to code correctly, the coordinator should contact the treating physician to assess which of these criteria where used by the physician to determine rapid improvement.

5. **Pre-hospital fluctuation**: Some patient's neurologic symptoms may fluctuate after symptom onset but prior to hospital arrival. As there are no validated methods to ascertain and quantify this change, this will be a qualitative assessment. Answer this question based on patient, family or EMS reports of significant changes, either improvement or deterioration, that occurred after symptom onset but prior to hospital arrival. Do not consider changes that occur after patient is first evaluated by hospital personnel. If more than one significant fluctuation occurs, please note so. However, in the case of 2 sequential changes in the same direction (i.e. improvement followed by improvement, or worsening followed by worsening) only record the direction of change or a single directional change. The data collection form (see attachment 8) asks the following question:

Did neurologic status change between onset of symptoms but prior to hospital arrival?
- ☐ No
- ☑ Yes

If YES, please note if they improved (↑) or worsened (↓). Note if more than one fluctuation.

- ☐ ☐ ☐

**Example 1**: Patient has remained unchanged with mild arm and leg weakness on the left and slurred speech.

Did neurologic status change between onset of symptoms but prior to hospital arrival?
- ☑ No
- ☐ Yes

**Example 2**: Initially unable to speak or move right side but improved during ambulance ride and now lifting arm and leg and speaking, although still slurred.

Did neurologic status change between onset of symptoms but prior to hospital arrival?
- ☐ No
- ☑ Yes
If YES, please note if they improved (↑) or worsened (↓). Note if more than one fluctuation.

- **Baseline NIHSS:** Please note that the individual components of the NIHSS need to be recorded in the CRF and in the GWTG-S MaRISS fields.

- **NIHSS prior to treatment decision:** In addition to the baseline NIHSS on arrival (baseline), a repeat NIHSS should be performed if patient is being considered for acute ischemic stroke treatment. That NIHSS and its individual components need to be collected.

**VISIT 2: 24 HOURS**
The investigator or the study coordinator/stroke coordinator will perform a **NIHSS at 24 hours (+/- 4 hours)** from symptom onset or before if neurological worsening occurs within 24 hours to document potential in hospital fluctuations. The total score its individual components need to be collected.

**VISIT 3: DAY 3 OR EARLIER IF DISCHARGE PRIOR TO DAY 3**
The 3rd visit should be completed on the 3rd day or at discharge if this occurs prior to day 3.

This visit consists of the following:

1. **NIHSS at day 3 or discharge:** record the total score and the individual components.

2. **TOAST classification** to determine the stroke mechanism. The TOAST should be completed by the investigator in consultation with the treating neurologist, and is based on the clinical, imaging and cardiac evaluations performed.

3. **Post-hospital fluctuation:** In addition to the sequential NIHSS, please record if **significant** changes, either improvement or deterioration, occurred **after hospital arrival**. Do not consider changes that occurred prior to arrival. If more than one significant fluctuation occurs, please note so. However, in the case of 2 sequential changes in the same direction (i.e. improvement followed by improvement, or worsening followed by worsening) only record the direction of change or a single directional change. The CRF asks the following question:

   Did neurologic status change after arrival to hospital?
   ☐ No
   ☐ Yes

   If YES, please note if they improved (↑) or worsened (↓). Note if more than one fluctuation.
   ☐ ☐ ☐

4. **Record Adverse Events:** Reporting is limited to the following situations:
   a) Only those treated with Alteplase that have AE need to be reported; and
b) Only Serious Adverse Events (SAE) related to the use of Alteplase, as well as all deaths, pregnancy and transmission of infectious agent through the administration of IV rtPA need to be reported. See section 8 for Adverse Event reporting. Adverse Events need to be reported within 24 hours of the research team being made aware of event.

5. Confirm contact information: ensure that the baseline contact information for patient, legally authorized representative and alternative contacts are correct.

VISIT 4: DAY 30 +/- 7 DAYS - TELEPHONE CALL
This brief (approximately 5-10 minutes) telephone call should include the following:
1. Perform the modified Rankin Scale.
2. Ask if patient has been re-hospitalized since discharge and the reason (Stroke, TIA, cardiovascular symptoms, other).
3. Ask if patient has had a serious adverse event as defined in section 8.
4. Verify participant/alternative phone numbers.
5. Remind participant of the 90-day phone call.

VISIT 5: DAY 90 +/- 10 DAYS - TELEPHONE CALL
This extended (approximately 20 minutes) telephone call should include the following:
1. Perform the modified Rankin Scale.
2. Obtain the Barthel Index.
3. Obtain the Stroke Impact Scale-16.
4. Obtain the EuroQOL.
5. Ask if patient has been re-hospitalized since discharge and the reason (Stroke, TIA, cardiovascular symptoms, other).
6. Ask if patient has had a serious adverse event as defined in section 8.
7. Thank participant and inform that his/her participation in the study finished.
8. A randomly selected group of 100 participants will participate in a web-based Patient Self-Reported Outcome (PRO). If a participant is pre-selected for PRO, direct them to this website.

All the research elements will be entered into the Get With The Guidelines-Stroke Registry along with the usual required items.

8. ADVERSE EVENT REPORTING

Although MaRISS is not an intervention trial, does not dictate the use of a specific treatment, and enrolls patients after treatment decision has been made, some patients will receive thrombolytics and therefore SAE need to be reported. However, reporting is limited to those treated with Alteplase that have reportable Adverse Events.

CONDITIONS THAT NEED TO BE REPORTED in ALTEPLASE-TREATED PATIENTS:
A. **Serious events that are related or caused by Alteplase:**

- Symptomatic intracranial hemorrhage: neurological deterioration by 4 NIHSS points within 36 hours of treatment.
- Systemic hemorrhage that requires transfusion, pressors or surgery.
- Other events that are life threatening.
- Events that cause significant and persistent disability or incapacity.
- Events that prolong hospitalization.

B. **Other events regardless of causal association:**

- All deaths.
- All pregnancies that occur during the study period or even beyond if the study team is made aware of it.
- Birth defect or congenital abnormality in infant born to mother treated with Alteplase.
- Transmission of an infection through the administration of Alteplase (i.e. Hepatitis, HIV, etc.)

**Determination of causality or relation to IV rtPA/Alteplase**

- It is temporally related to the administration of Alteplase (i.e. 36 hours).
- It is not readily explained by the subject’s clinical state, the stroke, or other concurrent therapies.
- It is a known pattern of response to Alteplase (i.e. hemorrhage, orolingual angioedema)

**Determination of Serious Adverse Event**

- The event is fatal.
- The event is life threatening.
- The event prolongs hospitalizations.
- The event results in persistent and significant disability or incapacity.

**Reporting Adverse Events**

- Reportable events should be faxed to the University of Miami within 24 hours of the study team being made aware of event.
- Complete the “Serious Adverse Event” MaRISS CRF. A copy is included as attachment 16.
- Collect supporting material (i.e. CT report, labs, etc.)
- Fax CRF and supporting material to the number provided to MaRISS sites or email to icampo@med.miami.edu
- For questions related to which events are reportable or how to complete CRF call 305-243-8018.

9. **MONITORING, COMPLIANCE, FORMS, DATA QUALITY CONTROL**

AHA will perform monitoring visits to the Participating Sites. Monitoring *performance* of the study includes review of:

- Participant recruitment.
- Flow of data.
- Quality control of the data.
• Adverse event reporting.
• Adherence to protocol.

9.1 COMPLIANCE WITH STUDY PROTOCOL

The following procedures will be implemented to maximize adherence to the protocol and enhance participant retention:
• Comprehensive training.
• Early review of the data.
• Routine communications with the sites.

Protocol violations include but are not limited to the following:
• Enrollment of an ineligible participant.
• Failure to obtain informed consent.
• Failure to keep IRB approval up to date.

Study staff should report a violation as soon as it is discovered. The Coordinating Center will maintain a log of protocol deviations and/or violations and will report them routinely to the Steering Committee. Occasional violations will require an explanation from the RS. Sites with serious continual problems may be terminated.

9.2 DATA COLLECTION AND STUDY FORMS

User Training
The participating site study staff will receive access to the MaRISS training module via email link, where they will be trained on the use of the research elements in the GWTG-Stroke Registry. The training module will include explanations on how to fully access the registry system and the importance of the system's security.

Activation of the MaRISS Tab in the GWTG-Stroke Registry.
Each MaRISS hospital will need to call the Outcome Help desk to request activation of the MaRISS PMT Tab. The ‘primary user’ from a hospital can contact the Quintiles helpdesk and request a new user account/login. If the name of this person is not known, the helpdesk should be able to provide a name.
Requests can be made via phone or email to the Outcome Help desk. Phone # 888-526-6700 email support@outcome.com.

Activation of the MaRISS Tab is required before your site can proceed with patient recruitment. If you have any questions please contact us at mariss@heart.org.

Source Documentation
To document study-specific data requirements, source data will be transcribed to a paper case report form (CRF) and subsequently entered into the GWTG-Stroke Registry. All essential study documents including CRFs must be retained by the study investigator. The following are considered participant file documents:
• Case report forms.
• Source documents (NIHSS, mRankin, Barthel Index, Euro QoL 5D, SIS 16, Toast classification).
• Signed participant consent and HIPAA forms.

Study Forms (CRFs)
MaRISS CRFs are located in the Get With The Guidelines-Stroke Registry research tabs; examples of the outcome measures data collection forms are included in the attachments section.

Data Flow
MaRISS Participating Sites will enter the research registry data into the GWTG-S Patient Management Tool (PMT). Through its relationship with Outcome Sciences/Quintiles, AHA will provide University of Miami study team access to the MaRISS data fields in the GWTG-S. To perform the statistical analysis, UM will be granted access to the clinical level data of patients that have provided informed consent to participate in the study.

Retention of Study Documents
All MaRISS study files and source documents are to be maintained at the Participating Site for a total of 10 years.

Administrative Forms

Facsimile Transmittal Sheet - cover page for all faxes, as required by MaRISS study.

1. **Telephone Contact Log** to record the telephone calls with participants regarding the study.
2. **Screening Log** to maintain a record of individuals who are screened for participation in the study. It should be arranged chronologically and be kept up to date.
3. **Participant Identification List** records each participant’s name, medical record number, study identification number and study entry and exit dates. This is confidential information. It should be maintained in a secured location apart from CRFs and data files at the study site.
4. **CRF Transmittal Sheet**: the cover page for each packet of CRFs submitted to the Coordinating Center.
5. **Signature Log**: this document must contain the signature of all members of the site study team. The Principal Investigator or his/her delegate (Clinical Research Coordinator/Stroke Coordinator) is responsible for listing the research personnel approved to participate in the MaRISS study, including initials and signature, as well as noting the date each study team member becomes involved in the study and the termination date.
6. **Site Visit Log**: All participating sites must maintain a Site Visit log to record the site initiation, every monitoring visit performed, training, and study close-out.
7. Each site will be required to complete and maintain all administrative forms.
8. During the periodic monitoring visit by AHA Program Manager, all participating sites must show that all administrative forms are accurately logged and maintained.

10. STUDY COMPLETION AND CLOSEOUT PROCEDURES

Participating Sites Closeout Procedures
Once the study target enrollment is achieved, study closeout activities will be initiated to confirm that the site investigator's study obligations have been met and post study obligations are understood. The following closeout activities will be performed at the Participating Sites:

- Completion of study procedures and data collection.
- Resolution of any standing data queries.
- Assurance that IRB correspondence and study files are accessible for external audit.
- Maintain study records for 10 years.
- Institutional IRB (or commercial IRB if applicable) is notified of study completion
- Obtaining a copy of the IRB study closure notification.
11. REFERENCES


12. RELEVANT WEB SITES

MaRISS website:

http://www.heart.org/HEARTORG/HealthcareResearch/GetWithTheGuidelinesHFStrokeRes
us/GetWithTheGuidelinesStrokeHomePage/MaRISS_UCM_452130_SubHomePage.jsp

University of Miami

http://neurology.med.miami.edu

American Heart Association/American Stroke Association

http://www.heart.org

NIH:

http://ohrp.osophs.dhhs.gov/polasur.htm
(Office of Human Research Protections’ Regulations on conducting research with human
subjects)

http://www.nih.gov/sigs/bioethics/IRB.html
(Bioethics Resources on the Web)

DHHS Office for Civil Rights - HIPAA Information:

http://www.hhs.gov/ocr/
http://privacyruleandresearch.nih.gov
(Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule)

Food and Drug Administration (FDA):

http://www.fda.gov/oc/gcp/regulations.html
(FDA Good Clinical Practice regulations)

http://www.fda.gov/cder/
(FDA Center for Drug Evaluation and Research)

(FDA regulations on electronic records and electronic signatures)
Mild and Rapidly Improving Stroke Study (MaRISS) 30-DAY Telephone call

Level of Function Survey-mRS-9Q

MaRISS Study ID: ____________   Patient's Initials: _____________   Date: ___ ___/___ ___/___ ___

1. Who provided the information collected?   □ Patient reported   □ Proxy reported

2. Ask patient/proxy the following questions exactly as they are written. DO NOT CHANGE the script.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any symptoms that are bothering you?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(For example, trouble with reading or writing, trouble speaking,</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>problems with vision, numbness, weakness, balance trouble, or problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with swallowing?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Are you able to do the same work as before?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Are you able to keep up with your hobbies?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have you maintained your ties to friends and family?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you need help making a simple meal, doing household chores, or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>balancing a checkbook?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>6. Do you need help with shopping or traveling close to home?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you need another person to help you walk?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you need help with eating, going to the toilet, or bathing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you stay in bed most of the day and need constant nursing care?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Go to the mRS calculator website at: http://www.modifiedrankin.com/ and click on the blue box “Continue to the Data Entry Page”

4. Enter patient/proxy answers.

5. Click on the blue box “Calculate the mRS”. Enter the calculated score here:  

The mRS-9Q Survey by Alexander C. Flint, M.D., Ph.D. is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

For reference: Levels of the modified Rankin Scale (mRS):

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance or unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden.

Form Completed by: _____________________________________________ (Print name)
Mild and Rapidly Improving Stroke Study (MaRISS) 90-DAY TELEPHONE CALL

MaRISS Study ID: __________________ Date: ___ ___/___ ___/___ ___

MaRISS Barthel Index  Patient reported  PROXY reported

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEEDING</strong></td>
<td></td>
</tr>
<tr>
<td>Unable</td>
<td>0</td>
</tr>
<tr>
<td>Needs help cutting, spreading butter, etc or requires modified diet</td>
<td>5</td>
</tr>
<tr>
<td>Independent</td>
<td>10</td>
</tr>
<tr>
<td><strong>BATHING</strong></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>0</td>
</tr>
<tr>
<td>Independent</td>
<td>5</td>
</tr>
<tr>
<td><strong>GROOMING</strong></td>
<td></td>
</tr>
<tr>
<td>Needs help with personal care</td>
<td>0</td>
</tr>
<tr>
<td>Independent face/hair/teeth/shaving (implements provided)</td>
<td>5</td>
</tr>
<tr>
<td><strong>DRESSING</strong></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>0</td>
</tr>
<tr>
<td>Needs help but can do about half unaided</td>
<td>5</td>
</tr>
<tr>
<td>Independent (including buttons, zips, laces, etc)</td>
<td>10</td>
</tr>
<tr>
<td><strong>BOWELS</strong></td>
<td></td>
</tr>
<tr>
<td>Incontinent (or needs to be given enemas)</td>
<td>0</td>
</tr>
<tr>
<td>Occasional accident</td>
<td>5</td>
</tr>
<tr>
<td>Continent</td>
<td>10</td>
</tr>
<tr>
<td><strong>BLADDER</strong></td>
<td></td>
</tr>
<tr>
<td>Incontinent, or catheterized and unable to manage alone</td>
<td>0</td>
</tr>
<tr>
<td>Occasional accident</td>
<td>5</td>
</tr>
<tr>
<td>Continent</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOILET USE</strong></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>0</td>
</tr>
<tr>
<td>Needs some help, but can do something alone</td>
<td>5</td>
</tr>
<tr>
<td>Independent (on and off, dressing, wiping)</td>
<td>10</td>
</tr>
<tr>
<td><strong>TRANSFERS (BED TO CHAIR AND BACK)</strong></td>
<td></td>
</tr>
<tr>
<td>Unable, no sitting balance</td>
<td>0</td>
</tr>
<tr>
<td>Major help (one or two people, physical) can sit</td>
<td>5</td>
</tr>
<tr>
<td>Minor help (verbal or physical)</td>
<td>10</td>
</tr>
<tr>
<td>Independent</td>
<td>15</td>
</tr>
<tr>
<td><strong>MOBILITY (ON LEVEL SURFACES)</strong></td>
<td></td>
</tr>
<tr>
<td>Immobile or &lt;50 yards</td>
<td>0</td>
</tr>
<tr>
<td>Wheelchair independent, including corners, &gt;50 yards</td>
<td>5</td>
</tr>
<tr>
<td>Walks with help of one person (verbal or physical) &gt;50 yards</td>
<td>10</td>
</tr>
<tr>
<td>Independent (but may use any aid; for example, stick) &gt;50 yards</td>
<td>15</td>
</tr>
<tr>
<td><strong>STAIRS</strong></td>
<td></td>
</tr>
<tr>
<td>Unable</td>
<td>0</td>
</tr>
<tr>
<td>Needs help (verbal, physical, carrying aid)</td>
<td>5</td>
</tr>
<tr>
<td>Independent</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOTAL SCORE (0-100)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Form Completed by: ______________________________(Print name)
MaRISS_EUROQoL (EQ-5D-5L)

Study ID: ___________________________         Date: ___ ___/___ ___/___ ___

A) Who provides the information collected?

☐ PATIENT reported

☐ PROXY reported

B) Explain to the patient/proxy what the questionnaire is about:

“Now I am going to read some statements about aspects of your health. Please tell me which statement best describes your own health today”

1. MOBILITY (PLEASE CHECK ONE)
Thinking about your health today, which of the following statements best describes your mobility?

(1) ☐ I have no problems walking about
(2) ☐ I have slight problems walking about
(3) ☐ I moderate problems walking about
(4) ☐ I have severe problems walking about
(5) ☐ I am unable to walk about

2. SELF-CARE (PLEASE CHECK ONE)
Thinking about your health today, which of the following statements best describes your self-care?

(1) ☐ I have no problems washing or dressing myself
(2) ☐ I have slight problems washing or dressing myself
(3) ☐ I moderate problems washing or dressing myself
(4) ☐ I have severe problems washing or dressing myself
(5) ☐ I am unable to wash or dress myself

3. USUAL ACTIVITY (PLEASE CHECK ONE)
Thinking about your health today, which of the following statements best describes your usual activities such as work, study, housework, family or leisure activities?

(1) ☐ I have no problems doing my usual activities
(1) ☐ I have slight problems doing my usual activities
(3) ☐ I am moderate problems doing my usual activities
(4) ☐ I have severe problems doing my usual activities
(5) ☐ I am unable to do my usual activities
4. PAIN/DISCOMFORT (PLEASE CHECK ONE)
Thinking about your health today, which of the following statements best describes any pain or discomfort you may be experiencing?

(1) I have no pain or discomfort
(2) I have slight pain or discomfort
(3) I am moderate pain or discomfort
(4) I have severe pain or discomfort
(5) I have extreme pain or discomfort

5. ANXIETY/DEPRESSION (PLEASE CHECK ONE)
Thinking about your health today, which of the following statements best describes any anxiety and depression you may be experiencing?

(1) I am not anxious or depressed
(2) I am slightly anxious or depressed
(3) I am moderately anxious or depressed
(4) I am severely anxious or depressed
(5) I am extremely anxious or depressed

6. Now I would like you to think of a scale between 0 and 100, where 0 is the worst health you can imagine and 100 the best you can imagine.

What number between 0 and 100 best describes your health today?

HEALTH SCALE numbered from 0 to 100.

- 100 means the best health you can imagine
- 0 means the worst health you can imagine

Form Completed by: ________________________________ (Print name)
1. Explain to the patient/proxy what the questionnaire is about: “Now I am going to ask some questions about how much difficulty you have had while performing some activities in the past 2 weeks.

2. Ask patient/proxy the following questions exactly as they are written. DO NOT CHANGE the script.

### SIS 16

<table>
<thead>
<tr>
<th>In the past 2 weeks, how difficult was it to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Dress the top part of your body?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Bathe yourself?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Get to the toilet on time?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Control your bladder (not have an accident)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Control your bowels (not have an accident)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Stand without losing balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Go shopping?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Do heavy household chores (e.g. vacuum, laundry or yard work)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Stay sitting without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j. Walk without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>k. Move from a bed to a chair?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>l. Walk fast?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>m. Climb one flight of stairs?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>n. Walk one block?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>o. Get in and out of a car?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>p. Carry heavy objects (e.g. bag of groceries) with your affected hand?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Form Completed by: ______________________________ (Print name)
MaRISS Study ID: __________________ Date: ____ ____/____ ____/____ ____ (mm/dd/yy)

Time: ________: _________ (24h)

MaRISS NIHSS RECORDED AT HOSPITAL ARRIVAL

1. A. Level of consciousness
   - 0 Alert; keenly responsive
   - 1 Not alert. Arousable by minor stimulation
   - 2 Not alert. Obtunded, requires strong stimulation to attend
   - 3 Unresponsive or motor or autonomic reflex responses only

B. LOC questions
   - 0 Answers both questions correctly
   - 1 Answers one question correctly
   - 2 Answers neither question correctly

C. LOC commands
   - 0 Performs both tasks correctly
   - 1 Performs one task correctly
   - 2 Performs neither task correctly

2. Best gaze
   - 0 Normal
   - 1 Partial gaze palsy; gaze is abnormal in one or both eyes
   - 2 Forced deviation or total gaze paresis

3. Visual
   - 0 Normal. No visual loss
   - 1 Partial hemianopsia
   - 2 Complete hemianopsia
   - 3 Bilateral hemianopsia (Blind including cortical blindness)

4. Facial Palsy
   - 0 Normal symmetrical movements
   - 1 Minor paralysis (flattened nasolabial fold, asymmetric smile)
   - 2 Partial paralysis (total or near-total paralysis of lower face)
   - 3 Complete paralysis of one or both sides

5. A. Motor, arm, left
   - 0 Normal
   - 1 Drifts before 10 seconds but maintains in air
   - 2 Some effort against gravity but unable to maintain in air
   - 3 Moves but unable to lift against gravity
   - 4 No movement
   - UN Amputation or joint fusion

B. Motor, arm, right
   - 0 Normal
   - 1 Drifts before 10 seconds but maintains in air
   - 2 Some effort against gravity but unable to maintain in air
   - 3 Moves but unable to lift against gravity
   - 4 No movement
   - UN Amputation or joint fusion

6. A. Motor, leg, left
   - 0 Normal
   - 1 Drifts before 10 seconds but maintains in air
   - 2 Some effort against gravity but unable to maintain in air
   - 3 Moves but unable to lift against gravity
   - 4 No movement
   - UN Amputation or joint fusion

B. Motor, leg, right
   - 0 Normal
   - 1 Drifts before 10 seconds but maintains in air
   - 2 Some effort against gravity but unable to maintain in air
   - 3 Moves but unable to lift against gravity
   - 4 No movement
   - UN Amputation or joint fusion

Form Completed by: ____________________________ (Print name)
MaRISS Study ID: __________________  Date: ____ ____/____ ____/____ ____ (mm/dd/yy)
Time: ________: _________ (24h)

**MaRISS NIHSS Recorded at Hospital Arrival**

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<thead>
<tr>
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<tbody>
<tr>
<td>0</td>
<td>Absent, patient cannot understand or is paralyzed</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Present in one limb</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Present in two limbs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unable to test due to amputation, joint fusion</td>
<td></td>
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</tbody>
</table>

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<tr>
<th></th>
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<tbody>
<tr>
<td>0</td>
<td>Normal. No sensory loss</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Mild-moderate loss. Feels less sharp or dull on the affected side</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Severe or total loss. Not aware of being touched</td>
<td></td>
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<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Mild-moderate aphasia, loss of fluency but able to communicate</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Severe aphasia, fragmentary expression, unable to communicate well</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Global aphasia, no usable speech or auditory comprehension</td>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Mild-moderate. Slurs some words but can be understood</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Severe, unintelligible slurred speech</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Unable to test, intubated or other physical barrier</td>
<td></td>
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<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>0</td>
<td>No abnormality</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Visual, tactile, auditory, spatial or personal inattention or extinction to bilateral simultaneous stimulation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Profound hemi-inattention or extinction to more than one modality; does not recognize own hands or orients to only one side of space</td>
<td></td>
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</table>
**Mild and Rapidly Improving Stroke Study (MaRISS)**

**DAY 3 VISIT**

**MaRISS Study ID:** ____________________________  **Date:** ____________________________

**Stroke Etiology**

**Modified TOAST Classification of Subtypes of Acute Ischemic Stroke**

- **Large-artery atherosclerosis**
  - (Evidence by imaging of ≥ 50% stenosis of extra or intracranial artery in the distribution or the stroke)
  - If you answered "Large-artery Atherosclerosis", please, check all that apply
    - Extracranial atherosclerotic disease (Carotid or Vertebral artery plaque)
    - Intracranial atherosclerotic disease
    - Aortic Arch atherosclerotic disease

- **Cardioembolism (high-risk/medium-risk)**
  - If you answered "Cardioembolism", please, check all that apply
    - Left atrial thrombus
    - Left ventricular thrombus
    - Atrial Fibrillation
    - Paroxysmal Atrial Fibrillation
    - Sick sinus Syndrome
    - Substained atrial flutter
    - Recent Myocardial infarction (within 1 month)
    - Rheumatoid mitral or aortic valve disease
    - Bioprosthetic and mechanical heart valve
    - Chronic myocardial infarction together with low ejection fraction < 28%
    - Symptomatic congestive heart failure with ejection fraction < 30%
    - Dilated cardiomyopathy
    - Nonbacterial thrombotic endocarditis
    - Infective endocarditis
    - Papillary fibroelastoma
    - Left atrial myoma
    - Other cardioembolic source: Specify

- **Small-artery occlusion (lacune)**

- **Stroke of undetermined etiology**
  - If you answered "Stroke of undetermined etiology", please, check all that apply
    - Multiple etiologies seem likely.
    - Specify:
    - Don’t know, despite thorough evaluation
    - Don’t know, evaluation incomplete

- **Other determined etiology**
  - If you answered "Other determined etiology", please, check all that apply
    - Hypercoagulable states (*)
    - Iatrogenic
    - Arterial dissection (carotid or vertebral)
    - Other. Specify:

  (*) If you answered "Hypercoagulable states", please, check all that apply
    - Malignancy
    - Antiphospholipid antibody syndrome
    - Inherited thrombophilia (including factor V Leiden deficiency, prothrombin gene mutation, protein C deficiency, protein S deficiency, antithrombin deficiency)
    - Other specified hypercoagulable state. Specify:

**Neurologist:** ____________________________________________  (Print name)
Mild and Rapidly Improving Stroke Study (MaRISS) BASELINE VISIT

MaRISS Study ID: __________________ Date: ___ ___/___ ___/___ ___

MaRISS_Criteria to code Rapidly Improving Stroke Symptoms

Provide the reason(s)/criteria that were considered to code participant’s ischemic event as Rapidly Improving Stroke (RIS). Check all that apply:

Defining Rapidly Improving Stroke:

☐ Neurological function or NIHSS improvement in absolute points from baseline
☐ Proportion or percent improvement in neurological function or NIHSS from baseline
☐ Final NIHSS value
☐ Improvement to non-disabling condition
☐ Other, Specify: __________________________________________________________

Form Completed by: ____________________________ (Print name)
Pre-Hospital Arrival Neurologic Fluctuations

Instructions: Some patient's neurologic symptoms may fluctuate after symptom onset but prior to hospital arrival. As there are no validated methods to ascertain and quantify this change, it has to be a qualitative assessment. Answer this question based on patient, family or EMS reports of significant changes, either improvement or deterioration, that occurred after symptom onset but prior to hospital arrival. Do not consider changes that occur after patient is first evaluated by hospital personnel. If more than one significant fluctuation occurs, please note so. Please consider the direction of change. For example, if the patient deteriorates twice without interval improvement, use a single (↓) rather than (↓↓).

1. Is there evidence by direct interview or documentation of neurologic status change between onset of symptoms but prior to hospital arrival?
   □ No
   □ Yes
   □ Unable to determine

2. If YES, please note if they improved (↑) or worsened (↓). Note if more than one fluctuation.

Form Completed by: ________________________________ (Print name)
Post-Hospital Arrival Neurologic Fluctuations

Instructions: Some patient’s neurologic symptoms may fluctuate after hospital arrival. As there are no validated methods to ascertain and quantify this change, it has to be a qualitative assessment. Answer this question based on patient, family or medical record reports of significant changes, either improvement or deterioration, that occurred after hospital arrival. If more than one significant fluctuation occurred, please note so. Please consider the direction of change. For example, if the patient deteriorates twice without interval improvement, use a single (↓) rather than (↓↓↓)

1. Is there evidence by direct interview or documentation of neurologic status change between hospital arrival and day 3 or hospital discharge, whichever occurred first?

☐ No
☐ Yes
☐ Unable to determine

2. If YES, please note if they improved (↑) or worsened (↓). Note if more than one fluctuation.

Form Completed by: ___________________________________________________________ (Print name)
MaRISS Appointment Reminder Cards

Phone Call Appointment Reminder

Your MaRISS Study 30-day Follow-up Telephone Call is on:

______/______/________

We will be speaking with you for about 5-10 minutes

Please contact us if you need to reschedule

Phone: ________________________________

Email: ________________________________

Phone Call Appointment Reminder

Your MaRISS Study 90-day Follow-up Telephone Call is on:

______/______/________

We will be speaking with you for about 10-15 minutes

Please contact us if you need to reschedule

Phone: ________________________________

Email: ________________________________
Web Assessment Reminder

Your MaRISS Study 90-day web assessment will be available on:

______ / ______ / ________

You will be assessing it from the website:

_________________________________________________________________________

Please contact us for assistance

Phone: ___________________________

Email: ____________________________
MaRISS follow up reminders

Text Message

• REMINDER from the Stroke Research team at [INSERT HOSPITAL NAME] that your 30-day follow-up phone call for the MaRISS study is coming up on [INSERT DATE]. Thank you for your time and cooperation. If you have any questions please contact us at [INSERT CONTACT INFO]

• REMINDER from the Stroke Research team at [INSERT HOSPITAL NAME] that your 90-day follow-up phone call for the MaRISS study is coming up on [INSERT DATE]. Thank you for your time and cooperation. If you have any questions please contact us at [INSERT CONTACT INFO]
Hello _______________________

As you may recall you are participating in MaRISS (Mild and Rapidly Improving Stroke Study), you were invited and consented to enroll in this study when you were admitted at ___________________________. [INSERT HOSPITAL NAME]

This a friendly reminder from your stroke team about your MaRISS 30-day follow-up telephone call appointment on

_____/_______/_____

I will be contacting you to ask a few brief questions about your health, this will take about 10 minutes. We truly appreciate your participation in this important study, and thank you for your cooperation.

If you have any questions or need to reschedule this call please contact me at: (_____)_________________ [INSERT CONTACT PHONE #]

30-day MaRISS Email Reminder
Dear __________________________ [Insert Participant Name]

As you may recall, you are participating in MaRISS (Mild and Rapidly Improving Stoke Study), you were invited and consented to enroll in this study when you were admitted at ________________________________ [Insert Hospital Name].

We are writing to remind you about your MaRISS 30-day follow-up phone call, which is scheduled on ____/______/_______. On this day, you will be receiving a call from one of the MaRISS study team members who will be asking a few questions concerning your health status.

If you need to reschedule your appointment date, please do not hesitate to contact us at ________________________________ [Insert contact phone number] or ________________________________ [Insert contact email], we look forward to speaking with you soon.

Thank you so much for your participation in MaRISS.

Sincerely

______________________________ [Name of Contact Person]

______________________________ [Signature]
Hello ______________________
As you may recall you are participating in MaRISS (Mild and Rapidly Improving Stroke Study), you were invited and consented to enroll in this study when you were admitted at ___________________________. [INSERT HOSPITAL NAME]

This a friendly reminder from your stroke team about your MaRISS 90-day follow-up telephone call appointment on

______/_______/_____

I will be contacting you to ask a few brief questions about your health, this will take about 10 minutes. We truly appreciate your participation in this important study, and thank you for your cooperation.

If you have any questions or need to reschedule this call please contact me at: (_____)_________________ [INSERT CONTACT PHONE #]

90-day MaRISS Email Reminder
Dear __________________________ [Insert Participant Name]

As you may recall, you are participating in MaRISS (Mild and Rapidly Improving Stroke Study), you were invited and consented to enroll in this study when you were admitted at __________________________ [Insert Hospital Name].

We are writing to remind you about your MaRISS 90-day follow-up phone call, which is scheduled on _____/_____/_______. On this day, you will be receiving a call from one of the MaRISS study team members who will be asking a few questions concerning your health status.

If you need to reschedule your appointment date, please do not hesitate to contact us at __________________________ [Insert contact phone number] or __________________________ [Insert contact email], we look forward to speaking with you soon.

Thank you so much for your participation in MaRISS.

Sincerely
Mild and Rapidly Improving Stroke Study (MaRISS)

Serious Adverse Event Form

MaRISS Study ID: __________________  Date: __ __/__ __/__ __ __ __

Instructions: Complete all the fields as soon as you become aware of each pertinent Adverse Event. Report events that are related to the use of rtPA/Alteplase and fulfill the following criteria for Serious Adverse Events or Adverse events of Special Interest: life threatening, prolongs hospitalization, results in disability/incapacity, symptomatic intracerebral hemorrhage. In addition, please report all deaths and pregnancy and infectious agent transmission during infusion of rtPA that occurs within the 90-day follow-up for Alteplase-treated patients only. Upon completion, the form and the de-identified supporting documents should be scanned and emailed to icampo@med.miami.edu and faxed to 305-243-7081. Complete one form for each SAE. If you have any questions about this form, please contact us at 305-243-8018.

1. Site & participant
   Investigator Name: ___________________________________________
   Site Name: _________________________________________________
   Participant data
     Initials: ____ ____ _____
     MaRISS Study ID: __________________
   Sex:  ☐ Male  ☐ Female
   Race:  ☐ White  ☐ Black
          ☐ Asian  ☐ Other

2. Serious Adverse Event (Complete one form for each SAE)
   Date of Serious Adverse Event: __ __/__ __/__ __ __ __
   Time of Serious Adverse Event: __ __ : __ __ (24h)

3. Type of SAE
   ☐ Non-fatal symptomatic intracranial hemorrhage
   ☐ Non-fatal systemic hemorrhage
   ☐ Other__________________________________

4. Event Seriousness
   Why was the event serious? (Check all that apply)
   ☐ Resulted in death
   ☐ Life-threatening
   ☐ New hospitalization
   ☐ Prolonged hospitalization
   ☐ Resulted in persistent or significant disability
   ☐ Pregnancy
   ☐ Congenital Anomaly/birth defect
   ☐ Other significant

5. SAE Outcome
   ☐ Fatal/Date of Death _________(dd/mm/yyyy)
   ☐ Resolved _________(dd/mm/yyyy)
   ☐ Resolved with sequelae _________(dd/mm/yyyy)
   ☐ Improved
   ☐ Persisting
   ☐ Worsened
   ☐ Unknown

SAE Form Completed by: ______________________________ (Print name) 1
6. Relationship with Alteplase

6.1 Was the SAE suspected to be caused by Alteplase administration?  Yes  No

6.2 If “No”, please provide suspected cause of SAE:
  - Disease that caused current admission
  - Concomitant medication
  - Concurrent illness
  - Other

7. Did SAE require specific treatment (s) or procedure(s)?  Yes  No

7.1 If “Yes”, please specify:
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

8. Is there any relevant previous disease to this event that contributed or explains SAE?  Yes  No

8.1 If “Yes”, please provide information:
1. __________________________________ Start date __________ End date __________ Ongoing
2. __________________________________ Start date __________ End date __________ Ongoing
3. __________________________________ Start date __________ End date __________ Ongoing

9. Please list the drugs being taken at the time of the event:
1. __________________________________ Start date __________ End date __________ Ongoing
2. __________________________________ Start date __________ End date __________ Ongoing
3. __________________________________ Start date __________ End date __________ Ongoing
4. __________________________________ Start date __________ End date __________ Ongoing
5. __________________________________ Start date __________ End date __________ Ongoing
6. __________________________________ Start date __________ End date __________ Ongoing
7. __________________________________ Start date __________ End date __________ Ongoing
8. __________________________________ Start date __________ End date __________ Ongoing
9. __________________________________ Start date __________ End date __________ Ongoing
10. __________________________________ Start date __________ End date __________ Ongoing
10. Description of SAE:
Include a history of the SAE chronologically including signs and characteristics, severity, dates and outcome of hospitalization and any other relevant information not capture elsewhere on the form. Please attach supporting documents such as discharge summary, physician notes, imaging and laboratory reports, with name and medical record number redacted and each page labeled with MaRISS Study ID.

____________________________________________________________________________________
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