Universitat de Girona

Effect of prehospital transfer model in patients with intracerebral hemorrhage

A RACECAT sub-analysis

FINAL DEGREE PROJECT

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1. ABBREVIATIONS

ABCDE: Airway, Breathing, Circulation, Disability and Exposure

CEIC: Clinical Research Ethical Committee

CICAT: Catalonia Stroke code register

CT: Computerized tomography

CVD: Cerebrovascular diseases

DOACs: Direct Oral Anticoagulants

DVT: Deep vein thrombosis

EEG: Electroencephalogram

EMS: Emergency medical services

EVT: Endovascular treatment

HE: Hematoma expansion

ICH: Intracerebral hemorrhage

INR: International Normalized Ratio

LDL: Low-density lipoprotein

LVO: Large vessel occlusion

MRI: Magnetic resonance imaging

mRS: Modified Rankin Scale

MSU: Mobile stroke units

NIHSS: National Institute of Health Stroke Score

OAC: Oral anticoagulant

PE: Pulmonary embolism

RACE scale: Rapid Arterial oCclusion Evaluation scale

RACECAT: Trial Comparing TRAnsfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory.

rTPA: Recombinant tissue plasminogen activator

SC: Stroke center

TIA: Transient ischemic attack

WHO: World Health Organization

2. ABSTRACT

Background: RACECAT was the first randomized study, in our territory, designed to evaluate if in nonurban areas with limited access to thrombectomy-capable centers, patients with large vessel occlusion would benefit from going directly to a center with the capacity to perform a mechanical thrombectomy compared with transport them to the closest local stroke center. 1401 patients were randomized into two groups: one group followed the usual route to the nearest stroke center (drip-and-ship model) and the other group was sent directly to a thrombectomy-capable center (mothership model). The scale used to recognize patients with LVO (RACE scale >4) did not allow differentiation between ischemic and hemorrhagic strokes, and therefore, 314 patients with intracerebral hemorrhage were included in the study. This meant that approximately half of these patients were referred to a more distant center with an average delay in hospital care of 49 minutes more than the group that went to the nearest stroke center. Intracerebral hemorrhage is a devastating type of stroke and during the first 3 hours, neurological deterioration can occur, mostly due to hematoma expansion. Early and intensive blood pressure control has proven to be effective in tapering hematoma expansion, especially during the first hours.

Objective: The aim of this study is whether bypassing the nearest local stroke center is harmful to patients suffering an intracerebral hemorrhage. Our main objective is to compare the Rankin score at 90 days of patients with intracerebral hemorrhage according to the prehospital circuit (drip-and-ship vs. mothership) they had in the RACECAT study.

Design: This study will be a retrospective subanalysis of RACECAT prospective cohorts. It is a multicenter study that includes 28 centers in Catalonia.

Participants: Patients older than 18 years old with intracerebral hemorrhage previously included in the RACECAT study.

Methods: All the data needed is going to be collected from the CICAT database. For the statistical analysis, we will use $\chi 2$-test and Exact Fisher test for qualitative variables, Mann-Whitney for discrete quantitative variables, and T-student to compare qualitative with quantitative variables. A confidence interval of 95% will be assumed and a $p<0,05$ will be considered statistically significant. The association between the independent and the dependent variables will be adjusted by a logic regression and general linear models in order to avoid possible confounders or effect modifiers.

Keywords: Intracerebral hemorrhage, prehospital circuit, drip-and-ship, mothership.

3. INTRODUCTION

3.1 Stroke

3.1.1 Definition

The World Health Organization (WHO) defined stroke as «rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin». (1)

If the theoretical definition of the WHO is broken down, stroke can be defined as a syndrome that has the following characteristics:

1. Sudden onset: the patient or relatives explain the onset of symptoms abruptly. This is reflected in the etymology of the word, from the Latin ictus, which means attack.
2. Focal involvement of the central nervous system: stroke produces symptoms and signs that correlate with the area of the brain supplied by the affected blood vessel, which can be pinpointed more precisely by neurologic examination and confirmed by imaging studies. However, if the area is very extensive, if there is a lot of edema or intracranial pressure increases, among others, several areas of the brain may be affected and as a consequence give diffuse symptoms.
3. Lack of rapid resolution: the classic definition of stroke implies that the symptoms persist for at least 24 hours, to differentiate it from a transient ischemic attack (TIA), although more recent definitions consider it as TIA when symptoms last < 1 hour.
4. Vascular cause: The etiology of the stroke is due to a vascular mechanism (such as thrombosis, embolus, rupture, or clotting disorders) that can be identified with subsequent etiological studies. (2)

3.1.2 Epidemiology

Cerebrovascular diseases (CVD) represent the second cause of death in Spain, the first in women, and the third in men after ischemic heart diseases and lung cancer. (3)
In Catalonia, there is an estimated incidence of 150-200 cases/100.000 people of CVD leading to 12.000 new cases/per year and a prevalence of 500-600 cases/100.000 people. (4)

The incidence of stroke has decreased, largely due to improved treatment of dyslipidemia, hypertension, diabetes, and a reduction in smoking. (2) Although the prevalence is increasing due to greater life expectancy and the greater incidence of factors such as atrial fibrillation in advanced ages.

Stroke risk increases with age, the incidence doubles every decade after the age of 45 and 70% of the CVD happen above 65.(5) This is explained by the increase in risk factors with age, such as atrial fibrillation, hypertension...

CVD are more frequent among men, except at older ages (>85 years), due, at least in part, to the longer life expectancy of women and certain vascular risk factors such as atrial fibrillation. (3)

3.1.3 Pathologic classification

Stroke can be classified according to the underlying pathologic process: ischemia or hemorrhage (2):

- *Ischemic stroke*: It represents 85% of all strokes, and it is caused by an interruption of blood flow that causes the death of brain tissue.
- *Hemorrhagic stroke*: is due to spontaneous bleeding in the brain because of the rupture of a blood vessel. Hemorrhagic stroke can be subdivided in:
    - Intracerebral hemorrhage (ICH): includes all the bleeding that is found in the brain parenchyma. Depending on the anatomical location we can classify them into:
        - *Lobar hemorrhages*: located in the cerebral lobes.
        - *Deep hemorrhages*: located in basal ganglia (putamen, thalamus...) hemispheric white matter, protuberance, and cerebellum.
    - Subarachnoid hemorrhage: consists of bleeding in the subarachnoid space.

3.2 Intracerebral hemorrhage

3.2.1 Epidemiology

ICH is the second most common cause of stroke (after ischemic etiology), but it is the first cause of stroke in people under 40. It represents 10-15% of all CVD.

The incidence in Spain is 15 cases per 100,000 inhabitants, with a higher incidence in older patients (176.3 cases per 100,000 inhabitants in patients aged 75 to 94 years). It affects more men than women. (4)(6)

It has been seen that there are differences in incidence according to ethnicity and according to the development of the country:

- The Asian race is the one with the highest incidence, followed by the black, Caucasian, and Hispanic races.
- In developing countries, the incidence is higher. In addition, the incidence in developed countries has decreased in recent years, while in developing countries it has increased.

3.2.2 Risk factors

Risk factors for cerebral hemorrhage can be divided into those that are modifiable and those that are non-modifiable. The most important are (7)(8):

- Modifiable:
    - Hypertension
    - Smoking
    - Drugs: anticoagulant, antithrombotic agent, sympathomimetics (cocaine, amphetamine, heroin).
    - High alcohol intake
- Non-modifiable:
    - Old age: ICH risk doubles for every decade after the 5th decade (9).
    - Male sex
    - Asian race

3.2.3 Etiology

The etiology of ICH can be divided into primary causes and secondary causes.

- Primary: represents 85% of all ICHs and encompasses two entities (10):
    - *Chronic hypertension*: mainly affects small perforating arteries giving rise to deep hemorrhages in the putamen, thalamus, pons, and cerebellum. It is responsible for half of ICH cases.
    - *Amyloid angiopathy*: it is the most common etiology in patients over 70 years of age with lobar hemorrhage, and the second most common cause overall. The progressive deposition of amyloid beta peptide in cortical vessels and the leptomeninges decrease compliance, making the vessel more susceptible to bleeding.

- Secondary: are those that are caused by an underlying structural pathology:
    - *Anticoagulants*: it is an increasingly frequent cause due to the great use of anticoagulants. It represents 10% of all cases.
    - *Hematological diseases*
    - *Tumors*: especially those that are highly vascularized such as glioblastoma multiforme or breast metastases or melanoma.
    - *Vasculitis*
    - *Sympathomimetic drugs*: such as cocaine, create a sudden increase in blood pressure due to vasospasm.
    - *Hemorrhagic transformation of ischemic stroke*
    - *Vascular malformations* (5% of all ICH): aneurysms, arteriovenous malformations, or cavernous angiomas. Within the group of patients under 45 years of age, they represent 38% of ICH, therefore it can be affirmed that it is a more frequent cause in young people. (4) (11)

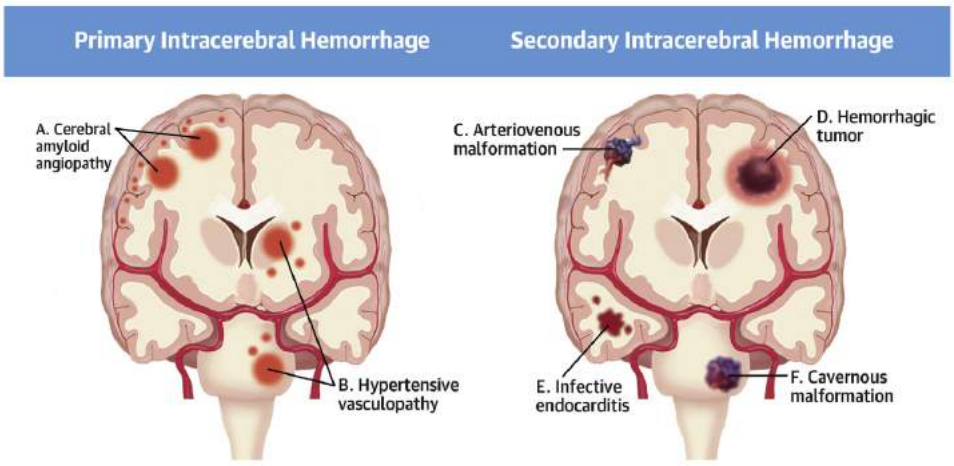

Figure 1. *Etiologies of primary and secondary hemorrhages.*

From (12)

SMASH-U is an acronym to classify the different possible etiologies of ICH structural lesions, related to medications, amyloid angiopathy, systemic diseases, hypertension, and undetermined. (13)

Etiologic classification SMASH-U	
S - Structural lesion	Image or pathology confirming structural vascular malformation diagnosed on the site of ICH
M - Medication	Warfarin use with INR greater than or equal to 2, direct oral anticoagulants within 3 days, therapeutic IV heparin, or systemic thrombolysis
A - Amyloid angiopathy	Lobar, cortical or subcortical hemorrhage and age ≥55 years
S - Systemic disease/other	Systemic disease or other ICH etiology except from anticoagulation, hypertension or amyloid angiopathy
H - Hypertension	Deep or infratentorial hemorrhage or pre-ICH hypertension, defined as: a) Most recent pre-ICH blood pressure ≥160×100 mmHg b) Mention of elevated blood pressure prior to ICH by patient, relative or medical records, with left ventricular hypertrophy as a biomarker of hypertension c) Any use of blood pressure medication prior to ICH
U - Undetermined	None of the above

SMASH-U: Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined; ICH: intracerebral hemorrhage; INR: international normalized ratio.

Table 1. *Etiologic classification SMASH-U*

From (13)

3.2.4 Pathophysiology

ICH leads to apoptosis and necrosis of neuronal tissue mainly through two mechanisms:

1. The hematoma creates a "mass effect" that compresses the brain tissue, thus increasing intracerebral pressure that will alter blood flow, as well as the release of neurotransmitters and neuronal depolarization. In addition to the above, the mass effect can also produce brain herniation.
2. The second mechanism is the "toxic effect" through thrombin activation as a consequence of endothelial damage and hemoglobin fall. Thrombin causes different actions that contribute to the perpetuation of inflammation:
    a. Causes inflammatory cells to infiltrate the brain
    b. Proliferates mesenchymal cells
    c. Promotes the formation of edema and scar tissue
    d. Activates the microglia (7)

Hypertensive vascular change

One of the most important risk factors for ICH is hypertension, this is because long-term hypertension causes arterial degeneration that ends up causing its rupture and the consequent hemorrhage. The anatomopathological changes observed in arteries degenerated by hypertension are the following:

- Degeneration of the tunica media
- Fibrinoid necrosis of the subendothelium
- Micro-aneurysms
- Lipohyalinosis (7)

The sudden elevation of blood pressure can cause ICH in the absence of chronic vasculopathy but is much less frequent (9).

3.2.5 Clinical diagnosis

A cerebrovascular accident should be suspected whenever there is an abrupt neurological focal deficit. The Spanish Society of Neurology defines the following symptoms as criteria for suspecting a stroke:

- Sudden loss of strength in the face, arm, or leg

- Inability to speak or understand what is being said to you, as well as sudden confusion
- Sudden loss of vision
- Severe and sudden headache
- Sudden onset tingling sensation in the face, arm, or leg
- Sudden loss of balance or coordination. (14)

Nausea and vomiting are unusual at the onset of infarction but may occur if there is an increase in intracranial pressure. (7)

Clinically, it is impossible to differentiate ischemic from hemorrhagic stroke, and therefore the initial management is the same.

In the acute phase of the stroke, it's necessary to obtain the information that allows to quickly know all those data that will condition the therapeutic decision or that is important for the treatment in the acute phase.

The most important thing in the anamnesis is to know the last time the patient was seen without symptoms, since this will be the time that is established as the start time of the stroke. It will be questioned to the patient and/or a witness about the chronology of the events and how the different focal neurological deficits have been established.

In the acute moment, it is also necessary to ask about important comorbidities and risk factors for stroke such as hypercholesterolemia, arterial hypertension, diabetes, and embolic arrhythmias... We will also carry out a quick anamnesis of the drugs that the patient is taking, emphasizing anticoagulants and antiaggregants, as well as toxins and drugs.

We will complete the clinical history with a history of infection, seizures, trauma, pregnancy, or other questions that we consider important to rule out stroke-like situations. (9) (14) (4)

We will perform a quick physical examination and determination of vital signs.

A neurological examination should be done aimed at objectifying the deficits that allow us to identify the location of the lesion and estimate the severity of the symptoms. For this, there are scales such as the NIH Stroke Scale (NIHSS) that allow us to evaluate all patients with suspected strokes in a standardized way and to be able to quantify their evolution. (15) (Annex 16.1)

It is also important to assess the degree of dependency both before the stroke and after it. For this, scales such as mRs can be used. (Annex 16.2)

3.2.6 Differential diagnosis

There are many pathologies that can have stroke-like symptoms, a study showed that 30% of patients that went to the emergency room with suspected stroke had another pathology (14), that is called "stroke mimic". The main entities with which the differential diagnosis must be made are shown in the following table:

Hypoglycemia	It can produce acute focal neurological deficits very similar to those of stroke, but these are resolved with the administration of glucose. For this reason, it is recommended to perform a capillary glycemia determination on all patients who arrive at the emergency room with suspected stroke. In the anamnesis, we can find history of diabetes and the patient will arrive at the emergency room with a decreased level of consciousness.
Migraine with aura	Migraine with aura can manifest as a motor or sensory neurological deficit, which although it can present acutely, it is normal for its onset to be more progressive. In the anamnesis, we will find key data that will help us differentiate this pathology such as: personal or family history of migraine, headache...

Epilepsy	The post-ictal period can give symptoms very similar to stroke (hemiparesis, aphasia, hemianopsia...), epilepsy is the pathology with which stroke is most confused. To differentiate them, the anamnesis is essential, we will ask for personal history of seizures, prodromes, and post-ictal period. If there are doubts an EEG can be performed.
Conversion disorder	Neurological disorder in which the patient unconsciously develops neurological symptoms due to a traumatic or stressful event. The physical examination is fundamental, where we will observe that it is inconstant and that the neurological symptoms do not follow a vascular distribution. Neuroimaging tests are essential to differentiate both entites.
Hypertensive encephalopathy	Entity that is made up of increased blood pressure with a focal neurological symptom. It may be indistinguishable from stroke, data that will guide the diagnosis is hypertensive retinopathy in the eye fundus or significant arterial hypertension.

Table 2. *Differential diagnosis of stroke.*
Own elaboration.

If there is any doubt about the etiology of the symptoms, the patient must be treated as if it were a stroke, since it is the most time-dependent disease. (14)

3.2.7.Prehospital stroke code in Catalonia

In 2004 the health department of the government of Catalonia created the stroke program which the main objective was to create a model for the entire territory of Catalonia that would allow early evaluation, diagnosis, and treatment of patients with acute cerebrovascular accidents based on a pre-existing system of Stroke Code. The stroke code began to fully function all across the territory in 2006. (16)

Stroke is a time-dependent disease and, moreover, many of the available treatment options have a therapeutic window in which they have to be effective. Therefore, rapid detection and transfer of patients are crucial.

Criteria to activate stroke code:

1. Patients with acute focal neurological symptoms. In Catalonia there is a scale that allows to identify quickly those patients who may have a stroke, it is called RAPID scale and rate the following items:
    - Deviates the corner of the mouth
    - Can't hold the limbs up
    - Can't understand when speaking (17)

    These are the 3 symptoms most frequently observed in stroke. (4)
2. Less than 24 hours from symptom onset or unknown onset.
3. Previous functional situation of independence, without the need for help from other people to carry out basic activities (Rankin scale 0-2). Besides from Rankin scale there is a scale called RANCOM that is often used in pre-hospital care which with 3 simple questions can determine if the person was independent. If the person has a negative RANCOM is considered autonomous, it is evaluated with this 3 items:
    - Walked or maintained mobility
    - Had the autonomy to go to the shower/bath
    - He could dress himself (17)

An important point to note is that there is no age limit to activate the stroke code. (18)

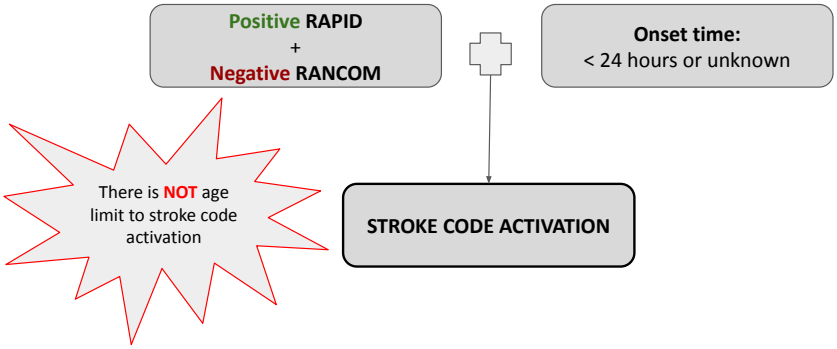

Figure 2. *Basic algorithm for stroke code activation.*

Own elaboration adapted from (17)

The stroke code can be activated by the EMS or by the emergency service if the patient goes directly to the hospital. In case of being activated from the EMS, the patient will be

transported to the nearest stroke or tele-stroke center, to ensure a rapid evaluation and rapid administration of rTPA if the patient is a candidate. During the transfer, the receptor center receives a pre-notification, in order to guarantee that the neurologist on call receives the patient immediately after the hospital arrival. (4) (19)

The RACE (see Annex 16.3) is a scale used to predict the probability of ischemic stroke with large-vessel occlusion at the prehospital level, and which are therefore candidates for endovascular reperfusion treatment.

Evaluates 5 items (facial, brachial, and crural paresis; oculocephalic deviation; aphasia/agnosia) and the score ranges from 0 to 9, a score ≥ 5 indicates that there is a probability of a large vessel occlusion with a sensitivity of 85% and specificity of the 69%. (20) (21). One of the main problems with this scale is that it does not allow you to differentiate between ischemic or hemorrhagic stroke, as well as stroke-mimic.

3.2.8 Patient transfer

Intracerebral hemorrhage is a medical emergency. A rapid transfer and handling of patients greatly reduce morbidity and mortality.

The patient will be treated as a critical patient and the ABCDE will be checked, ensuring correct cardiovascular and respiratory support.

During transfer to a hospital capable of caring for stroke patients, vital signs such as heart rate, blood pressure, temperature, and oxygen saturation will be recorded. It is also important to determine capillary glycemia to diagnose hyper or hypoglycemia.(15) Nevertheless, the ambulances used to transport stroke patients are conventional ambulances in which it is not possible to monitor these constants or prescribe medication during transport.

3.2.9 Management of the acute phase

The first thing that has to be checked in front of a patient with ICH is their hemodynamic and respiratory status (ABC). If the Glasgow is less than 8 points, endotracheal intubation will be performed. (14)

When the patient arrives at the emergency department, the patient's constants are measured again and we repeat the anamnesis to the patient and/or family, as well as a new neurological examination (if the level of consciousness allows it) with scales such as NIHSS.

One of the most important actions in patients with ICH is the reduction of blood pressure. High blood pressure has been related to increased hematoma growth, more neurological deterioration, and increased mortality in patients with ICH. The therapeutic objective that must be achieved is to reduce blood pressure below 140 mmHg with hypotensive drugs such as labetalol, and urapidil... in the first hour after attention. (4)

Upon arrival at the emergency room, the following analytic and imaging tests will be performed:

- Capillary blood glucose: if it has not been done during the transfer.
- An analysis with blood count, basic biochemistry with ionogram and kidney function and a study of coagulation.
- Measurement of the INR if the patient takes an oral vitamin K antagonist anticoagulant.
- An electrocardiogram
- Chest X-ray
- Toxic in urine

It is fundamental to do a neuro-imaging test (CT or brain MRI): CT is normally performed in the emergency room due to greater availability and faster imaging.

- Basal-CT: Cerebral hemorrhage in the acute phase will be seen as a hyperdense lesion. Basal-CT allows us to differentiate between hemorrhagic and ischemic strokes as well as stroke-simulating lesions. (22). It has been seen that there are

baseline CT parameters that can help us predict the growth of the hematoma, including:

- ICH volume: larger hemorrhages have a higher risk of expansion.
- ICH shape: irregular margins have more risk of hemorrhage growth
  - One specific type of irregular ICH shape is the island sign, which represents multifocal bleeding points and predicts poor functional outcome. Its defined as the presence of ≥3 separate small hematomas or ≥4 small hematomas that are partially connected to the main hematoma. (23)

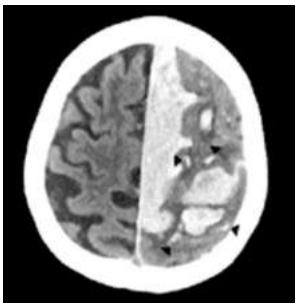

Figure 3. *Islands signs.*

Non-contrast TC showing islands signs (arrowheads)

From (23)

- ICH density: heterogenous hemorrhage has more risk of expansion because there are areas of hyperdense mature blood and hypodense fresh blood indicating ongoing bleeding (23). Specific signs for ICH density are:
  - Black hole sign: is an area of hypodensity that is completely encapsulated by a hyperdense area of hematoma (difference of 28 Hounsfield units between the 2 areas). Black hole predict hematoma expansion as well as poor functional outcome.

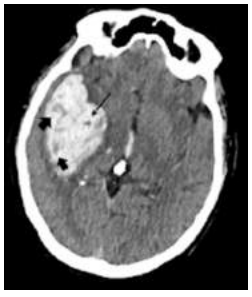

Figure 4. *Black hole sign and hypodensities.*

Non-contrast TC showing black hole sign (thin arrow) and hypodensities (thick arrows).

From (23)

- Blend sign: predict hematoma expansion and it is represented as a well-defined area of hypodensity next to the hyperdense area of hematoma (difference of 18 Hounsfield units between the 2 areas). (23)

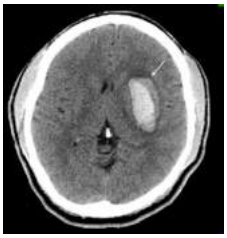

Figure 5. *Blend sign.*

Non-contrast TC showing blend sign.

From (23)

- Fluid level: it is seen as a hypodense area above a hyperdense area with a line of separation. (24)

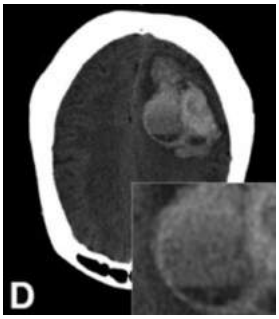

Figure 6. *Fluid level.*

Non-contrast TC showing fluid level.

From (24)

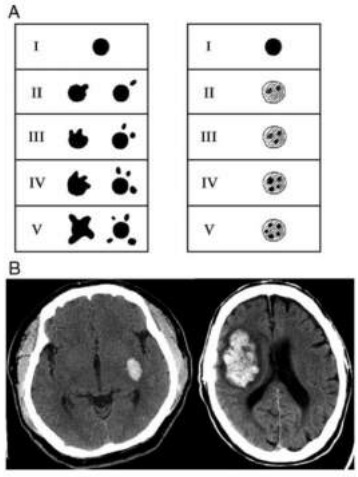

Figure 7. *Shape (left) and density (right) categorical scales. From less irregular or heterogenic to more.*

From (25)

- Angio-CT: in the acute phase of intracerebral hemorrhage it can be useful for detecting possible secondary causes of the hemorrhage potentially treatable as well as for detecting signs with predictive value for the growth of the hemorrhage, such as the spot sign.
    - The spot sign consists of the extravasation of contrast in the arterial phase inside the ICH. Contrast extravasation is an independent factor of intra- and out-of-hospital mortality and worse clinical and radiological evolution. (4)

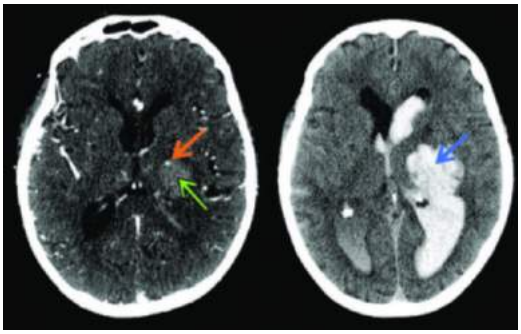

Figure 8. *Spot sign and hematoma growth.*

On the left, a CT angiography can be seen showing an ICH (green arrow) and the spot sign (orange arrow). The image on the right shows a control CT scan at 24 hours in which a growth of the hematoma is observed.

From (26)

The admission of the patient will preferably take place in a Stroke Unit, since it has been shown that it increases the survival and functionality of patients with ICH.

3.2.10 Stroke unit and general treatment

The stroke unit is a non-intensive or semi-critical acute care unit dedicated exclusively to the care of stroke patients, made up of a multidisciplinary and trained team.

In it, patients with stroke are admitted for at least 72 hours (since it is the period where most complications occur) and continuous monitoring is established (4):

- The patient is initially at rest with the headrest at 30º. Seating and progressive ambulation will be performed. It is important to do a progressive mobilization of the patient but not too soon, because it has been shown that early aggressive

mobilization within the first 24 hours after ICH appears to worsen 14-day mortality. (27)

- Monitoring of blood pressure, heart rate, breath rate and oxygen saturation will be performed.
- Control of the tympanic temperature every 4 hours during the first 48 hours and every 8 the following days, since fever has been associated with hematoma growth and a worse prognosis.
- Upon admission, a dysphagia test will be performed and a nasogastric tube will be placed if there is vomiting or decreased level of consciousness, in order to avoid bronchial aspiration.
- Capillary glycemia every 6 hours during the first 24 hours. It is recommended to avoid both hyper and hypoglycemia.
- Monitoring of neurological symptoms by both nurses and neurologists.
- Placement of intermittent pneumatic compression stockings to prevent deep venous thrombosis and pulmonary embolism. When the hemorrhage is radiologically stabilized it can be initiated prophylactic treatment with low molecular weight heparin.
- Progressive cognitive, physical and/or speech therapy rehabilitation based on the patient's deficits.

3.2.11 Specific medical treatment

There is currently no specific treatment for ICH, but in secondary causes, the alteration that has produced the hemorrhage can be corrected:

- If the patient takes an anticoagulant, we must reverse its effect because ICH while anticoagulated high mortality and morbidity (27):
    - Vitamin K antagonist oral anticoagulants: if the patient with ICH takes one of these drugs, their intake will be discontinued immediately. In addition, the INR will be measured, if it is greater than 1.4, 10mg of vitamin K + prothrombin complex 25U/Kg of weight will be added. After 15 minutes, the INR is measured again and if it continues to be greater than 1.4, 500U more of the prothrombin complex will be added.

- If the patient takes sodium or low molecular weight heparin, we can reverse it with protamine sulfate (1mg per 100 U of heparin with a maximum of 50mg), in low molecular weight the reversal may not be complete.
- New direct anticoagulants: we must measure the half-life, because most of them have a short half-life, if it needs it, it can be reversed with:
  - Dabigatran: It has a specific antidote, idarucizumab.
  - Factors Xa inhibitiors, such as rivaroxaban, apixaban, and edoxaban: their specific antidote is andexanet alfa. (27)

- Specific treatment of the tumor or vascular malformations.

3.2.12 Surgical treatment

The role of surgery in patients with hemorrhage is controversial. (28) There is only one clinical situation in which surgical treatment has been shown to be effective, and that is in those cerebellar hemorrhages of >15 mL or those of smaller size but have neurological deterioration compress the brainstem or cause hydrocephalus. (4)

Recently minimally invasive techniques such as endoscopic hematoma evacuation for supratentorial ICH and intraventricular hemorrhage showed better functional outcomes compared to medical treatment. (27)(29)

There are other situations in which we can consider surgical treatment although they lack evidence:

- Patients with neurologic deterioration that have lobar hemorrhages (located <1 cm from the cortical) with significant volume (>30 mL).
- In the presence of ventricular hemorrhage, the placement of a ventricular drainage catheter is limited because of the difficulty in maintaining the permeability of the catheter. (4)

3.2.13 Complications

ICH complications are one of the main predictors of early mortality and poor functional outcome (30). The principal complications of ICH are:

- Hematoma expansion (HE): it is defined as an increase in the volume of 33-50%, which is a frequent and severe complication. 40% of the growth of the hematoma takes place in the first hours after the stroke. HE is associated with early neurological deterioration and is an independent predictor of poor functional outcomes and increased mortality. (30) There are radio markers for both simple CT and CT angiography that can help us predict hematoma growth (mentioned in section 3.2.9).
- Intracranial hypertension: it is one of the main complications of ICH due to the growth of the hematoma, edema or the presence of hydrocephalus. The treatment is based on:
    - Basic measures: elevation of the headboard of the bed to 30º, analgesia, treatment of fever, control of tension and antacids to prevent gastric ulcer.
    - Intracranial pressure monitoring is recommended in patients with a low level of consciousness, hydrocephalus or intubated patients.
    - Specific treatment: there are several specific treatments, such as osmotherapy with 20% mannitol or hypertonic saline serum, transient controlled hyperventilation or surgical decompression with the evacuation of the hematoma or decompressive craniectomy stand out.
- Epileptic seizures: they usually appear after lobar intracerebral hemorrhages. In the first week they can occur in up to 16% of cases. Prophylactic treatment with antiepileptics is not recommended. (4)
- Infections: Post-stroke infections have been shown to interfere with the patient's recovery and have worse functional outcomes (31). The two most frequent types of infections are:
    - Bronchoaspiration pneumonia: Risk factors are intubation, dysphagia, congestive heart failure, and male sex. (32)
    - Urinary tract infection: affects between 10% and 19% of stroke patients. Risk factors are female sex and bladder catheterization. (32)

- Deep-vein thrombosis (DVT) and pulmonary embolism (PE): The probability of suffering one of these events in the short-term post-ICH is 1-4% for DVT (but subclinical DVT can reach up to 17%) and 1-2% for pulmonary thromboembolism. The risk factors for developing these events are immobility due to motor paralysis, extensive infarction, advanced age, and discontinuation of antithrombotic agents. It has been seen that women and black patients are more likely to have thrombotic events. These events are associated with a 30-day mortality of 35-52%, and slow down the rehabilitation and recovery of the patient. To prevent these events, patients admitted to the stroke unit wear intermittent pneumatic compression socks. The treatment of these events generates a therapeutic dilemma, since if you do not treat DVT the risk of PE is very high, but anticoagulants increase the risk of HE or rebleeding. This therapeutic decision must be made individually for each patient, measuring the benefit-risk of each situation. (30)

3.2.14 Etiological study

After the acute phase of the hemorrhage and normally during the stay in the stroke unit, an etiological study is carried out (the main causes of stroke are mentioned in 3.2.3).

The etiological study begins by completing the clinical history, emphasizing:

- Family history of stroke or vascular malformations
- Toxic habits (tobacco, alcohol and sympathomimetic drugs)
- Personal history of hypertension, systemic diseases (highlighting tumoral, hematological and vasculitis diseases), neurological diseases such as epileptic seizures and migraine or a history of hemorrhage in other parts of the body.
- Intake of antiaggregants or anticoagulants.

Complete physical examination aimed at finding signs of systemic diseases that guide us to the etiology.

Blood analysis with complete blood count, liver and kidney function, ionogram, coagulation and toxic urine.

The basic study would be completed with the measurement of vital signs as well as cardiac monitoring and chest x-ray.

This would be the basic etiological study, depending on the patient we will carry out more complex tests:

- If it is a patient diagnosed with hypertension and a typical location of hypertension bleeding (deep location), no further studies are needed.
- If hemorrhage is lobar, complementary studies are usually required, such as performing an MRI that allows detecting, above all, microbleeding. If the location of the microbleeds is at the cortical level and they are multiple, it is typical of amyloid angiopathy.
- In younger patients where vascular malformations have to be suspected above all, an angioCT or angioMR will be performed. If no alteration is detected, an arteriography will have to be considered. (4)

3.2.15 Preventive treatment

Patients who have already suffered an ICH have a cumulative risk of 1-5% of recurrence of intraparenchymal hemorrhage. Although the risk is greater during the first year, the risk of recurrence can be maintained for years, especially in those patients with lobar hemorrhage. (28)

Those patients who are at higher risk of presenting a second ICH are:

1. Lobar location of hemorrhage
2. Presence of several microbleeds in the gradient echo MRI
3. Taking anticoagulation
4. Presence of apolipoprotein E alleles ε2 or ε4
5. Older people
6. Presence of hypertension

Lifestyle modifications including exercise, reduction of alcohol intake, cessation of tobacco as well as drugs such as cocaine are recommended to all patients.

Regardless of the etiology, all patients must receive hypotensive treatment since all hemorrhages benefit from lowering blood pressure. The objective that we must achieve is a systolic pressure of less than 130 mmHg and a diastolic pressure of less than 80 mmHg.

Withdrawal of the anticoagulant is controversial, but the general recommendation is to reintroduce the oral anticoagulant 4 weeks after ICH in cases with deep locations of hypertensive etiology. Nowadays, several clinical trials are ongoing to study if the reintroduction of anticoagulant treatment is efficacious and safe.

The use of statins is also controversial since high levels of LDL cholesterol have been described as a protective factor for ICH, but a meta-analysis with 91,588 patients did not show an association between LDL cholesterol and ICH, on the other hand, it did reduce total mortality. (15) This topic is being analyzed in another clinical trial.

3.3 The RACECAT study

The RACECAT is a study that was carried out in Catalonia which began in March 2017 and was published in May 2022. It is a Trial Comparing TRAnsfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory.

The main question that this study tried to answer is whether there is a difference in the evolution of patients in whom large vessel occlusion is suspected if they are sent to the nearest stroke center or are sent to a center with thrombectomy.

This study was motivated by the differences in the geographical distribution of thrombectomy centers. Most of the centers with endovascular treatment are in the metropolitan area of Barcelona, so those patients with a mechanical thrombectomy center as their referral had higher rates of endovascular recanalization treatment than

those who went to the nearest stroke center, in addition to receiving endovascular treatment 90-120 minutes earlier.

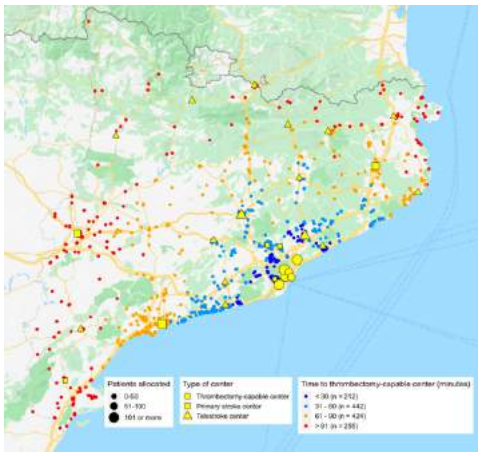

Figure 9. *Catalonia geographical distribution of stroke centers. From (30)*

Thrombectomy is the main treatment in patients with large vessel occlusion (LVO) because is related to a better outcome than thrombolysis alone (33). The beneficial effect of thrombectomy is highly time-dependent, a recent study showed that in the first hours after onset for each 30 minutes delay in EVT initiation the likelihood of regaining functional independence drops 10-15%. (34). All this evidence raises the question about where should a patient with a suspected LVO stroke be primarily transferred.

3.3.1 Study objective

The main objective of the study was: To evaluate if direct transfer of acute ischemic stroke patients with clinically suspected LVO to an EVT-SC, by-passing Local-SC, compared to transfer to the closest Local-SC offers a better clinical outcome.

3.3.2 Study design

RACECAT is a multicenter study (28 centers in Catalonia participated: 10 centers with mechanical thrombectomy and 18 stroke centers[1]: 8 primary stroke centers and 14

[1] Stroke centers: are those centers that can receive stroke patients from the emergency services some with a vascular neurologist present (primary stroke center) and another through virtual consultation with a vascular neurologist (tele-stroke center). These centers are able to perform fibrinolytic treatment with i.v. rTPA but they can't perform the endovascular treatment.

telestroke centers) prospective, cluster randomized controlled, blinded-endpoint trial. (35)

Endovascular stroke centre	Closest stroke centre	
	Primary stroke centre	Telestroke centre
H. Universitari de Bellvitge H. Vall d'Hebron H. U. Germans Trias I Pujol H. Clínic de Barcelona H. del Mar H. de la Santa Creu i Sant Pau H. Josep Trueta (Girona)* H. Arnau de Vilanova (Lleida)* H. Joan XIII (Tarragona)* H. Parc Taulí (Sabadell)*	H. Josep Trueta (Girona) H. Arnau de Vilanova (Lleida) H. Joan XIII (Tarragona) H. de Tortosa Verge de la Cinta (Tortosa) H. Althaia (Manresa) H. Parc Taulí (Sabadell) H. Mútua Terrassa H. de Sant Joan Despí Moisès Broggi (Barcelona)	H. U. de Vic H. Gral. De Granollers H. de Mataró H. d'Igualada H. Sant Camil H. Comarcal de li'Alt Penedès H. de Figueres H. de Palamós H. Comarcal del Pallars Fundació Sant Hospital de la Seu d'Urgell H. Comarcal de Móra d'Ebre H. de Cerdanya H. Olot H. Campdevànol

Table 3. *Participating hospitals of RACECAT.*

**Hospitals that operate as part-time Endovascular Stroke Centers (working hours), and as Local Centers in non-working hours.*

Adapted from (32)

1401 patients with suspected long-vessel occlusion and who did not have as a reference center a center with thrombectomy were included in RACECAT study. They were identified as LVO by the emergency services with more than 4 points on the RACE scale (mentioned in the stroke code section).

These patients were randomized into 2 groups of transfer:

- Drip-and-ship model (reference model in areas where the thrombectomy center is not the referral center): A patient with suspected LVO is transferred to the nearest stroke center. This usually involves faster care at the closest stroke center, but thrombectomy is often delayed as a second transfer is needed.
- Mothership model (the experimental model in areas where the thrombectomy center is not the referral center): patient with suspected LVO is transferred directly to a center with the capacity to perform endovascular treatment (by-

passing the closest local stroke center). The first assessment by a neurologist is made later than in the other model, but if a thrombectomy is required, it will be performed earlier.

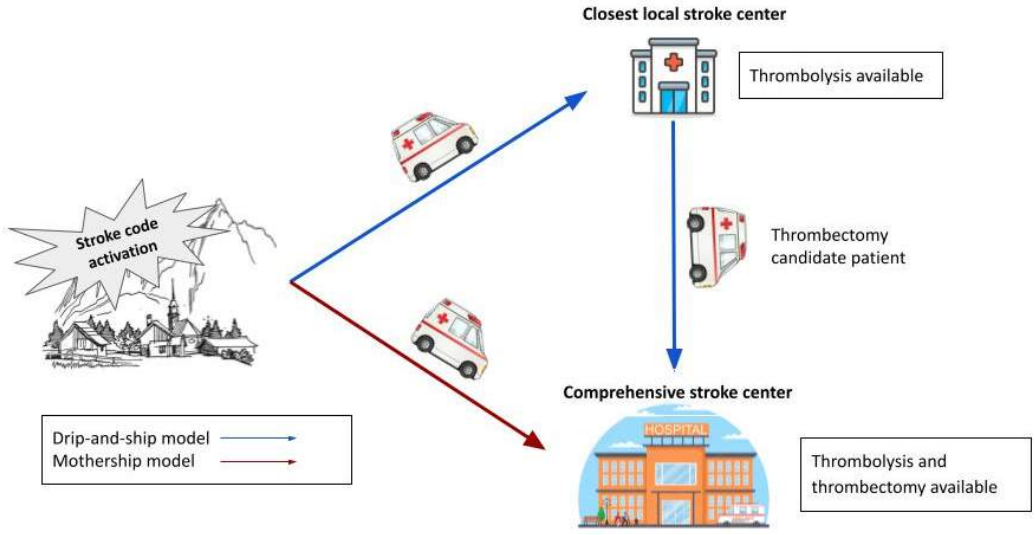

Figure 10. *Transfer models.*
Own elaboration.

The randomization was done according to 3 strata: time band (two groups of 12 hours), territory (metropolitan versus provincial area) and weekday (working versus weekend day). Finally, 688 patients were randomly transported to a thrombectomy center (mothership model) and 713 patients were transported to the nearest stroke center (drip-and-ship model). (35)

To compare the clinical response of the two groups, residual functional disability is evaluated using the Rankin scale at 90 days. This evaluation was blind since the interviewer did not know to which centers these patients had been transported. (35)

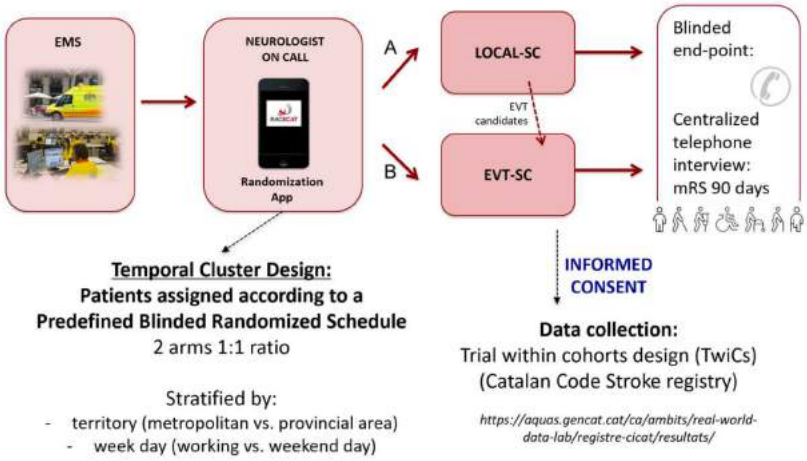

Figure 11. *Scheme of RACECAT design.*
From (32)

3.3.3 Results and conclusion

There was **no statistically significant** difference in the distribution of Rankin scale scores at 90 days between those sent to a thrombectomy center and those sent to the nearest stroke center (median mRS score, 3 [IQR, 2-5] in the thrombectomy-capable center group vs 3 [IQR, 2-5] in the local stroke center group; adjusted common OR, 1.03; 95% CI, 0.82-1.29). (35)

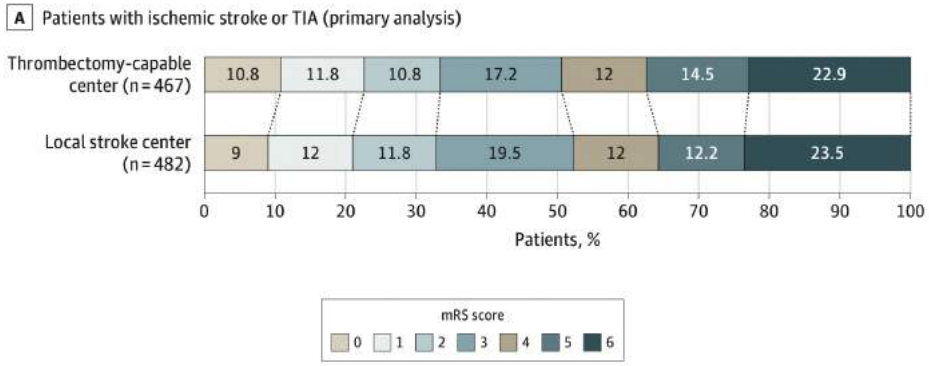

Figure 12. *Distribution of mRS at 90 days in ischemic stroke.*
From (30)

3.3.4 Intracerebral hemorrhage in RACECAT study

Of 1401 randomized patients, several did not have LVO strokes:

- 314 intracranial hemorrhage: 141 were sent to a thrombectomy-capable center and 173 to a local stroke center.
- 106 with stroke-mimic
- 200 patients with no-LVO ischemic stroke

This is because neither the RACE scale nor any pre-hospital method can differentiate between these types of entities clinically.

The average time from symptom onset to first hospital arrival is very different for the two types of transfers compared in RACECAT:

- 91 minutes for drip-and-ship model
- 140 minutes for mothership model

The delay in the mothership model could damage ICH patients because, as mentioned earlier in the introduction, although there is no specific effective treatment for ICH it has been shown that rapid management of blood pressure, avoidance of hypo-, hyperglycemia and fever and an immediate admission to a stroke unit improves the functional prognosis of this patients.

4. STUDY JUSTIFICATION

Stroke is a major health problem, representing the second most frequent cause of death and the most frequent cause of disability in our country (3). Up to 15% of strokes are of hemorrhagic origin (7). Among all stroke subtypes, intracerebral hemorrhage is the deadliest form with early mortality of around 40% (27).

Since 85% of strokes are ischemic and have a specific treatment with a therapeutic window, most of the information available on pre-hospital management is focused on ischemic stroke. It has been seen in non-randomized studies that direct transport to a thrombectomy center could be beneficial for patients with suspected LVO (33), since it is the most effective treatment in these patients and thus increases the number of patients who are candidates for it.

RACECAT was the first randomized study in our territory aimed to know whether patients with large vessel occlusion, who did not have a thrombectomy center as a referral center, would benefit from going directly to a center with this treatment. For this purpose, 1401 patients with suspected large vessel occlusion (>4 points on the RACE scale) were randomized into two groups: one group followed the usual route to the nearest stroke center and the other group was sent directly to a center with thrombectomy. (35)

As it is not possible to differentiate stroke types by clinical features, 314 patients with intracerebral hemorrhage were included in the study. This meant that approximately half of these patients were referred to a more distant center with an average delay in hospital care of 49 minutes more than the group that went to the nearest stroke center. Intracerebral hemorrhage is a time-dependent disease, since it has been shown that prompt attention and stabilization improve the functional prognosis of these patients.

The final results of RACECAT were that direct referral to a center with thrombectomy was not observed to be better than the traditional circuit. The results of this study, which are not consistent with the published literature advocating the beneficial role of direct referral of patients with thrombectomy, maybe in part because the analyses included patients with ICH in whom not receiving early care is detrimental.

This study aims to demonstrate that bypassing the nearest stroke center, in all stroke code activations, and sending them directly to a thrombectomy center is harmful to patients with intracerebral hemorrhage.

5. HYPOTHESIS

Main hypothesis

The main hypothesis is that the clinical outcome in patients with ICH at 90 days (assessed by Rankin scale) in patients transported to the closest stroke center is better compared to those who bypass the closest stroke center.

Secondary hypothesis

1. Early mortality and 90-days mortality in patients transported to the closest stroke center are lower than in patients who bypass the closest stroke center.
2. The hemorrhage growth is lower in those patients who went to the nearest stroke center.
3. The number of complications (bronchoaspiration, urinary infection, deep vein thrombosis, seizures and orotracheal intubation) is lower in those patients with intrecerebral hemorrhage who are referred to the closest stroke center.

6. OBJECTIVES

Main objective

To compare the Rankin score at 90 days in patients with intracerebral hemorrhage according to the prehospital circuit (drip-and-ship vs. mothership).

Secondary objectives

1. To compare early mortality and 90-day mortality of patients with intracerebral hemorrhage according to the prehospital circuit (drip-and-ship vs. mothership).
2. To compare the presence of hemorrhage growth in patients with intracerebral hemorrhage according to the prehospital circuit (drip-and-ship vs. mothership).
3. To compare the number of medical complications (bronchoaspiration, urinary infection, deep vein thrombosis, seizures and orotracheal intubation) of patients with cerebral hemorrhage depending on the prehospital circuit (drip-and-ship vs. mothership).

7. MATERIALS AND METHODS

7.1 Study design

The study is a retrospective substudy of a population-based prospective observational cohorts (RACECAT study). We will use RACECAT data to see the effects of bypassing the closest stroke center in patients with intracerebral hemorrhage.

7.2 Study population

The target population of this study will be those patients that were included in the RACECAT study who had an intracerebral hemorrhage.

Inclusion criteria

1. Patients above 18 years old.
2. Previously independent (mRS of ≤2).
3. The presence of intracerebral hemorrhage demonstrated with neuroimaging test.
4. Signature of RACECAT informed consent.

Exclusion criteria

1. Patients with ischemic stroke or subarachnoid hemorrhage in neuroimaging test.
2. Stroke mimic.
3. Patients in coma (defined as a score of 3-5 on the Glasgow Coma Scale).
4. Critical patients who need intensive care.
5. Not spontaneous intracerebral hemorrhage (secondary to tumors, trauma...).

7.3 Sample

7.3.1 Sample size

The fact that our study is based on a subgroup of an already conducted study, makes the sample size of our study limited. However, we have calculated the ideal sample size we should have.

The dependent variable of the study is the Rankin scale at 90 days, as it is a discrete quantitative variable it is expressed in median and interquartile range. Therefore, to be able to perform the calculations with the GRANDMO calculator, we had to assume an equivalence between the median and mean in order to be able to perform the calculations with mean and standard deviation. The interquartile range of the Rankin scale for patients with hemorrhagic stroke is IQR [4-6].(35) If we infer that our variable follows a normal distribution in which the interquartile range is approximately 3/4 of the standard deviation. If the IQR is 5 we assume a standard derivation of 3.7.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 215 subjects are necessary for the first group and 215 for the second to recognize as statistically significant a difference greater than or equal to 1 unit. The common standard deviation is assumed to be 3.7. Has been anticipated a drop-out rate of 0% because all data are already collected.

7.3.2 Sample selection

Our sample is all the patients with ICH in the RACECAT study which suits our inclusion and exclusion criteria.

Of the 1401 people randomized in the RACECAT study 688 were randomized to transport to a thrombectomy-capable center and 713 to the local stroke center. In the first group 141 intracerebral hemorrhages were included and in the second group 173 patients with intracerebral hemorrhages. So we will select the 314 patients with ICH from RACECAT study to perform our study.

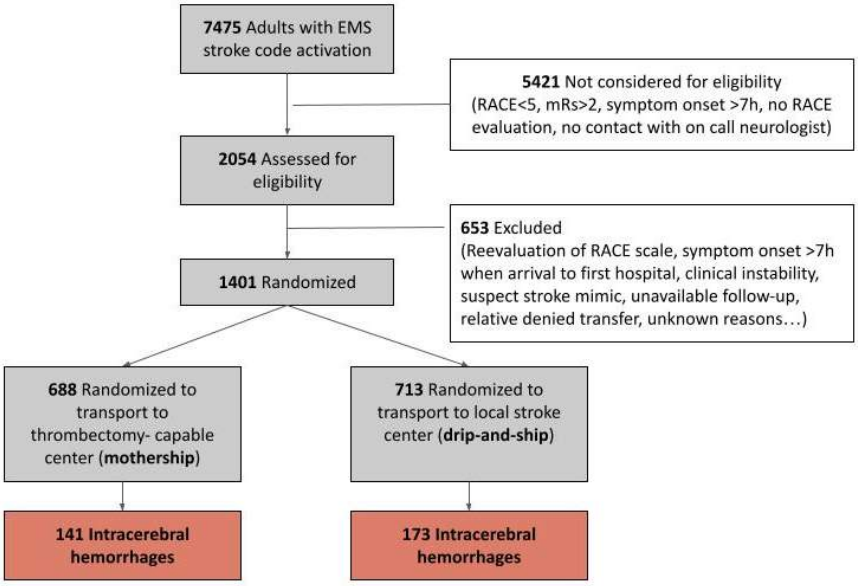

Figure 13. *P*articipant flow through the RACECAT Trial.
Adapted from (35)

7.4 Variables

7.4.1 Independent variable

1. *Prehospital circuit*

   We will look at which center the patients with intracerebral hemorrhage were sent to in the RACECAT study, it could be:

   - Drip-and-ship model: The patient was transferred to the closest stroke center. A stroke center is defined as those centers that can receive stroke patients from the emergency services, some with a vascular neurologist present (primary stroke center) and others through a virtual consultation with a vascular neurologist (tele-stroke center). These centers are able to perform fibrinolytic treatment with i.v. rTPA but they can't perform endovascular treatment.
   - Mothership model: The patient was transferred to an endovascular capable stroke center. These centers have the benefits of stroke centers in addition to having the capacity to perform endovascular treatment.

7.4.2 Dependent variable

In the study, there are several dependent variables to respond to all the proposed objectives. The main dependent variable is:

1. *Modified Rankin Scale at 90 days*: we will look at the values collected in RACECAT database of Rankin scale at 90 days, and compare it with the destination of the patient.

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

Table 4. *Modified Rankin Scale.*
Own elaboration.

The secondary dependent variables are:

1. *Early mortality and 90-day mortality*

   It will be defined as the presence or absence of deaths during the hospitalization of the patients (early mortality) or at 90 days after medical discharge (90-day mortality). If the patient had early mortality will not be included in the 90-day mortality category.

2. *Presence of hematoma growth*

   It is going to be compared the growth of the hematoma from the admission CT to the 24-72 hours CT, which is defined as an increase > 33% and/or 6 ml between both CTs. It will be treated as a dichotomous nominal qualitative variable (presence of hematoma growth or non-hematoma growth).

3. *Medical complications: broncoaspiration, urinary infection, deep vein thrombosis, seizures, and oral tracheal intubation*

   These complications were collected in all patients included in RACECAT, so we will look at the presence or absence of these complications in the database in patients with ICH.

7.4.3 Covariables

The following variables have an important role in the clinical evolution of the patient with intracerebral hemorrhage, so we must take them into account in the analysis.

1. *Age*

   Will be treated as a quantitative continuous variable. The age of more than 80 years is associated with more morbidity and mortality after intracerebral hemorrhage in the following 30 days after stroke (36).

2. *Sex*

   Dichotomous nominal qualitative variable, expressed as male or female.

3. *Neurological state*

   Measured with NIHSS (Annex 16.1) at first neurologist evaluation and at discharge. It will be expressed as <4 Mild, <16 Moderate, <25 Severe and ≥25 Very severe.

4. *Baseline hemorrhage initial volume*

   It is a continuous quantitative variable, but the hemorrhage will be categorized into two groups (<30 mL or ≥30 mL), so we will treat it as an ordinal qualitative variable. We divided these two groups because intracerebral hemorrhages of more than 30 mL are associated with a worse prognosis. (36)

5. *Stroke unit admission*

   Dichotomous nominal qualitative treated as admission or non-admission. It has been shown that patients admitted to the stroke unit have better functional recovery and increased survival. (37)

6. *Hemorrhage location*

   Dichotomous nominal qualitative: lobar or deep location. Each location is normally associated with an underlying etiology (lobar location with amyloid angiopathy and deep location with chronic hypertension).

7. *Intraventricular blood*

   Dichotomous nominal qualitative treated presence or absence. Defined as the presence inside the cerebral ventricles in neuroimaging test, which is associated with a poorer prognosis because is often related to large hematomas. (36)

8. *Taking antiaggregants or anticoagulants*

   Treated as a nominal qualitative variable with the following categories: no previous or antiaggregant anticoagulant, OAC antivitamin K and DOACs. Those intracerebral hemorrhages in patients who take antiaggregants or anticoagulants are associated with higher 90-day mortality. (38)

9. *Wake-up stroke*

   Is defined as the situation where the patient went to sleep without symptoms and awakens with stroke symptoms, it is associated with poor outcomes. (39)

10. *Presence of CT growth predictors*

    In particular we are going to look the black hole sign, blend sign and fluid level. (The definition of each sign is in section 3.2.9)

11. *Time from stroke onset to admission on first hospital*

    It will be quantified in minutes, and it goes from the time that has been established as the start of the stroke until arrival at the emergency room door and identification of the patient.

The following table summarizes all the study variables:

	Variable	Type	Mesurment tool	Categories or values
INDEPENDENT	**Prehospital circuit**	Dichotomous nominal qualitative	CICAT database	- Drip-and-ship - Mothership
DEPENDENT	**Modified Rankin Scale (90 days post-stroke)**	Discrete quantitative	CICAT database	- 0: No symptoms - 1: No significant disability - 2: Slight disability - 3: Moderate disability - 4: Moderately severe disability - 5: Severe disability - 6: Death
	Early mortality	Dichotomous nominal qualitative	CICAT database	- Yes - No
	90-day mortality	Dichotomous nominal qualitative	CICAT database	- Yes - No
	Broncoaspiration	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Urinary infection	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Deep vein thrombosis	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Seizures	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Orotracheal intubation	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Haemathoma growth	Dichotomous nominal qualitative	CICAT database	- Growth - Non-gwowth

COVARIABLES	**Age**	Continuous quantitative	CICAT database	- Years
	Sex	Dichotomous nominal qualitative	CICAT database	- Male - Female
	NIHSS at admission	Discrete quantitative	CICAT database	- Mild < 4 - Moderate < 16 - Severe < 25 - Very Severe ≥ 25
	NIHSS at discharge	Discrete quantitative	CICAT database	- Mild < 4 - Moderate < 16 - Severe < 25 - Very Severe ≥ 25
	Stroke unit admission	Dichotomous nominal qualitative	CICAT database	- Admission - Non admission
	Hemorrhage location	Dichotomous nominal qualitative	CICAT database	- Lobar - Deep
	Hemorrhage size	Dichotomous ordinal qualitative	CICAT database	- < 30 mL - > or = 30 mL
	Intraventricular blood	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Previous antiaggregant or anticoagulant treatment and type	Nominal qualitative	CICAT database	- No previous or antiaggregant anticoagulant - OAC antivitamin K - DOACs
	Wake-up stroke	Dichotomous nominal qualitative	CICAT database	- Yes - No
	Non-contrast CT-radiomarkers	Dichotomous nominal qualitative	CICAT database	- Present - Absent
	Time to admision	Continuous quantitative	CICAT database	- Minutes

Table 5. *Summary of variables and covariables of the study.*
Own elaboration.

7.4.4 Data collection

The data that we need for this study is going to be collected retrospectively from RACECAT study. All RACECAT data is collected in the CICAT registry which is a government-mandated, population-based registry of all stroke code activations reaching any stroke center in Catalonia. To obtain this data we will need to contact de scientific committee of CICAT.

8. STATISTICAL ANALYSIS

The statistical analysis will be done by a qualified statistician.

8.1 Univariable analysis

To analyze each variable of the study separately, we will use different tests depending on the type of variable:

- Quantitatives variables: will be expressed with measures of central tendency and measures of dispersion. If the follow normal distribution we will use mean and standard derivation (SD). If they don't follow normal distribution will be expressed as median and interquartile range.
- Qualitative variables: will be expressed as proportions ± confidence interval (95%)

8.2 Bivariable analysis

To demonstrate or not statistical significance between 2 variables under study, the following tests will be used:

- To compare two dichotomic qualitative variables we will use:
    - $\chi 2$-test if the variables have a normal distribution.
    - Exact Fisher test if the variables do not follow a normal distribution.
- To compare a qualitative variable with a quantitative one we will use:
    - U-Mann-Whitney test if the quantitative variable is discrete because we need to use a non-parametric test.

8.3 Multivariable analysis

A multivariate analysis will be performed to establish the statistical association between two variables but taking into account the covariables that could act as confounders or effect modifiers.

For qualitative dependent variables (with a qualitative independent variable) a logistic regression will be performed.

For quantitative dependent variables (with a qualitative independent variable) general linear models will be performed.

We will assume a confidence interval of 95% and p value of <0.05 to consider that there is a significance difference.

9. ETHICAL AND LEGAL CONSIDERATIONS

The RACECAT protocol was approved on July 8, 2016 by the CEIC of the Germans Trias i Pujol hospital, which acted as the reference CEIC for the study. In addition, the protocol was also presented and approved by the CEIC of each of the hospitals that participated in the study.

Permission will be requested from the RACECAT steering committee to use the data from their study. All the information necessary to carry out this sub-study is in the CICAT database. To access it, the approval of the protocol of this sub-analysis by the CICAT scientific committee is necessary. The objections performed by the scientific committee will be considered and introduced.

All the patients included in RACECAT study signed and have one copy (the other copy is in the database) of a written informed consent (Annex 16.4) where they gave permission to include the clinical data in the electronic register and to be further analyzed, so a new informed consent is not needed. An information sheet on RACECAT study was also given to the patients (Annex 16.5).

Personal data protection will be submitted to the following the *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation* and the *Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los derechos digitales.* Personal data in the database is anonymous (using a number's code) and will only have access the research team for research purposes. Further publication of study results in scientific journals or conferences will maintain patient data confidential.

This study will be done in commensurate with the requirements expressed in the *Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects* signed by the World Health Association in October 2013, and to *ministerial order SAS/3470/2009* defined in the current legislation in Spain related with the conduct of observational studies.

The research coordinator agrees to publish the results of the study when the study is completed, regardless of the study's outcome.

The investigators declare they have no conflicts of interest in any aspect of the study.

10. STRENGTHS AND LIMITATIONS OF THE STUDY

10.1 Study strengths

- Our study is a retrospective subanalysis of a prospective study already performed, so all the data needed for this study are already collected and put into a database. This feature makes it a very quick study to perform and more economical than a prospective study.
- Since all the variables to be studied are already collected and the study model does not require follow-up, there will be no loss of patients in the study.
- The study raises few ethical issues since it is a study where patients do not have to undergo any additional procedures.
- As it is a sub-analysis of a multicenter study (28 centers in Catalonia), the results can be extrapolated to the population of Catalonia.

10.2 Study limitations

- Since is a retrospective study, the study variables are limited to those collected in the RACECAT.
- There are covariates than can modify the results. This confounding bias will be minimized using multivariate analysis to adjust results to the confusing factors.
- Another limitation of the study is that only patients with ICH included in the RACECAT will be included in this study, so that:
    - Only ICHs with RACE > 4 are included.
    - An exclusion criteria of the RACECAT was patients with a decreased level of consciousness and clinical instability, which could exclude some patients with ICH.
- The characteristics of the study are designed according to the pre-hospital stroke code model that exists in Catalonia, so applications outside this territory are limited.
- Secondary outcomes show wide-range results and an unstable regression model because of the small sample size.
- Since there is no stereotyped rehabilitation, each patient can perform more or less post-study rehabilitation, a fact that could influence the results of the RANKIN scale at 90 days.

11. WORK PLAN

11.1 Research team

- Principal investigator: it will be a specialist in intracerebral hemorrhage. He or she will elaborate the protocol and once the statistical analysis is done will participate in the discussion of the results, the elaboration of the final report and posterior dissemination.
- Coinvestigators: neurologists with expertise in intracerebral hemorrhage, from participating centers of the RACECAT study. They will be in charge, with the principal investigator, of deciding the inclusion and exclusion criteria for the study, and drafting the study objectives and variables to be selected from the CICAT to be submitted to the CICAT scientific committee. They will also discuss the results obtained once the analysis is done, as well as the dissemination of the results.
- Statistic specialist: responsible for carrying out statistical analysis.

11.2 Study stages

The study will last approximately 1 year. The different phases that will be followed are detailed below:

STAGE 0: Study request and design. *From September to November 2022*

In this phase, the researchers will contact RACECAT researchers to request a sub-analysis of their study. Once permission is obtained, investigators review relevant literature, and discuss the variables they will need from CICAT database and the methodology of the study. Finally, the study protocol will be elaborated.

- Personnel involved: Main investigator and coinvestigators.

STAGE 1: Scientific committee evaluation. *From November 2022 to January 2023*

The protocol is going to be presented to the scientific committee of CICAT, to access to the database and obtain the variables that the investigators need for the study.

- Personnel involved: Main investigator and the scientific committee of CICAT.

STAGE 2: Coordination meeting. *January 2023*

We will do a coordination meeting with all the people involved with the study to clarify the role of each integrant, as well as define delivery terms.

- Personnel involved: The whole team

STAGE 3: Database creation. *From February to March 2023*

The research team will create a database with all the CICAT variables, to organize them and review if we have all the data of all patients with ICH included in the RACECAT.

- Personnel involved: Principal investigator and coinvestigators

STAGE 4: Statistical analysis. *April 2023*

A qualified statistician will process the data collected by performing a univariate, bivariate and multivariate analysis.

- Personnel involved: Statistician

STAGE 5: Interpretation of the results and article redaction. *From May to July 2023*

The researchers will meet to interpret the results and discuss the findings on the statistical analysis as well as make conclusions.

- Personnel involved: Principal investigator and coinvestigators

STAGE 6: Publication of the article and dissemination of results. *From July to September 2023*

Submission of the article to selected scientific journals and dissemination of the results in meetings, conferences...

- Personnel involved: Principal investigator and coinvestigators

11.3 Chronogram

STAGE	TASK	MEMBER	PERIOD												
			2022				2023								
			SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP
0	Request a sub-analysis of RACECAT	Principal investigator													
	Review literature and discuss methodology of the study	All investigators													
	Protocol elaboration	Principal investigator													
1	Scientific committee evaluation	Principal investigator and scientific committee of CICAT													
2	Coordination meeting	Whole team													
3	Database creation	All investigators													
4	Statistical analysis	Statistician													
5	Interpretation of the results	All investigators													
	Article redaction	Principal investigator													
6	Publication	Principal investigator													
	Dissemination of results	All investigators													

12. BUDGET

The budget that is expected to be spent on carrying out this study is detailed below:

1. Research team: all investigators involved in this study work for their respective hospitals, so there is no additional cost. The only personnel we will need to hire is a qualified statistician.
2. Execution expenses: No costs in this section are expected.
3. Publication of the study: the budget for this part includes revision, edition, formatting layout, graphic design and preparation of the digital data.
4. Attendance to conferences: for the dissemination of the results there is a part of the budget destined to attend to congresses considering the inscription cost and the expenses derived from the trip.

The expected cost for each of these sections is detailed in the following table:

		COST PER UNIT	TOTAL UNIT	FINAL COST
PERSONNEL EXPENSES	Statistician	40 €/ hour	40 hours	1600 €
PUBLICATION EXPENSES	Article publication	2000 €/ study	1 study	2000 €
CONGRES EXPENSES	Inscription to congress	400 €/ person	2 investigators	800 €
	Transport	200 €/ person		400 €
	Accomodation	150 €/ person		300 €
	Meals	200 €/ person		400 €
TOTAL COST				**5500 €**

Table 6. *Study budget.*
Own elaboration.

13. FEASIBILITY

This study is expected to be feasible mainly because of its retrospective design which makes this study low-cost, quick to perform and does not involve any extra procedures for the patient.

The research team will be composed of doctors who are experts in intracerebral hemorrhage and who currently work for their respective hospitals. The only additional member that has to be hired is the statistics specialist.

Patients included in the study are not required to actively participate since all data needed has been already collected, for this reason it is not expected any patient loss.

14. FUTURE DIRECTIONS

One of the main problems in the prehospital transfer of stroke patients is the impossibility of differentiating between them clinically. Therefore, until arrival at the first hospital center where a neuroimaging test is performed, it is not possible to distinguish whether the stroke is of ischemic or hemorrhagic origin. This means that prehospital circuits cannot be adapted to the specific needs of each type of stroke.

Future directions that can help with this problem are:

- *Use of medicalized ambulances for the stroke code*: the stroke code in our country is operated by basic ambulances, in which no drugs can be administered. We could study the cost-benefit of a medicalized ambulance for stroke code in which blood pressure and fever, among others, could be controlled earlier.
- *Mobile stroke units (MSU)*: consist of ambulances with a CT, a laboratory, and the possibility of administering drugs (fibrinolytic treatment or reversal anticoagulant treatment). Broadly speaking, it could be defined as "bringing the hospital to the patient". These units allow for a shorter time to treatment, as well as a vascular imaging-based triage of patients (40). Studies suggest that they reduce 90-day mortality compared to ambulance care. In our territory they haven't been studied yet, so it will be great to study the impact on patients as well as the cost-benefit of MSU in the coming years.

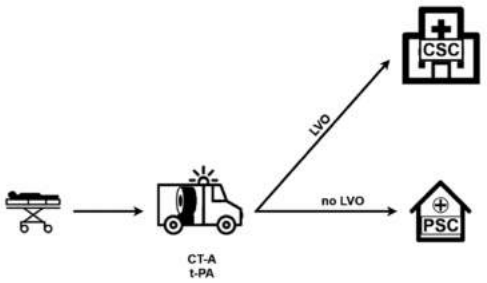

Figure 14. *Pre-hospital circuit with a MSU.*

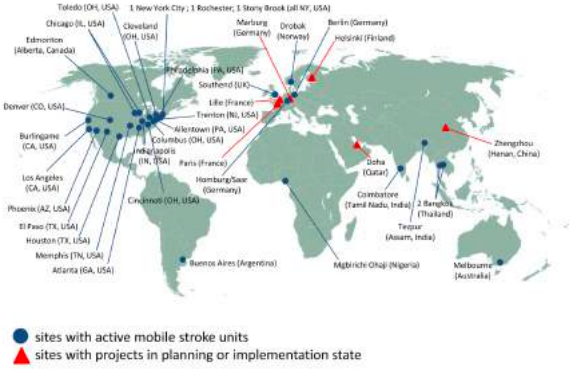

Figure 15. *World map of mobile stroke unit projects. From (40)*

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16. ANNEXES

16.1 NIH stroke scale

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

N I H STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

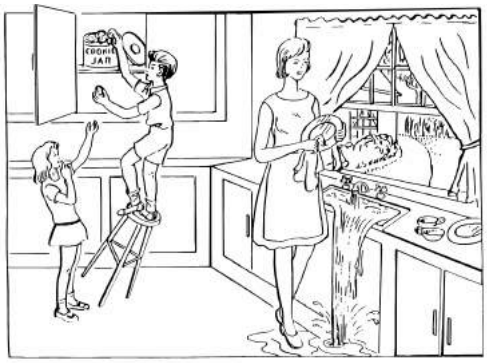
Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. **Extinction and Inattention (formerly Neglect):** Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality**; does not recognize own hand or orients to only one side of space.	_____



You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

16.2 Rankin scale

Rater Name: _____

Date: _____

Score Description

0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

16.3 RACE scale

RACE SCALE	
1. Facial palsy:	
Facial movement is normal, symmetric	0
Facial gesture when showing the teeth or smiling is slightly asymmetrical	1
Facial gesture when showing the teeth or smiling is completely asymmetrical	2
2. Arm motor function:	
Maintain the arm against gravity >10 seconds	0
Maintain the arm against gravity <10 seconds	1
Cannot maintain the arm against gravity and drops immediately	2
3. Leg motor function:	
Maintain the leg against gravity >5 seconds	0
Maintain the leg against gravity <5seconds	1
Cannot maintain the leg against gravity and drops immediately	2
4. Head and gaze deviation	
Absent	0
Present	1
5A. Agnosia / Negligence (if left hemiparesis)	
Asomatognosia (do not recognize the left part of his/her body) *Anosognosia (do not recognize his/her weakness)*	
There is no asomatognosia nor anosognosia	0
There is asomatognosia or anosognosia	1
There is asomatognosia and anosognosia	2
5B. Aphasia / Language (if right hemiparesis)	
Ask the patient: "Close your eyes" and "Make a fist"	
Perform both tasks correctly	0
Perform one task correclty	1
Perform neither tasks	2
TOTAL	

16.4 Information sheet of RACECAT

Promotor: Fundació privada ICTUS malaltia vascular
Código del estudio: RACECAT Versión 3 de fecha 06 June 2019

HOJA de INFORMACIÓN al PACIENTE

Estudio Comparando el T**RA**slado de Pacientes con Ictus Agudo y Sospecha de Oclusión de Gran Vaso Cerebral al **CE**ntro Local de Ictus más Cercano vs. Traslado Directo a un Centro Endovascular en el territorio **CAT**alán (RACECAT)

1. INTRODUCCIÓN

Nos dirigimos a usted para invitarle a participar en el estudio RACECAT, promovido por la *Fundació Privada ICTUS Malaltia Vascular*, que se llevará a cabo en varios hospitales de Cataluña.
Antes de que usted acepte, es importante que entienda el objetivo de este estudio y lo que supone para usted participar en él.
Por favor tómese el tiempo necesario para leer cuidadosamente y entender la siguiente información. Su médico le aclarará las dudas que le puedan surgir después de leer esta hoja y además, puede consultar con las personas que considere oportuno, antes de tomar una decisión.
Se le invita a participar, porque usted ha sufrido un ictus o accidente vascular cerebral con sospecha de oclusión de una arteria importante del cerebro (gran vaso cerebral) y ha sido trasladado para su tratamiento, mediante una ambulancia del servicio de emergencias médicas (SEM), a un centro hospitalario del territorio catalán.

2. OBJETIVO DEL ESTUDIO

El estudio RACECAT pretende comparar dos estrategias:

A) el traslado en ambulancia al centro hospitalario más cercano donde se pueda ofrecer una primera valoración y tratamiento del ictus, tras lo cual, si el equipo médico lo considera necesario, se procederá al traslado a otro hospital en el que se pueda realizar un tratamiento endovascular (procedimiento para abrir la luz del vaso mediante la introducción de catéteres),
B) el traslado directo a un centro hospitalario donde se pueda realizar un tratamiento endovascular.

Se realizará un seguimiento clínico observacional de los participantes hasta los 90 días, a fin de determinar en qué grupo de estudio la evolución ha sido más favorable.
En la actualidad se desconoce qué circuito de traslado permite a los pacientes que sufren un ictus con una oclusión de gran vaso acceder al tratamiento más efectivo lo antes posible. Este es el motivo de realizar el estudio RACECAT.

3. METODOLOGÍA EMPLEADA

En este estudio se incluyen pacientes que presenten un ictus agudo con sospecha de oclusión de gran vaso, lo cual se evalúa a través de la escala neurológica RACE. Dicha escala es de fácil uso a nivel extra-hospitalario, y permite hacer una valoración de la gravedad del ictus, detectando los pacientes más graves y con mayor probabilidad de tener una oclusión de gran vaso.
Tras la identificación de un paciente candidato, el personal del SEM contacta con un neurólogo vascular de guardia (que abarca la red Teleictus) quien confirma los criterios de elegibilidad y asigna el circuito de traslado de acuerdo con un calendario previamente elaborado. Una vez trasladado al centro hospitalario, los pacientes incluidos reciben el tratamiento de su enfermedad de acuerdo con la práctica clínica habitual.
El consentimiento del paciente o representante, para la recogida de datos del registro, se obtiene posteriormente.Si decide que está dispuesto a participar, se le pedirá a usted o a su representante (cuando su condición médica le impida entender este escrito) que firme este documento de consentimiento informado para la recogida de datos médicos.

El personal del estudio, sólo observará y documentará estos datos acerca del tratamiento que usted reciba y su evolución hasta los 90 días después del ictus.
Durante el estudio, se recogerá información acerca de cualquier acontecimiento relacionado con la salud y otros datos acerca de su condición y evolución clínica.

4. COLABORACIÓN DEL PARTICIPANTE EN EL ESTUDIO

Si usted decide participar en el estudio RACECAT, deberá dar su consentimiento por escrito después de haber leído esta hoja detenidamente y de haber realizado las preguntas que crea oportunas a su médico.
Usted recibirá una copia de este documento firmada por el investigador, para que la conserve.
La duración del seguimiento del estudio será de 90 días y se recogerán datos clínicos en distintas ocasiones: al inicio de su participación, a las 24 horas de su ingreso, a los 5 días o al alta (lo que ocurra antes) y a los 90 días de haber sufrido el ictus.
En cada visita del estudio, sea presencial o telefónica, se recopilarán datos de su historial médico que sean de interés para el estudio, así como los medicamentos que toma habitualmente y el tratamiento recibido para el ictus. También se recopilarán datos acerca de las exploraciones médicas habituales, se evaluará su estado clínico y se registrará cualquier complicación relevante en su evolución.
Aunque decidiera no participar en este estudio, estas exploraciones se le realizarían igualmente, para diagnosticar adecuadamente el alcance de su enfermedad y evaluar su evolución tras el tratamiento recibido.
El registro no exige ninguna prueba adicional durante el periodo en estudio, sólo se le realizarán las que su médico considere necesarias debido a su estado de salud.
Es importante que mientras participe en el registro, informe a su médico o personal del estudio, acerca de cualquier hospitalización o visita a urgencias, así como de cualquier síntoma o molestia que experimente, tan pronto como le sea posible.

5. BENEFICIOS ESPERADOS Y RIESGOS POTENCIALES

Puede ser que usted no obtenga ningún beneficio personal por su participación en este estudio, pero los resultados del mismo contribuirán al avance del conocimiento en esta área médica.
Como el presente estudio es observacional su participación en este proyecto no supone ningún riesgo adicional para usted.
Su médico le informará acerca de los riesgos generales asociados al ictus agudo con oclusión de gran vaso cerebral y su tratamiento.

6. PARTICIPACIÓN VOLUNTARIA

Su participación en este estudio es voluntaria, por lo que es usted libre de negarse a participar. También puede retirarse del estudio en cualquier momento, sin dar ninguna razón, comunicando su decisión al investigador responsable o a cualquier miembro del personal asignado al estudio.
Su decisión de no participar en este estudio o de retirarse, no afectará en ningún caso la calidad de la atención, ni a los servicios a los que tiene derecho, ni a su relación con el investigador responsable del estudio u otros implicados.
Su médico o el promotor pueden decidir suspender su participación en el registro en cualquier momento y sin su consentimiento previo. Si esto sucede, recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio.

7. PROTECCIÓN DE DATOS PERSONALES Y CONFIDENCIALIDAD

Su participación en el estudio RACECAT es totalmente confidencial.

El promotor se compromete a cumplir con la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales complementaria del Reglamento (EU) 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD).

De acuerdo con lo que establece la ley de protección de datos, usted tiene derecho al acceso, modificación, oposición y cancelación de datos, y puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Igualmente, tendrá derecho a retirar el consentimiento sobre el tratamiento de datos, no obstante, dicha retirada podría determinar su cese en la participación del ensayo. Para ejercitar sus derechos, diríjase al investigador principal del estudio. Le recordamos que los datos no se pueden eliminar, aunque deje de participar en el ensayo o aunque retire su consentimiento sobre el tratamiento de datos para garantizar la validez de la investigación y cumplir con los derechos legales y los requisitos de autorización de medicamentos. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

Tanto el Centro como el Promotor son responsables respectivamente del tratamiento de sus datos y se comprometen a cumplir con la normativa de protección de datos en vigor. Los datos recogidos para el estudio se identificarán mediante un código, de manera que no incluya información que pueda identificarle, y solo su médico del estudio / colaboradores podrán relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a ninguna otra persona salvo a las autoridades sanitarias, cuando así lo requieran o en casos de urgencia médica o requerimiento legal.
El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustarán a lo dispuesto en esta ley.

Los datos se recogerán en un fichero de investigación responsabilidad de la institución y se tratarán en el marco de su participación en este estudio.

Es un requerimiento que su participación en este estudio se refleje en su historial médico.

El promotor adoptará las medidas apropiadas para garantizar la protección de su privacidad y no permitirá que sus datos se crucen con otras bases de datos que pudieran permitir su identificación.
Los Comités de Ética de la Investigación, los representantes de la Autoridad Sanitaria en materia de inspección y el personal autorizado por el Promotor (monitores, auditores, etc.), únicamente podrán tener acceso para comprobar los datos personales, los procedimientos del estudio clínico y el cumplimiento de las normas de buena práctica clínica (siempre manteniendo la confidencialidad de la información).

El Investigador y el Promotor son responsables de conservar los datos recogidos para el estudio al menos 5 años tras su finalización. Posteriormente, su información personal solo se conservará por el centro para el cuidado de su salud y por el Promotor para otros fines de investigación científica (si así se especifica en el CI), y si así lo permite la ley y los requisitos éticos aplicables.

Si usted decide retirar su consentimiento para participar en este estudio, ningún dato nuevo se añadirá a la base de datos, pero sí se utilizarán los que ya se hayan recogido.

Si realizáramos transferencia de sus datos codificados fuera de la UE a las entidades de nuestro grupo, a prestadores de servicios o a investigadores científicos que colaboren con nosotros, los datos del participante quedarán protegidos con salvaguardas tales como contratos u otros mecanismos por las

autoridades de protección de datos. Si el participante quiere saber más al respecto, puede contactar al Delegado de Protección de Datos del promotor (francesciglesias@fundacioictus.com).

8. COMPENSACIÓN

Su participación en este estudio no le supondrá ningún gasto, pero tampoco recibirá ninguna compensación por su participación en el mismo.
Le informamos que la realización de este estudio conlleva un trabajo de investigación específico por lo que, tanto el hospital como los profesionales que participan en él, pueden recibir una compensación económica por parte del promotor.

9. ASPECTOS ÉTICOS

El Comité Ético de Investigación Clínica del hospital aprobó este proyecto de investigación, así como esta hoja de información y consentimiento, según regulación aplicable a este tipo de estudios.
Además, deberá aprobar cualquier revisión o modificación del protocolo de investigación, de la hoja de consentimiento informado o de la hoja de información al paciente.
El presente estudio se llevará a cabo de acuerdo a lo establecido en el RD 1090/2015 de 4 de diciembre, que regula los ensayos clínicos con medicamentos, Real Decreto Legislativo 1/2015, de 24 julio Ley de garantías y uso racional de medicamentos y productos sanitarios, Real Decreto 577/2013 de 26 de julio, que regula la farmacovigilancia y la Orden SAS/3470/2009, de 16 de diciembre, sobre estudios posautorización, todas ellas en lo que les sea de aplicación, así como la Declaración de Helsinki y las guías de buena práctica clínica.

10. PREGUNTAS

Si tiene alguna pregunta sobre el estudio, le rogamos se comunique con el investigador responsable o el personal implicado en el estudio:

Investigador Principal: Dr.……..
Teléfono: ……

16.5 RACECAT informed consent

Promotor: Fundació privada ICTUS malaltia vascular
Código del estudio: RACECAT Versión 3 de fecha 06 June 2019

CONSENTIMIENTO por ESCRITO del PACIENTE

Estudio Comparando el T**RA**slado de Pacientes con Ictus Agudo y Sospecha de Oclusión de Gran Vaso Cerebral al **CE**ntro Local de Ictus más Cercano vs. Traslado Directo a un Centro Endovascular en el territorio **CAT**alán (RACECAT)

Yo (nombre y apellidos) .....

He leído la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido respuestas satisfactorias a mis preguntas.

He recibido suficiente información sobre el estudio.

He hablado con el Dr: .....

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:
1º Cuando quiera
2º Sin tener que dar explicaciones
3º Sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

_____	_____
Fecha (paciente)	**Firma del paciente**
_____	_____
Fecha (investigador)	**Firma del investigador**

1 ejemplar para el paciente, 1 ejemplar para el investigador