



Universitat de Girona

# Blood pressure levels and haematoma growth in patients with Intracerebral Haemorrhage (ICH)

A retrospective observational study



**FINAL DEGREE PROJECT**

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# **BLOOD PRESSURE LEVELS AND HAEMATOMA GROWTH IN PATIENTS WITH INTRACEREBRAL HAEMORRHAGE**

A retrospective observational study

## **1) Abstract**

Intracerebral haemorrhage (ICH) is a spontaneous extravasation of blood into brain parenchyma. Although ICH represents approximately only 15% of all strokes, it is one of the major causes of stroke-related death and disability. One of the causes of poor outcome is the haematoma growth.

The association between elevated blood pressure (BP) and haematoma enlargement in acute ICH has not been clarified. Our objective is to try to identify this relationship that may suggest an immediate target for intervention to possibly improve outcomes in patients with spontaneous ICH and might settle the controversy surrounding the optimal management of blood pressure. We propose a retrospective revision using a sample present in our database of approximately 250 patients with primary ICH and less than 12h from symptoms onset. Systolic blood pressure levels (SBP) are assessed at baseline, at 6h, at 12h, at 24h and at 72h, being these last four the average levels of the different recordings during those time intervals. Haematoma growth will be defined as an increase in the volume of intraparenchymal haemorrhage of >33% as measured by image analysis on the 24-hour CT or 72-hour CT compared with the baseline CT scan. A qualified neuroradiologist not informed of the aim of the study, will review the CT images. The secondary objective will be to correlate the BP levels in the acute phase of ICH with clinical outcome. We will evaluate early neurologic deterioration at 72h by using the National Institutes of Health Stroke Scale (NIHSS); outcome at 90 days by using the modified Rankin scale and mortality at 72h and 90 days. The statistical analysis will be adjusted by possibly confounding variables.

Keywords: ■ *Intracerebral haemorrhage* ■ *haematoma growth* ■ *blood pressure* ■ *clinical outcome*

## **2) INTRODUCTION**

Intracerebral haemorrhage (ICH) is a spontaneous extravasation of blood into brain parenchyma. The overall incidence of ICH is 12 to 15 cases per 100,000 per year<sup>(1)</sup> and it is the cause of 10% to 15% of first-ever strokes.<sup>(2)</sup> In Spain the incidence is similar with 15 cases per 100000 per year, being more frequent in males over 55 years-old.<sup>(3)</sup>

More than 85% of ICH occurs as a primary (spontaneous) event related to the rupture of small penetrating arteries and arterioles that have been damaged by chronic arterial hypertension or amyloid angiopathy. Hypertension is responsible for between 60% and 70% of primary ICH<sup>(4)</sup> and in the elderly amyloid angiopathy accounts for up to one-third of the cases.<sup>(5)</sup> Secondary ICH can be related to multiple causes such as vascular malformation, coagulopathies and tumours.<sup>(5)</sup>

Although ICH accounts for only 10% to 30% of all stroke-related admissions to hospital, it is one of the major causes of stroke-related death and disability. Overall mortality ranges from 30% to 52% at 30 days, and approximately half of all ICH-related mortality occurs within the first two days after the initial haemorrhage.<sup>(6)</sup> Functional outcome in survivors is also poor with fewer than 20% being independent at six months.<sup>(2)</sup> However, there are no specific therapeutic options and treatment is based on general measures and the surgical approach is only useful in very specific cases<sup>(2)</sup>

ICH was previously considered to be a single haemorrhagic event with the whole volume being reached at the beginning, but it is now known that it is a complex, dynamic process with three distinct phases: 1) initial vascular rupture, 2) haematoma expansion, and 3) perihematoma oedema.<sup>(7-9)</sup>

Disease progression and outcome are primarily influenced by two of these factors: haematoma expansion and perihematoma brain oedema.

Perihematoma brain oedema develops early, evolves over many days, and could be a cause of neurological deterioration after the first day.<sup>(10)</sup> However, the studies performed have failed to agree as to whether oedema is relevant for the clinical outcome.<sup>(11)</sup>

Haematoma growth occurs mainly in the first six hours.<sup>(12,13)</sup> In one study, haematoma volume increased significantly (>33% from baseline or >12.5 mL) in the first 24 hours in approximately one-third of patients.<sup>(14)</sup> In another study, 38% of patients had an increase in haematoma volume of >33% within 24 hours of stroke onset and, in two-thirds, the haematoma growth was present within one hour of the baseline scan, suggesting continued bleeding in the hyperacute phase. Haematoma growth was associated with early neurological deterioration.<sup>(15)</sup>

The mechanisms of early haematoma growth are unclear but are thought to be related to sudden increases in intracranial pressure (ICP), causing local tissue distortion and disruption, vascular engorgement secondary to obstructed venous outflow, blood-brain barrier disruption, and a local coagulopathy secondary to the release of tissue thromboplastin.<sup>(16)</sup>

Haematoma expansion is an important cause of early neurological deterioration, the severity of which depends on original haematoma size and the subsequent expansion rate.<sup>(15)</sup> There is an exponential increase in mortality when the haematoma volume exceeds 30mL.<sup>(17)</sup> The 30-day mortality of patients with haematoma volume >60 mL in association with a Glasgow Coma Scale (GCS) score <8 is >90%, compared with 19% for those with a haematoma volume <30mL and a GCS score >9.<sup>(6)</sup>

Factors that have been proved to be related with poor prognosis and mortality in ICH are large haematoma volume (>30mL), poor neurological condition at admission, intraventricular bleeding, do-not-resuscitate orders and haematoma growth (each 10% enlargement of the haematoma resulting in a 5% increased hazard of death).<sup>(18-20)</sup> We can have no influence over the first three factors but haematoma growth can potentially be modified.<sup>(18)</sup>

Therapeutic efforts to stop this growth have been mainly focussed on two strategies: the administration of recombinant factor VIIa and blood pressure (BP) management.

Haemostatic therapy was one of the most promising therapeutic options available to us. Factor VIIa, a potent initiator of haemostasis, acts locally in areas of tissue damage and altered vascular wall by binding to the tissular factor, generating small amounts of thrombin, which in turn causes platelet activation. In 2005, a phase IIb placebo-controlled study showed that treatment with recombinant factor VII (rFVIIa) within four hours of ICH significantly reduced haematoma growth in association with a reduction in mortality and improved functional outcome in survivors at three months.<sup>(21)</sup> This improvement was seen despite a small increase in thromboembolic complications in rFVIIa-treated patients (7% vs. 2% for rFVIIa and placebo, respectively,  $p=0.12$ ). However, a subsequent phase III trial in 841 patients, the Factor VII for Acute Hemorrhagic Stroke (FAST) study, failed to replicate these clinical outcomes.<sup>(22)</sup> In this two-dose study (rFVIIa 20 and 80  $\mu\text{g}/\text{kg}$ ), the dose-related reduction in haematoma expansion was not found to be associated to a decrease in the risk of death and severe disability. Post hoc analysis of the FAST data suggests that rFVIIa might be effective in a subgroup of younger patients (<70 years) with baseline ICH volume <60 mL if administered within 2.5 hours of the onset of symptoms with the exclusion of low Glasgow scores and infratentorial haemorrhage.<sup>(23)</sup> Early CT angiography might identify patients most at risk of haematoma expansion and who therefore might have the most to gain from rFVIIa treatment.<sup>(24)</sup> Further studies are required to define more accurately the potential target population that might benefit from rFVIIa. Until such time, investigations are restricted to the management of BP.

BP monitoring and management is critical after ICH, but the targets for treatment remain controversial.<sup>(2)</sup> Even in previously normotensive patients, hypertension is a very common finding (up to 90% of the patients) and is associated with worse outcome, probably due to the fact that hypertension is a cause of haematoma expansion. This conclusion has been supported

by some retrospective studies<sup>(25-27)</sup> but prospective studies have found the relationship between these two variables to be inconsistent.<sup>(15,28,29)</sup>

Aggressive BP lowering may reduce haematoma expansion and is a strategy that is widely available even in the absence of specialized equipment or personnel. A report from the National Institute of Neurological Disorders and Stroke Workshop on priorities for clinical research in ICH in December 2003 recommended that clinical trials should be conducted to evaluate BP management in acute ICH as a main priority.<sup>(30)</sup>

A small, single-centre study suggested that BP reduction in patients with acute ICH is safe and that aggressive reduction might reduce the risk of neurological deterioration in the first 24 hours after admission.<sup>(31)</sup> Two recently completed multicentre studies have provided more robust preliminary data on BP control after ICH. In the INTensive blood pressure Reduction in Acute Cerebral haemorrhage Trial (INTERACT) 404 patients with ICH were randomized within six hours of stroke onset. 203 patients were assigned to a group in which they were required to reach a target SBP of 140 mmHg within one hour and maintained for at least 24 hours after ICH. A second group was made up of 201 patients who were set a more conservative SBP target of 180 mmHg.<sup>(32)</sup> This pilot study established the safety of decreasing BP, determined by the absence of a significant excess risk of death, dependency, or cardiovascular morbidity, within the first hours of ICH, and demonstrated a tendency toward reduction of haematoma expansion within the first six hours. As this study was not designed to detect clinical outcomes, a further study, INTERACT2, assessed whether early intensive BP-decreasing therapy can reduce death and disability after ICH in 2800 patients.<sup>(33)</sup> The results from this study have shown that blood pressure treatment continues to be safe and effective in secondary outcomes, although the rate of primary outcomes (death or major disability) was not significantly affected. The fact that it was only possible to achieve the target BP in the aggressively treated group in only 33.4% of patients during the first hour after the stroke may explain the lack of significant results.

The Antihypertensive Treatment in Acute Cerebral Haemorrhage (ATACH) study evaluated the feasibility and safety of three escalating levels of antihypertensive treatment with IV nicardipine in patients with ICH-related acute hypertension.<sup>(34)</sup> The three levels were SBP between 200 and 170 mmHg; SBP between 170 and 140mmHg, and SBP between 170 and 140mmHg. Preliminary data from this study suggest that a reduction in the SBP to 110-140 mmHg in the first 24 hours after ICH is well tolerated and associated with a reduced risk of haematoma expansion, neurological deterioration, and in-hospital mortality. Only patients with a presentation GCS score >8 and haematoma volume <60mL were recruited into the ATACH study so its results will be relevant only to the less severe end of the ICH spectrum.

A new study, ATACH2, is now underway.<sup>(35)</sup> This study is expected to reach firm conclusions as to the therapeutic benefits of the intensive treatment and to evaluate the benefit in the proportion of haematoma expansion. INTERACT3, which will evaluate the effect of a particular drug on the reduction of BP, is currently being set up.

Before this current set of studies, other studies were published associating aggressive BP reduction with poor outcome. A retrospective review found that a rapid decline in MAP within 24h after presentation was independently associated with increased mortality.<sup>(36)</sup> One of the possible explanation was that haematoma may produce a zone of ischaemia in the surrounding tissue. Adequate cerebral blood flow (CBF) in the ischaemic penumbra is necessary for viability, so the BP lowering could have increased the ischaemia, so explaining the poor clinical outcome. Furthermore, the cerebral autoregulation of patients with chronic hypertension shifts to the right increasing vulnerability to hypotension. This may explain the conservative treatment of BP levels in the acute phase of the ICH. Nevertheless, this hypothesis cannot be regarded as having been proven. One study, using multisequence magnetic resonance imaging (MRI) protocols, found no evidence of potentially salvageable ischaemic penumbra in the acute phase after ICH, suggesting that perihematoma hypoperfusion is a consequence of reduced metabolic demand rather than true tissue ischaemia.<sup>(37)</sup> Furthermore, the ATACH and INTERACT studies, as has been said before, seem to tip the scales in favour of the safety of rapid BP reduction.

The continued controversy over the targets for BP control after ICH is reflected in current management guidance, which is based simple on expert recommendations rather than evidence from clinical trials as to when to start and how aggressive the treatment should be.

The American Heart Association/American Stroke Association recommends the following cautious management of severe hypertension with continuous infusion of antihypertensive drugs such as labetalol, esmolol, or nicardipine: if SBP is >200 mmHg or mean arterial blood pressure (MAP) >150 mmHg, aggressive BP reduction, guided by frequent BP monitoring (at least every 5 minutes), should be considered; if SBP is  $\geq$ 180 mmHg or DBP is  $\geq$ 105 and there is no evidence or suspicion of increased ICP, a modest reduction in BP to 160/90 mmHg (MAP 110 mmHg) is recommended.<sup>(2)</sup>

The European Union Stroke Initiative (EUSI), however, recommends BP targets determined by the premorbid state of the patient.<sup>(38)</sup> An upper limit of SBP of 180 mmHg and a diastolic BP of 105mmHg is recommended for patients with known hypertension or signs of chronic hypertension (e.g., electrocardiogram or retinal changes) and, if treatment is necessary, the recommended target BP is 160/100 mmHg (or MAP 120 mmHg). In patients without known hypertension, the upper recommended limits are 160/95 mmHg, and the target BP is 150/90 mmHg (or MAP 110 mmHg). However, the EUSI also recommends that mean BP reduction should always be limited to  $\leq$ 20% of baseline. The optimal timing of conversion from IV to oral antihypertensive therapy is unknown but, in stable patients, a time of between 24 to 72 hours is usually recommended.

Given this current state of knowledge, we were interested in investigating whether there is an association between high blood pressure levels and haematoma expansion. Since the haematoma growth is an independent predictor of both mortality and poor functional outcome, and also a potentially modifiable factor, the prevention of such expansion by appropriate management of blood pressure levels could represent an opportunity to improve the evolution of these patients.

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## **4) HYPOTHESIS**

- High blood pressure levels are associated with hematoma growth and poor outcome in patients with Intracerebral Haemorrhage (ICH)

## **5) OBJECTIVES**

- To evaluate whether high BP levels in the acute phase of ICH are associated with posterior haemorrhage growth
- To investigate whether BP levels during the acute phase of ICH are related with clinical outcome

## **6) METHODOLOGY**

### Study design

Historical cohort: Retrospective revision with prospectively collected patient data.

### Study subjects

Patients admitted to the Doctor Josep Trueta University Hospital in Girona with the diagnostic of a primary hemispheric ICH between 2005 and 2013.

- Inclusion criteria:
  - Patients above 18 years old
  - ICH of less than 12 hours from symptoms onset
  - Previously independent (Rankin scale of  $\leq 2$ )
- Exclusion criteria:
  - Patients with initial coma state (defined as a score of 3-5 on the Glasgow Coma Scale).
  - Patients with terminal illness (expected to live less than 6 months).
  - Patients with secondary-related haematomas: anticoagulant treatment (ACO), arteriovenous malformation, tumour or traumatism.
  - Patients with early surgery planned to evacuate the haematoma

## Sample and sampling

A non-probabilistic consecutive sampling-method is used. The sample is collected from a previous database in our hospital.

We expect a study-population of around 250 patients with the characteristics listed before. Each year there are about 500 stroke-related admissions in our hospital within the 15% being ICH. It means 75 patients each year in our database that becomes more or less a sample of 50 patients after the exclusion of the ones that don't match criteria for our study.

To get an idea of the power that would give us our sample size if we separated it into a group with normal BP levels and another with hypertension we can use as an example the INTERAC1 trial because it had a sample size quite similar to ours. In that case, accepting an alpha-risk of 0,05 in a bilateral contrast with 174 patients in the intensive treatment group and 172 in the guideline group, the power of the hypothesis testing is of 85% to detect as statistically significantly the difference between the 0,16 in the first group and the 0,06 in the second group referring to haematoma growth.

## Variables

### Sociodemographic variables

- Sex
- Age

### Clinical variables

- Date and time of stroke onset. Time of stroke onset is defined on the basis of initial symptoms observed by the patient or by a witness. In some cases, the precise time of onset could not be identified because the patient was found unconscious or aphasic. We include those patients who were last seen as asymptomatic at a time that was not more than 12 hours before the time that they arrived to the hospital.
- Presence of vascular risk factors: hypertension, diabetes, previous stroke, dementia, coagulopathy, smoking and alcohol habits.

### Outcome variables

- **Early neurological deterioration:** by using the validated NIHSS: National Institutes of Health Stroke Scale (explained in the annexes). The NIHSS is evaluated every day by the neurologists. We consider early neurological deterioration (dependent variable of the secondary objective of the study) as an increase in  $\geq 4$  points in the scale between the baseline and the assessment at 72h.

- **Outcome:** Evaluated by using the modified Rankin Scale (mRS, see in the annex) at 90 days in the outpatient control by the neurologists. Clinical outcome (dependent variable of the secondary objective of the study) will be defined as:
  - Poor prognosis if there is a punctuation of  $>2$  in the mRS (including dead since it's a punctuation of 6 in the scale).
  - Good prognosis if there is a punctuation of  $\leq 2$  in the mRS
  
- **Mortality:** Considered at the first 72h and at 90 days. It is also a dependent variable of our second objective and it is defined as: Yes/No.

### Neuroimaging variables

- **ICH volume:** Calculated on the cranial computed tomography scan (CT) at baseline (after the blood-extraction sample), at the 24h and at 72h.

The CT scans are performed and evaluated applying the same protocol. The slices are parallel to the orbitomeatal line. The images are obtained with the use of a 350x350 matrix with a variable thickness depending on the localization. The slices in the posterior cranial fossa have a thickness between 2,5 and 3mm with a 5mm of interval. The supratentorial slices have 8mm thickness and also 8mm interval. All are non-contrast CT scans.

A qualified neuroradiologist, blinded to clinical and outcome variables, will review the CT images.

The volume is calculated by the formula  $(A \times B \times C)/2$ , where A is the greatest longitudinal haemorrhage diameter by CT, B is the greatest axial diameter perpendicular to A, and C is the number of CT slices with haemorrhage multiplied by the slice thickness.

Other things evaluated in the CT apart from the volume size are: previous ischemic lesions, leucoaraiosis, intraventricular haemorrhage (IVH), associated mass effect (midline shift, decreasing in ventricular size, cistern obliteration) and the site of the haematoma (lobar or deep).

The images are copied as computer files in DICOM format concealing all personal identification and stored in the SAP computer software.

- **Hematoma growth** (as the principal dependent variable of our study): will be defined as an increase in the volume of intraparenchymal hemorrhage of  $>33\%$  as measured by image analysis on the 24-hour CT or 72-hour CT compared with the baseline CT scan. A 33% change in the volume of a sphere corresponds to a 10% increase in diameter, a clear difference to the naked eye of a physician viewing serial CT scans of a patient with ICH. . In this way we are able to be confident that the CT definition of growth represents true haemorrhage growth and not variability in CT imaging.

**Analytical variables**

- Laboratory: leucocytes, platelets, hematocrit, hepatic enzymes (AST and ALT), INR, fibrinogen. These variables were evaluated with the routine baseline blood test before any treatment.
- Tympanic temperature. Evaluated at admission
- **BP levels:** SBP and DBP will be assessed repeatedly during hospitalization. The first measurement will be the baseline when the patient enters the emergency room. After the initial evaluation and treatment (if necessary) the patient is moved to the Stroke Unit where the BP is monitored constantly. In the first few hours the consecutive BP levels are recorded more frequently: every hour during the first 24 hours and later every 8h until the 72h, by which time stabilization is usually achieved. Any marked changes in BP will result in the BP being recorded more frequently.

BP measures were recorded and introduced in the SAP computer software by nursing staff. These measurements were extracted from there for the analysis of the variable.

The recordings are all cuff measurements. We used a digital sphygmomanometer (GE Critikon Classic-cuf, adult size, 23-33 cm, navy, latex free). All sphygmomanometers used are calibrated periodically. The cuff is adequate for the upper arm perimeter of each patient and the measurement is always applied on the non-paretic arm (if existing).

It is important to note that all patients receive BP treatment if  $SBP \geq 180\text{mmHg}$  and/or  $DBP \geq 105\text{mmHg}$ , according the American Guidelines recommendations that are also implemented in the stroke protocols of our hospital. Labetalol or urapidil are used for this treatment.

To set up the independent variable of our study, SBP levels will be analyzed:

- At baseline (only one measurement). Before treatment and excluded from the analysis.
- At 6h: the average between the one after the baseline and 6h]
- At 12h: average between (6h and 12h]
- At 24h: average between (12h and 24h]
- At 72h: average between (24h and 72h].

The results of BP levels will be classified into 4 groups at each time point for the second part of the statistical analysis (explained below):

- 1) SBP<140mmHg
- 2) SBP 140-160mmHg
- 3) SBP 160-180mmHg
- 4) SBP>180mmHg.

The groups two and three received special attention because, nowadays, as we said before, we treat BP levels when SBP $\geq$ 180 and/or DBP $\geq$ 105. We think that if we observed ICH growth in patients with BP measurements between 140 to 180mmHg, treatment recommendations would be different.

### **Treatment variables**

- BP treatment received: We recorded if the patient received any treatment and which one. As said, treatment was applied when SBP $\geq$ 180 and/or DBP $\geq$ 105

### **Data source**

We work with a pre-existent database in our hospital prospectively collected with the aim to study the haematoma growth. Inclusion criteria were previously independent patients admitted at our centre with a diagnosis of a primary ICH of less than 12 hours from symptoms onset.

All the patients from our sample were prospectively included in this database and data were retrospectively incorporated. The process used for the collection of this data has been explained before. We selected the variables that we needed for our study from the database.

## **7) STATISTICAL ANALYSIS**

### **Univariant description:**

- Independent variable: **BP levels.**
  - 1) For the first statistical analysis it will be presented as a continuous normal-distributed variable during the whole evolution in time. Described by averages and standard deviation.
  - 2) For the second statistical analysis it will be presented as a qualitative categorical and ordinal variable. Described by proportions
- Dependent variables:
  - **Hematoma enlargement.** Categorical nominal dichotomous variable. Described by proportions.



- **Prognostic:** Categorical nominal dichotomous variable. Described by proportions.
- **Neurological deterioration:** Categorical nominal dichotomous variable. Described by proportions.

The bivariate analysis: The comparison of a continuous normal-distributed variable with a categorical one will be realized with a Student's t-test. The comparison of two categorical variables will be realized with a Chi-squared test.

Multivariate analysis:

- 1) For the association between BP levels over time and haematoma enlargement, we will use a General Linear Mixed Model of repeated measures (GLMM) adjusted for the co-variables\*. BP levels will be expressed as a continuous variable and evaluated during the whole evolution in time.
- 2) For the rest of the analysis (second part) we will use a Logistic Regression Model adjusted for the co-variables\*. Here the BP levels will be expressed as a qualitative ordinal variable with 4 grades.

\*co-variables: the ones with probability values of  $p < 0,05$  obtained during the bivariate analysis.

## **8) ETHICAL AND LEGAL ASPECTS**

We worked on a database from previous prospective study where the written informed consent was already given (annex) by patients or by legal surrogate (for those who were unable to give consent themselves). Informed consent was obtained at admission and was in accordance with national regulations (*Ley Orgánica 15/1999, del 13 de diciembre, de Protección de Datos de Carácter Personal*). The study protocol was approved by the appropriate ethics committee at each participating site, in this case by the "CEIC" (Comité Ètic d'Investigació Clínica) of "Hospital Doctor Josep Trueta".

We guarantee the anonymity of the patient's data. The database uses the medical record number instead of the names of patients.

The study also respects the *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. June 1964. Last revision, October 2013.*

## **9) STUDY LIMITATIONS**

- As it is an historical cohort, it is difficult to control the possible confounding variables. In order to avoid this problem we collected data for those variables that we thought could influence the results (based also with those collected in previous studies). Then we adjust the results with a multivariate analysis.
- The sample size is small but reasonable according to the possibilities in our hospital (the cohort is been running during 5 consecutive years). In order to solve this problem we could wait more years before starting to have more patients in our database, or it would be better to perform a multicentre study.
- Inter-observer variability: the BP levels will be recorded by different nurses at different times.
- Complete medical data will not be available for all the patients:
  - In some patients we don't have all the blood pressure measures over time according to the protocol used in our hospital (described before). It happens when the patient was not in the hospital room due to undergoing tests. This information bias is reduced by analyzing this variable using the average BP levels at the intervals in time.
  - Some patients included in the study sample may not have the image CT-tests required due to their poor neurologic status. These patients are lost of follow-up in the evaluation of the haematoma enlargement but not for outcome.

## **10) SCHEDULE**

- **Stage 1: Data management. September - October 2013**
  - Revision of the patients in the previous database. We select the patients suitable for our study according to the exclusion/inclusion criteria. Performed by Dr. Yolanda Silva.
  - A neuroradiologist will calculate the ICH volumes of patients who did not have this information in its database.
  - Revision and calculation of averages with the BP levels. Performed by Alba Masó (medical student).
  - Alba Masó and Dr.Silva will have different meetings in order to monitor the process and discuss possible problems.
  - Dr. Silva will introduce this new data to the database and prepare it for the statistical analysis.
  
- **Stage 2: Statistical analysis. October-November 2013**
  - A qualified person in statistics will process the data with the adequate software.
  
- **Stage 3: Interpretation of the results. November 2013**
  - The investigation team will keep contact and meet to analyze and interpret the preliminary results.
  
- **Stage 4: Publication of the results: November- December 2013**
  - The results will be presented in an international conference (European Stroke Conference 2014, deadline 13 of January 2014) and if it's possible to others. We will also attempt to publish it in a neurology journal (*Stroke journal* is the preference).

**11) BUDGET**

Study budget	Cost
<u>Staff costs</u>	/
<u>Goods and service costs:</u> <ul style="list-style-type: none"> <li>▪ Qualified statistician:               <ul style="list-style-type: none"> <li>○ 50€/h x 3h/day x 2days/week x 3 weeks.....</li> </ul> </li> </ul>	900 € <hr/> Subtotal: 900 €
<u>Travel and subsistence costs:</u> <ul style="list-style-type: none"> <li>▪ International conferences attendance: European Stroke Conference. Nice 2014               <ul style="list-style-type: none"> <li>○ Inscription.....</li> <li>○ Travel costs.....</li> <li>○ Accommodation.....</li> </ul> </li> <li>▪ International conference attendance: International Stroke Conference. San Diego 2014               <ul style="list-style-type: none"> <li>○ Inscription .....</li> <li>○ Transport costs.....</li> <li>○ Accommodation.....</li> </ul> </li> </ul>	450 € 150 € 350 €  400 € 550 € 280 € <hr/> Subtotal: 2180€ pp
<u>Publications costs:</u> <ul style="list-style-type: none"> <li>▪ Publication of the results in the Stroke AHA journal:               <ul style="list-style-type: none"> <li>▪ 70 \$ each printed page .....</li> <li>▪ Papers exceeding 4.500 words: 425 \$ per additional 1000 words.....</li> </ul> </li> </ul>	1540 \$ (1139,6 €)  425 \$ (314,5€) <hr/> Subtotal: 1454,1€ (1965 \$)
	<b><u>Total: 4534,5€</u></b>

## **12) EXPERIENCE OF THE INVESTIGATION TEAM**

The research team in our hospital currently has more than 15 years of investigation experience in the area of cerebrovascular diseases, both infarction and intracerebral haemorrhage, and has become a consolidated investigation group being included in the “Red RENEVAS, RD07/OO26/2002 RETICS”.

In the ICH area, various multicenter studies have been done, with 2 of them receiving a subvention by Carlos III Institute. Some of the different topics studied are: role of inflammation and metalloproteases in the preihaematoma hipodensity (*Neurology* 2002; 58: 624-629, *Cerebrovasc Dis* 2002; 13 (suppl3): 43), predictors and associated factors of early neurologic deterioration in ICH (*Neurology* 2004; 63: 461-467), predictors of good prognosis in mid-large haematomas (*J Neurol Neurosurg Psychiatry* 2005; 76: 691-695) and the haematoma growth topic (*Stroke* 2005; 36: 86-91; *Lancet Neurology* 2012; 11 (4): 307-14) .

Also the team has taken part in numerous clinical trials in the acute phase of ICH: NOVOSEVEN (*Mayer et al. N Engl Med* 2005; 352: 777-785), FAST (*Mayer et al. N Engl J Med* 2008; 358:2127-2137), INTERACT II (*N.Engl J Med* 2013. DOI: 10.1056/NEJMoal1214609).

In fact, the study of the haemorrhage growth has been the objective for the doctoral thesis of Dr. Silva entitled: “*Mecanismos fisiopatológicos del crecimiento de la hemorragia intracerebral: estudio de marcadores biológicos de daño endotelial y de inflamación, UAB 2004*”, which identifies certain inflammation and endothelial damage markers as independent predictors of early haematoma growth.

Furthermore, a study that was granted a research fund in 2006 (FIS: “Fondo de Investigación Sanitaria”) was about the relationship between several polymorphisms associated with the action of thrombin and growth of cerebral haemorrhage and cerebral oedema. It was entitled: “*Pilot study about the haematoma growth and perilesional oedema in ICH: genetic, molecular and radiology markers*”. In 2009 another research fund was obtained for the “*Prediction of intracerebral haematoma growth by the contrast extravasation in cerebral RM: a prospective study*”.

Finally, they also actively participated in several clinical trials evaluating neuroprotective drugs and rFVIIa.

## **13) IMPACT OF THE PROJECT ON THE NATIONAL HEALTH SYSTEM**

Intracerebral haemorrhage is a disease with a high clinical relevance but nowadays, there's still no specific treatment proved to be effective. The haematoma growth during the acute phase is associated with poor outcome and taking into account that is potentially modifiable factor, most of the actual research efforts in this topic are focused on preventing that enlargement. Hypertension is frequent in patients with ICH and could have an impact on haematoma enlargement. The aim of our study is to investigate if high BP levels are associated with the enlargement of the haematoma. If we can prove a relationship at particular BP levels, new objectives of treatment could be established, being them less conservative than the actual ones.

We are aware of the limitations of our study in the design and sample size. Because of that, it wouldn't have a big and direct impact on the clinical practice but it could let to the development of new prospective multicentre studies to prove these statements. From here on, new clinical controlled trials could be done with the goal to apply the antihypertensive treatment according to the correct levels and evaluate if there is reduction in the haematoma enlargement.

The determination of critical high blood pressure levels for the prognosis of ICH could open a way towards a specific treatment for these patients. Blood pressure treatment is simple and widely available, so the adequate application of this treatment could lead to the paradigm of ICH management.

## **14) ANNEX**

1. **The National Institutes of Health Stroke Scale (NIHSS):** A systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. It is the main neurologic evaluation tool used in our hospital.

It is a 15-item clinical deficit scale that was first described in 1989 and assesses levels of consciousness, gaze, vision, facial palsy, arm and leg strength, limb ataxia, sensory loss, neglect, dysarthria, and aphasia. The possible punctuation goes from 0 to 42.<sup>a</sup>

The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. Now, the scale is also widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine appropriate treatment, and predict patient outcome. In fact, baseline severity as measured by the NIHSS is the most important predictor of ultimate outcome.

Initial evaluation of the scale confirmed that it could be administered in a mean of 6.6 minutes across a range of severities. Inter-rater agreement is excellent (mean  $k = 0.69$ ) and intra-rater agreement is also good, especially when the rater is a neurologist ( $k = 0.77$ ).<sup>b</sup>

The scale is designed to be a simple, valid, and reliable tool that can be administered at the bedside consistently by physicians, nurses or therapists with the correct training. However, in our case all the NIHSS's punctuations used are performed by the neurologists of our department.

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<sup>a</sup> Stroke Clinical Updates: [http://www.stroke.org/site/DocServer/SCU\\_-\\_Jan-Feb\\_2006.pdf?docID=5166](http://www.stroke.org/site/DocServer/SCU_-_Jan-Feb_2006.pdf?docID=5166)

<sup>b</sup> Kasner, S. E., Chalela, J. a., Luciano, J. M., Cucchiara, B. L., Raps, E. C., McGarvey, M. L., Localio, a. R. (1999). Reliability and Validity of Estimating the NIH Stroke Scale Score from Medical Records. *Stroke*, 30(8), 1534–1537. doi:10.1161/01.STR.30.8.1534

# 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  $\pm$ 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
<p><b>1a. Level of Consciousness:</b> 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.</p>	<p>0 = <b>Alert;</b> keenly responsive.                      1 = <b>Not alert;</b> but arousable by minor stimulation to obey, answer, or respond.                      2 = <b>Not alert;</b> 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.</p>	_____
<p><b>1b. LOC Questions:</b> 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.</p>	<p>0 = <b>Answers</b> both questions correctly.                      1 = <b>Answers</b> one question correctly.                      2 = <b>Answers</b> neither question correctly.</p>	_____
<p><b>1c. LOC Commands:</b> 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.</p>	<p>0 = <b>Performs</b> both tasks correctly.                      1 = <b>Performs</b> one task correctly.                      2 = <b>Performs</b> neither task correctly.</p>	_____
<p><b>2. Best Gaze:</b> 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.</p>	<p>0 = <b>Normal.</b>                      1 = <b>Partial gaze palsy;</b> gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.                      2 = <b>Forced deviation,</b> or total gaze paresis not overcome by the oculocephalic maneuver.</p>	_____



# 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 \_\_\_\_\_ (\_\_\_\_)

<p><b>3. Visual:</b> 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.</p>	<p>0 = <b>No visual loss.</b>                  1 = <b>Partial hemianopia.</b>                  2 = <b>Complete hemianopia.</b>                  3 = <b>Bilateral hemianopia</b> (blind including cortical blindness).</p>	<p>_____</p>
<p><b>4. Facial Palsy:</b> 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.</p>	<p>0 = <b>Normal</b> symmetrical movements.                  1 = <b>Minor paralysis</b> (flattened nasolabial fold, asymmetry on smiling).                  2 = <b>Partial paralysis</b> (total or near-total paralysis of lower face).                  3 = <b>Complete paralysis</b> of one or both sides (absence of facial movement in the upper and lower face).</p>	<p>_____</p>
<p><b>5. Motor Arm:</b> 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.</p>	<p>0 = <b>No drift;</b> limb holds 90 (or 45) degrees for full 10 seconds.                  1 = <b>Drift;</b> limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.                  2 = <b>Some effort against gravity;</b> limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.                  3 = <b>No effort against gravity;</b> limb falls.                  4 = <b>No movement.</b>                  UN = <b>Amputation</b> or joint fusion, explain: _____</p> <p>5a. <b>Left Arm</b></p> <p>5b. <b>Right Arm</b></p>	<p>_____                  _____</p>
<p><b>6. Motor Leg:</b> 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.</p>	<p>0 = <b>No drift;</b> leg holds 30-degree position for full 5 seconds.                  1 = <b>Drift;</b> leg falls by the end of the 5-second period but does not hit bed.                  2 = <b>Some effort against gravity;</b> leg falls to bed by 5 seconds, but has some effort against gravity.                  3 = <b>No effort against gravity;</b> leg falls to bed immediately.                  4 = <b>No movement.</b>                  UN = <b>Amputation</b> or joint fusion, explain: _____</p> <p>6a. <b>Left Leg</b></p> <p>6b. <b>Right Leg</b></p>	<p>_____</p>

# 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 \_\_\_\_\_ (\_\_\_\_-\_\_\_\_)

<p><b>7. Limb Ataxia:</b> 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.</p>	<p>0 = Absent.                  1 = Present in one limb.                  2 = Present in two limbs.                  UN = Amputation or joint fusion, explain: _____</p>	<p>_____</p>
<p><b>8. Sensory:</b> 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.</p>	<p>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.</p>	<p>_____</p>
<p><b>9. Best Language:</b> 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.</p>	<p>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.</p>	<p>_____</p>
<p><b>10. Dysarthria:</b> 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.</p>	<p>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: _____</p>	<p>_____</p>

# N I H STROKE SCALE

Patient Identification. \_\_\_\_\_

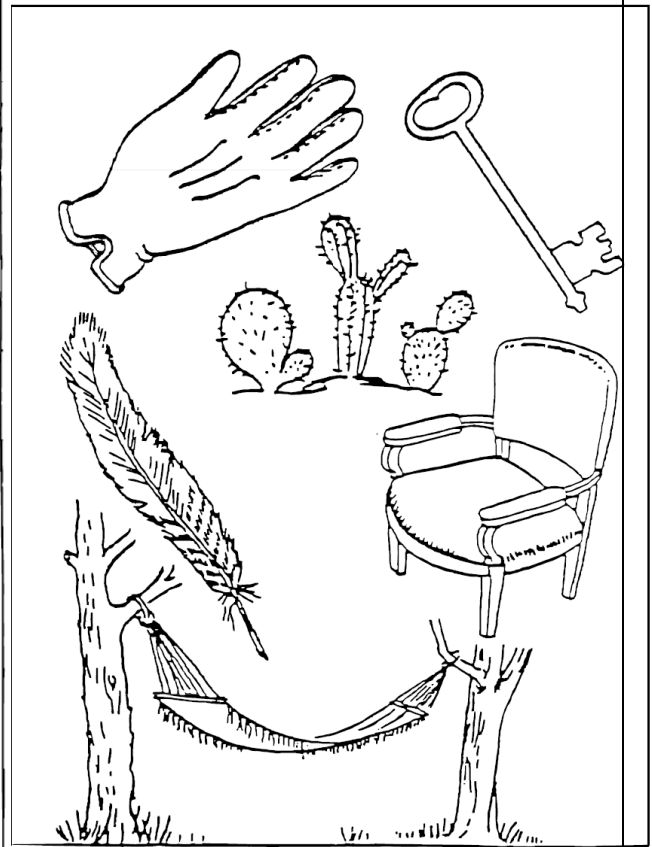
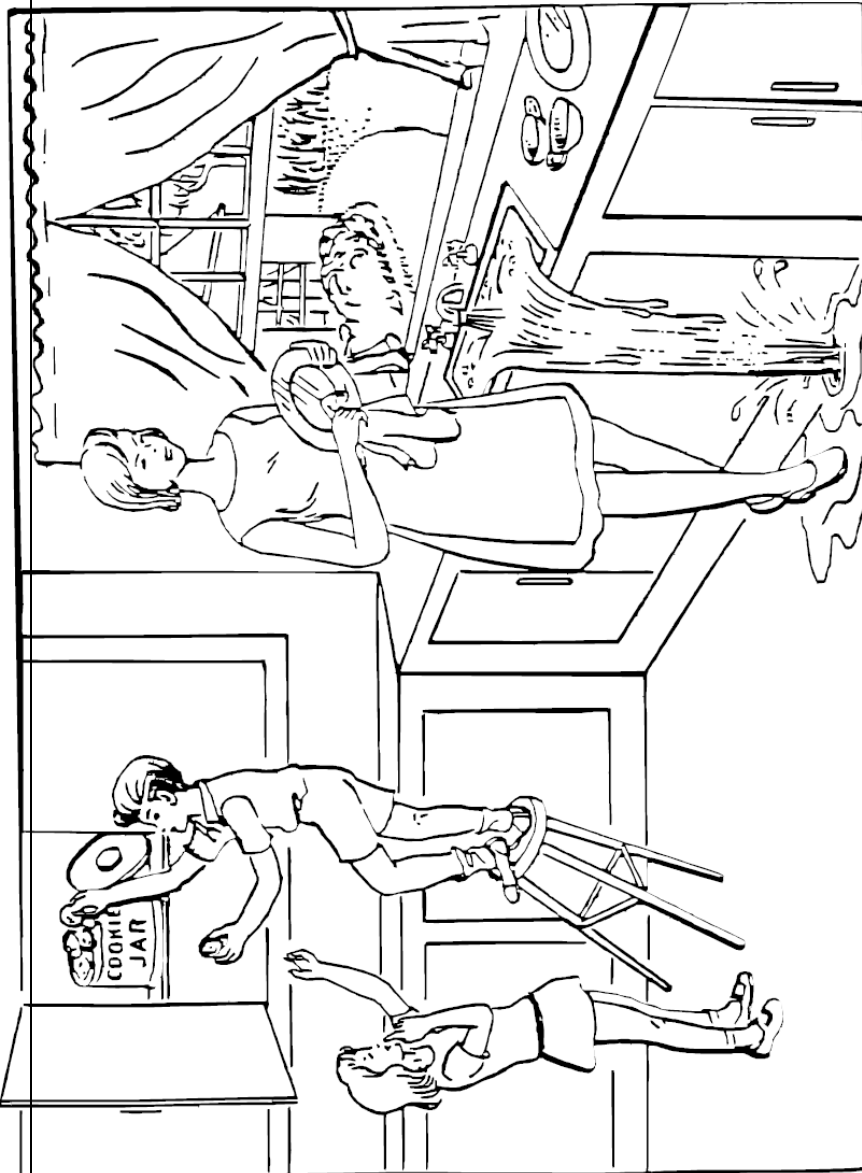
Pt. Date of Birth \_\_\_\_/\_\_\_\_/\_\_\_\_

Hospital \_\_\_\_\_ (\_\_\_\_-\_\_\_\_)

Date of Exam \_\_\_\_/\_\_\_\_/\_\_\_\_

Interval:  Baseline  2 hours post treatment  24 hours post onset of symptoms  $\pm$ 20 minutes  7-10 days  
 3 months  Other \_\_\_\_\_ (\_\_\_\_)

<p><b>11. Extinction and Inattention (formerly Neglect):</b> 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.</p>	<p>0 = No abnormality.</p> <p>1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</p>	<p>_____</p>
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**You know how.**

**MAMA**

**Down to earth.**

**TIP – TOP**

**I got home from work.**

**FIFTY – FIFTY**

**Near the table in the dining  
room.**

**THANKS**

**They heard him speak on the  
radio last night.**

**HUCKLEBERRY**

**BASEBALL PLAYER**

**2. Modified Rankin Scale (mRS):** Is a clinician-reported measure of global disability that has been widely applied for evaluating recovery from stroke and as a primary end point in randomized clinical trials (RCTs) of emerging acute stroke treatments.

The mRS was published in 1988 and consists of 6 categories (grades 0 to 5) rather than 5 for the RS (original Rankin Scale); an additional category, grade “6” denoting death, is usually incorporated into the mRS for RCT purposes. In the mRS: grade 1 of the original RS (“no significant disability”) is replaced by 2 grades, 0 and 1, with grade 0 describing patients without symptoms and grade 1 describing patients without significant disability “despite symptoms.” This finer discrimination of mild strokes increases the usefulness of the mRS in evaluating RCTs of acute stroke interventions. Additionally, grade 2 in the mRS (“unable to perform all previous activities”) is more definitive compared with that grade of the RS (“unable to carry out some of previous activities”).

A “favourable” outcome defined as mRS grade 1 or 2 was estimated to be more powerful than dichotomization at higher grades.

Inter-rater reliability with the mRS is moderate and improves with structured interviews (K= 0.56 versus 0.78); strong test-re-test reliability (k=0.81 to 0.95) has been reported. Numerous studies demonstrate the constructed validity of the mRS by its relationships to physiological indicators such as stroke type, lesion size, perfusion and neurological impairment.<sup>c</sup>

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<sup>c</sup> Banks JL, Marotta C a. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007 Mar; 38(3):1091–6.

**MODIFIED  
RANKIN  
SCALE (MRS)**

**Patient Name:** \_\_\_\_\_

**Rater Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_

<b>Score</b>	<b>Description</b>
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):** \_\_\_\_\_

### **3. Informed consent**

**Títol de l'estudi: Estudi per a la predicció del creixement de l'hematoma i l'evolució dels pacients amb hemorràgia cerebral mitjançant l'ús de la TC cranial amb un bolus de contrast**

Aquest consentiment informat, del qual se li ha entregat una còpia, resumeix quins són els objectius de l'estudi i quina és la seva participació. Si vostè vol més detalls sobre l'estudi, pregunti lliurement a l'investigador i prengui's tot el temps necessari per a llegir i entendre aquest document.

L'hemorràgia cerebral és una malaltia que tot sovint comporta una elevada mortalitat o possibilitat de seqüeles en els pacients que la presenten. Un fet comú és que l'hematoma cerebral presenta un creixement del seu tamany durant les primeres 3 a 6 hores de presentació. Aquest creixement pot produir la compressió de les estructures adjacents portant a un ràpid deteriorament neurològic. Fins al moment no existeix cap prova d'imatge que sigui capaç de predir en quins pacients es produirà aquest creixement i l'evolució dels pacients. En aquest estudi es pretén esbrinar si determinades tècniques de Tomografia Computeritzada (TC) i d' Angiografia per TC poden ajudar a predir el creixement de l'hematoma durant les primeres hores i també l'evolució clínica dels pacients als 3 mesos.

Vostè pot participar en aquest estudi si ha patit una hemorràgia cerebral. La seva participació en l'estudi durarà tres mesos. Vostè rebrà el mateix tractament que rebran la resta de pacients amb una hemorràgia cerebral. Vostè serà examinat per un neuròleg que li realitzarà una exploració neurològica, un electrocardiograma, una analítica de sang i una TC cranial per confirmar que ha presentat una hemorràgia cerebral. Després de la TC cranial estàndard, se li administrarà un contrast via sanguínia (si no hi ha cap contraindicació) per a realitzar un angiograma, que permet visualitzar les artèries del cervell. Posteriorment es realitzarà una TC cranial a les 24 hores de l'inici dels símptomes. Si en qualsevol moment es detecta un empitjorament neurològic es realitzarà de forma urgent una TC cranial. Durant el seu ingrés hospitalari es realitzaran les proves necessàries per a investigar la causa de la seva malaltia, com es fa a la resta de pacients. Després de l'alta hospitalària es farà un seguiment clínic i se'l citarà per a una visita de control al mes i als 3 mesos. Durant aquesta visita es realitzarà una exploració neurològica.

Criteris d'exclusió:

Vostè no pot participar en l'estudi si:

- Té una malaltia al ronyó
- Els símptomes pels que consulta es van iniciar 6 hores abans de l'arribada a l'hospital
- L'hemorràgia cerebral és molt extensa, és a dir superior a 100 cc
- Té un tumor o una malformació vascular al cervell
- Presenta una malaltia greu o terminal
- Està embarassada
- Presenta una malaltia neurològica que dificulta la seva avaluació en l'estudi
- Està prevista la realització de cirurgia de l'hematoma en les següents 24 hores

Riscos o efectes adversos

Vostè pot presentar efectes adversos lleus deguts a l'administració del contrast, que generalment passen de seguida. Aquests efectes adversos poden ser sensació d'escalfor, nàusees, vòmits, alteracions del gust....Generalment no requereixen tractament o bé responen ràpidament al tractament administrat. En rares ocasions poden presentar-se efectes adversos greus.

Donat que es realitza una angiografia per TC hi ha un increment en la radiació rebuda en comparació a si es realitza únicament una TC cranial. El risc degut a l'increment de la radiació és molt petit.

Les dones embarassades no poden ser incloses en l'estudi. Les dones lactants no poden donar el pit fins passades 24 hores, per tal d'eliminar el contrast.

Si vostè participa en aquest estudi pot o no pot tenir efectes beneficiosos derivats de la inclusió en l'estudi. La informació que s'obtindrà en aquest estudi pot ajudar a identificar predictors del creixement de l'hematoma que podrien ajudar per a trobar nous tractaments en el futur per pacients amb hemorràgia cerebral.

Confidencialitat

La informació (clínica i de neuroimatge) recollida serà confidencial. Les imatges obtingudes seran emmagatzemades de forma confidencial en una base de dades, a partir de la qual es podran fer anàlisis i publicacions posteriors que ajudin a fer conèixer a la comunitat científica les troballes resultants de l'estudi. Vostè té el dret de contactar amb els investigadors en qualsevol moment i retirar les imatges i la seva informació clínica de la base. També, en cas de mort, la seva família pot sol·licitar aquesta informació.

Els resultats d'aquest estudi poden ser presentats en congressos i en publicacions, però la seva identificació no serà mai revelada. La identificació de les imatges serà sempre confidencial.

La seva participació en l'estudi no comportarà compensacions econòmiques. En el cas que no acceptés participar en l'estudi, se seguirà el maneig diagnòstic i terapèutic habitual per la malaltia que vostè presenta.

### **Consentiment**

La seva signatura en aquest document indica que vostè ha entès la informació en relació a la seva participació en aquest estudi de recerca i que està d'acord en participar. En qualsevol moment pot retirar-se de l'estudi sense que aquest fet afecti el seu tractament mèdic. En cap moment aquest document allibera als investigadors o a les institucions implicades, de les seves responsabilitats legals i professionals. En qualsevol moment pot sol·licitar qualsevol aclariment sobre la seva participació dins l'estudi.

Si té qualsevol pregunta sobre l'estudi pot contactar amb Dra Silva.

Signatura del participant  
o representant legal

Nom

Data

Signatura de l'investigador

Nom

Data