

# SYNTHESIS

## Local versus systemic thrombolysis for acute stroke

---

SYNTHESIS is a randomized, controlled, multicenter, clinical trial, open-label, with blinded follow-up, to determine whether intra-arterial rt-PA within 6 hours of an ischemic stroke, as compared with intravenous infusion of the same drug within 3 hours, increases the proportion of independent survivors at 3 months.

---

Address for correspondence:

Alfonso Ciccone, MD  
Stroke Unit  
Department of Neurosciences  
Ospedale Niguarda Ca' Granda  
Piazza Ospedale Maggiore 3  
20162 Milano  
Tel: ++39 02 64442696  
Fax: ++39 02 64442819  
E-mail: [Alfonso.Ciccone@pmp.it](mailto:Alfonso.Ciccone@pmp.it)

## **INDEX**

### **1. AIMS**

#### **1.1 Primary aims**

#### **1.2 Secondary aim**

### **2. TREATMENT COMPARISONS**

### **3. RATIONAL**

### **4. STUDY DESIGN**

### **5. PATIENT ELIGIBILITY**

#### **5.1 Clinical inclusion criteria**

#### **5.2 Clinical and laboratory exclusion criteria**

#### **5.3 Computed tomographic (CT) scan exclusion criteria**

### **6. CONSENT AND ETHICAL APPROVAL**

### **7. NON RANDOMIZED ELIGIBLE PATIENTS**

### **8. RANDOMIZATION**

### **9. TREATMENTS**

#### **9.1 LIA rt-PA allocation: treatment procedure**

#### **9.2 IV rt-PA allocation: treatment procedure**

#### **9.3 Associated therapies**

#### **9.4 Protocol deviations**

### **10 CLINICAL ASSESSMENT AND FOLLOW-UP**

#### **10.1 Assessment during hospital stay: data collection forms**

#### **10.2 Long-term assessment**

### **11. SAMPLE SIZE**

### **12. STUDY DURATION**

### **13. STUDY ORGANIZATION**

#### **13.1 Steering and Organizing Committee**



- 13.2 Participating Centers**
- 13.3 Data Management Office**
- 13.4 Neuroradiologic Reviewing Committee**
- 13.5 Data monitoring Committee**
- 14. ANALYSES**
  - 14.1 Primary analysis**
  - 14.2 Secondary analysis**
  - 14.3 Safety and interim analysis**
- 15. SOURCE OF SUPPORT**
- 16. APPENDIX A: GLOSSARY**
- 17. APPENDIX B: MANAGEMENT DURING THE FIRST 7 DAYS**
  - 17.1 Components of care after admission into the Hospital**
  - 17.2 Acute treatment of hypertension**
  - 17.3 Acute anticoagulant therapy**
  - 17.4 Treatment of increased intracranial pressure**
  - 17.5 Treatment of intracranial hemorrhage following thrombolysis**
- 18. REFERENCES**
- 19. CONTRIBUTIONS AND CONFLICT OF INTEREST**

## **1. AIMS**

### **1.1 Primary aims**

To assess whether local intra-arterial (LIA) recombinant tissue plasminogen activator rt-PA, as compared to intravenous (IV) rt-PA, increases survival free of disability (modified Rankin score of zero or 1) at 3 months.

### **1.2 Secondary aim**

To assess whether:

1. LIA rt-PA improves the 7-day neurological deficit, as compared to IV rt-PA.
2. LIA rt-PA is safe as compared to IV rt-PA, on the base of events reported within 7 days: symptomatic intracranial hemorrhages, fatal and non-fatal stroke, death from any cause, neurological deterioration.

## **2. TREATMENT COMPARISONS**

- Patients allocated LIA thrombolysis will receive up to 0.9 mg per kilogram of body weight (maximum 90 mg) of rt-PA, within the thrombus by means of microcatheter, over 60 minutes, within 6 hours of the onset of the ischemic stroke.
- Patients allocated to IV thrombolysis will receive rt-PA in a dose of 0.9 mg per kilogram of body weight (maximum 90 mg), over 60 minutes, within 3 hours of onset of the ischemic stroke.

### 3. RATIONAL

---

Stroke is a major cause of death and severe disability. In Caucasians the majority of strokes are ischemic and due to arterial thrombosis<sup>1,2</sup>. One logical treatment is to dissolve the occluding clot promptly to limit tissue injury. The only effective, available therapy, within few hours of stroke onset, is rt-PA<sup>3-5</sup>, a thrombolytic agent.

Rt-PA, administered intravenously within 3 hours of symptoms onset of an ischemic stroke, increases by about 12% absolute incidence of complete recovery (modified Rankin score scale 0 or 1), according to the results of the NINDS trial<sup>6</sup>. However, in the US, where the FDA has approved this treatment in 1996<sup>5</sup>, only a minority of ischemic stroke patients admitted to the hospital can be treated with rt-PA<sup>7</sup>. This low rate of treatment is due to the narrow therapeutic time window, and, probably, to diffidence of clinician in its use for the fear of hemorrhagic transformation. LIA thrombolysis could overcome these two difficulties both prolonging the therapeutic window and lowering the risk of hemorrhage transformation.

LIA thrombolysis is performed with microcatheters, which are positioned close to, or within the thrombus, allowing local thrombolytic delivery. Thrombolysis may be further aided by mechanical thrombus disruption. IA treatment is attractive because of higher rates of recanalization and lower doses of thrombolytic used compared with IV therapy<sup>8,9,10</sup>. Many case series and three randomized controlled trials have been published on local thrombolysis, PROACT<sup>11</sup> and PROACT II<sup>12</sup> compared the use of recombinant pro-urokinase (pro-UK) plus intravenous heparin to intravenous heparin in patients with middle cerebral artery occlusion. PROACT<sup>11</sup> demonstrated recanalization in 58% of patients after two hours of infusion of pro-UK/heparin compared with 14% after infusion of a placebo/heparin in 40 randomized patients. The frequency of symptomatic intracranial hemorrhage in the group treated with 6 mg of pro-UK plus 5000-7000 IU (100 IU/Kg) bolus of heparin was 27%. For this reason, the total heparin dose was decreased to 3000 IU and hemorrhagic transformation reduced to 7%. The clinical benefit was not statistically significantly different between pro-UK and placebo treated patients, but the study was not powered to demonstrate this.

PROACT II<sup>12</sup> examined clinical efficacy. One hundred eighty patients with angiographic proven main stem (M1) or major branch (M2) MCA occlusion were randomized within 6 hours of symptoms onset to receive either 9 mg of recombinant pro-UK over 2 hours plus heparin (2000 units bolus at time of angiography followed by 500 IU/hour for 4 hours) versus heparin alone (same dosage). Recanalization was obtained in 66% of patients in the r-pro-UK group and 18% of the control group. The incidence of symptomatic ICH in the pro-UK group was 10% versus 2% in the placebo group. On the intention-to-treat analysis 40% of patients in the pro-UK group had slight or no disability (modified Rankin scale score of 0 to 2) at 3 months compared with 25% of control patients (odds ratio 2.13, 95% CI 1.02-4.42). This study demonstrated that the therapeutic window for ischemic stroke might be extended to at least to 6 hours using LIA therapy. Most patients in PROACT II were treated within 3-6 hours from symptoms onset. The magnitude of benefit for LIA in PROACT II may have been more substantial if more patients were randomized within 3 hours. However, given the major investment in time, personnel, and equipment required by LIA as compared to IV thrombolysis, its use should be justified only with a definite evidence of superior clinical efficacy.

The EMS Bridging Trial<sup>13</sup> was a double blind, randomized, placebo-controlled pilot study, of IV rt-PA (0.6 mg/Kg) or IV placebo followed by immediate cerebral angiography and local IA administration of r-TPA (10 mg/h for up to 2 hours after a bolus injection of 2 mg into the clot) in 35 patients. IA rt-PA was delivered if the angiogram demonstrated an occlusion appropriate to the patient's symptoms. Angiography was carried out on all patients and IV treatment was initiated within 3 hours of symptoms onset. Recanalization was complete in 6 of 11 IV/IA patients versus 1 of 10 placebo/IA patients but there was no difference in the treatment groups in the 7 and 90 days clinical outcome. Symptomatic intracerebral hemorrhage occurred in 2 IV/IA patients and in 1 placebo/IA. Mortality was greater in the IV/IA group with 5 death within 90 days compared to 1 death in the placebo/IA group. The excess in mortality in IV/IA group did not seem related to treatment assignment. Inferences on this study are limited because of the small number of patients.

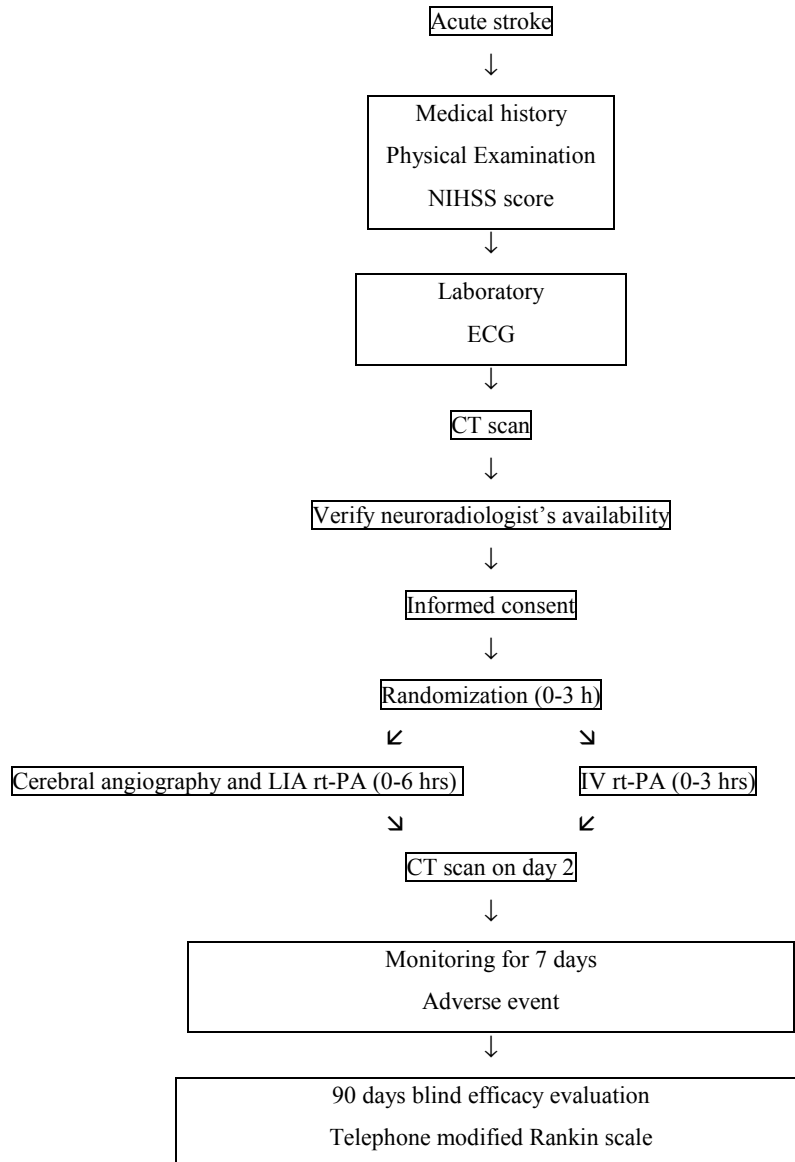


In conclusion, the hypothesis to be tested is whether LIA thrombolysis is safer and more effective than IV thrombolysis.

#### **4. STUDY DESIGN**

SYNTHESIS is a randomized, controlled, multicenter, open-label clinical trial with blinded follow-up. The characteristics of the study are shown in the figure.

## **SYNTHESIS: trial organization and treatments**



## **5. PATIENT ELIGIBILITY**

### **5.1 Clinical inclusion criteria**

- Sudden focal neurological deficit attributable to a stroke
- Clearly defined time of onset, allowing initiation of intravenous treatment within 3 hours of symptoms onset and intra-arterial treatment within 6 hour of symptoms onset.
- Age between 18 and 80 years

### **5.2 Clinical and laboratory exclusion criteria**

- Disability preceding stroke consistent with a modified Rankin scale score of 2-4 (see glossary for Rankin scale)
- Coma at onset
- Severe stroke as assessed clinically (e.g. NIHSS>25)
- Rapidly improving neurological deficit or minor symptoms
- Seizure at onset of stroke
- Clinical presentation suggestive of a subarachnoid hemorrhage (even if CT scan is normal) or condition after subarachnoid hemorrhage from aneurysm
- Previous history of or suspected intracranial hemorrhage
- Previous history of central nervous system damage (i.e. neoplasm, aneurysm, intracranial or spinal surgery)
- Septic embolism, bacterial endocarditis, pericarditis
- Acute pancreatitis
- Arterial puncture at a non compressible site (e.g. subclavian or jugular vein puncture) or traumatic external heart massage or obstetrical delivery within the previous 10 days
- Another stroke or serious head trauma within the preceding 3 months
- Major surgery or significant trauma in past 3 month
- Urinary tract hemorrhage within the previous 21 days
- Documented ulcerative gastrointestinal disease during the last 3 months, esophageal varices, arterial-aneurysm, arterial/venous malformations

- Neoplasm with increased bleeding risk
- Severe liver disease, including hepatic failure, cirrhosis, portal hypertension (esophageal varices) and active hepatitis
- Current therapy with intravenous or subcutaneous heparin or oral anticoagulants (e.g. warfarin sodium) to rise the clotting time
- Known hereditary or acquired hemorrhagic diathesis, baseline INR greater than 1.5, aPTT more than 1.5 times normal, or baseline platelet count less than 100,000 per cubic millimeter
- Baseline blood glucose concentrations below 50 mg per deciliter (2.75 mm/L) or above 400 mg per deciliter
- Hemorrhagic retinopathy, e.g. in diabetes (vision disturbances may indicate hemorrhagic retinopathy)
- Any history of prior stroke and concomitant diabetes
- Prior stroke within the last 3 months
- Known contrast sensitivity
- Severe uncontrolled hypertension defined by a blood pressure  $\geq 185$  mmHg systolic or diastolic  $\geq 110$  mm Hg in 3 separate occasions at least 10 minutes apart or requiring continuous IV therapy
- Prognosis very poor regardless of therapy; likely to be dead within months.
- Unlikely to be available for follow-up (e.g., no fixed home address, visitor from overseas). Any other condition which local investigators feels would pose a significant hazard in terms of risk/benefit to the patient, or if therapies are impracticable.

### **5.3 Computed tomographic (CT) scan exclusion criteria**

- Intracranial tumors except small meningioma
- Hemorrhage of any degree
- Acute infarction (since this may be an indicator that the time of onset is uncorrected)

## **6. CONSENT AND ETHICAL APPROVAL**

The trial will be run according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the Declaration of Helsinki. Local Ethics Committee (or local equivalent) approval is needed for each participating center before recruitment can begin. A patient information leaflet will support the consent process. In general, signed informed consent will be sought.

If a patient is unable to provide written consent, center coordinators should seek advice from the appropriate ethics committee. In general, it is considered ethically acceptable to record witnessed verbal consent for patients who are able to give consent but who are unable to write because of dominant hand weakness, apraxia or ataxia. If the patient is mentally incapable due to the acute stroke (e.g. aphasia, inattention, drowsiness etc.), a consent by the nearest available relative should be sought. If the a relative is unavailable a waiver consent may be obtained following the guidelines by the US Food and Drug Administration and the Department of Health and Human Services that allows waiver of informed consent in certain emergency situations<sup>14</sup>.

## **7. NON RANDOMIZED ELIGIBLE PATIENTS**

A stroke-register will be kept for non-randomized patients, which will include patient's initials, sex, age, date of observation, and reason for exclusion. These patients will be not followed-up.

## **8. RANDOMIZATION**

A computer-generated randomization procedure in blocks of four will be used, with each center allocated at least one block of the treatment groups. At each center, eligible patients will be randomly assigned treatment at baseline by means of sequential patient numbers concealed to the investigators.

## **9. TREATMENTS**

### **9.1 LIA rt-PA allocation: treatment procedure**

An angiogram is performed as soon as possible after randomization. Treatment is started as soon as possible and, in any case, within 6 hours from symptoms onset.

Intravenous heparin will be initiated with a 2000 U bolus followed by 500 U/hr infusion till the termination of the angiography. An infusion microcatheter (<3.0F) with a single end hole will be placed into the middle of the thrombus using a steerable microguidewire. If the intrathrombus positioning of the infusion catheter is not possible, the tip of the catheter is to be placed as close to the proximal face of the thrombus as possible for rt-PA infusion. A superselective angiogram is to be performed through the microcatheter to document catheter placement. Rt-PA infusion is then started at a rate of about 0.9 mg/Kg/hr (maximum 90 mg/hr) while the catheter is withdrawn to the proximal surface of the thrombus. Contrast is injected though the guide catheter every 15 minutes to assess the progress of lysis and the microcatheter is repositioned as necessary. If recanalization has not been successful, injection of potential collateral vessels may be required. Fibrinolytic therapy continues for a maximum of one hour and the overall dose of rt-PA infused should not exceed the dose of 0.9 mg per kilogram of body weight (maximum 90 mg in case of body weight exceeding 100 Kg). If complete lysis occurs the rt-PA infusion is stopped. Mechanical thrombus disruption is possible during the procedure passing through the thrombus with the infusion microcatheter. Clot retrieval is allowed whilst balloon angioplasty is prohibited.

IV thrombolysis is prohibited for patients allocated in this group.

LIA thrombolysis is not performed if the angiogram does not show any arterial thrombus congruous with patient's symptoms.

### **9.2 IV rt-PA allocation: treatment procedure**

Treatment is started immediately after randomization, within 3 hours of the onset of symptoms. Rt-PA, in a dose of 0.9 mg per kilogram of body weight (maximum 90 mg), 10% of which is given as a bolus followed by delivery of the remaining 90% as a constant infusion over 60 minutes.

LIA thrombolysis is prohibited for patients allocated in this group.

### **9.3 Associated therapies**

All the patients in the two groups of treatment will be given the most appropriate medical treatment.

- Antiplatelet therapy within 24 hours of symptoms onset should be avoided
- Low dose unfractionated heparin (5000 IU subcutaneous qd) or low molecular heparin (preferably) at prophylactic doses may be used for patient at high risk of deep venous thrombosis (e.g. obesity and bed rest)
- Full-dose oral anticoagulant or unfractionated heparin (e.g. to PT, INR > 1.5 with oral anticoagulant; to aPTT 1.2 fold normal with unfractionated heparin) within 24 hours of symptoms onset should be avoided.
- The use of any antiplatelet or anticoagulant agent during the first week will be recorded in the “In-Hospital Data Collection Form”.
- All patients should be treated long term with an antiplatelet or oral anticoagulant agent, when indicated, for secondary prevention of stroke.

### **9.5 Protocol deviations**

Whenever prohibited treatments or procedures are used, they will be considered protocol deviations and will be recorded in the in-hospital evaluation form.

## **10 CLINICAL ASSESSMENT AND FOLLOW-UP**

### **10.1 Assessment during hospital stay: data collection forms**



**IN-HOSPITAL DATA COLLECTION FORM  
BEFORE RANDOMIZATION**

Hospital \_\_\_\_\_ Dpt \_\_\_\_\_ City \_\_\_\_\_ State/Country \_\_\_\_\_ / \_\_\_\_\_

**Patient's identifiers:**

Family name \_\_\_\_\_ Given name(s) \_\_\_\_\_

Date of Birth (Day/Month/Year) \_\_\_/\_\_\_/\_\_\_ Sex (Male/Female) \_\_

**Estimated body weight (Kgs)** \_\_\_\_\_

**Arterial Blood pressure now** (Systolic/Diastolic mmHg) \_\_\_/\_\_\_

**Yes No**

**Atrial fibrillation now**

(Please tick (√) one box)

	<b>Value</b>	<b>Normal range</b>	<b>Unit of measure</b>
<b>Hemoglobin</b>			
<b>Platelet count</b>			
<b>Serum glucose</b>			
<b>INR</b>			
<b>APTT</b>			

**Previous antiplatelet therapy** (please tick (√) one box on each line)

**Received in the previous 48 hours**      **Yes**      **No**

Any anticoagulant                                   

Any aspirin                                           

Dypiridamole                                       

Ibuprofen                                             

Ticlopidine                                          

Clopidogrel



**Before admission for this stroke:**

	<b>Yes</b>	<b>No</b>
Treatment for hypertension	<input type="checkbox"/>	<input type="checkbox"/>
Treatment for Diabetes mellitus (insulin or other medication)	<input type="checkbox"/>	<input type="checkbox"/>
A history of previous stroke or TIA	<input type="checkbox"/>	<input type="checkbox"/>
A history of myocardial infarction	<input type="checkbox"/>	<input type="checkbox"/>
Did the patient live alone?	<input type="checkbox"/>	<input type="checkbox"/>
Was the patient independent in everyday activities?	<input type="checkbox"/>	<input type="checkbox"/>

	<b>Hour/Minute</b> 24 hour clock	<b>Date</b> dd/mm/yyyy
<b>Time of known stroke onset</b> (local time)	__/__/__	__/__/__
<b>Neurological deficit: NIHSS score:</b> _____	__/__/__	__/__/__
<b>CT scan</b> [hemorrhage and infarction excluded]	__/__/__	__/__/__
<b>Randomization</b>	__/__/__	__/__/__

**Consent modality** (please tick (√) one box)

Patient signed form       Patient gave verbal consent       Assent by relatives   
 Waiver of consent       If waiver please give reason \_\_\_\_\_

**Treatment allocation** (please tick (√) one box on each line)

Local IA rt-PA       IV rt-PA  y

Name of doctor randomizing \_\_\_\_\_ Today date (dd/mm/yyyy) \_\_/\_\_/\_\_

**IN-HOSPITAL DATA COLLECTION FORM**

**AFTER RANDOMIZATION**

Please complete at 7 days, or discharge, or transfer to another hospital, or death, whichever occurs first.

Hospital \_\_\_\_\_ Dpt \_\_\_\_\_ City \_\_\_\_\_ State/Country \_\_\_\_\_ / \_\_\_\_\_



**Patient's identifiers:**

Family name \_\_\_\_\_ Given name(s) \_\_\_\_\_

Date of Birth (Day/Month/Year) \_\_\_/\_\_\_/\_\_\_

<b>Treatment administered according to protocol?</b>	<b>Yes</b>	<b>No</b>
For patient randomized local IA rt-PA	<input type="checkbox"/>	<input type="checkbox"/>
For patient randomized IV rt-PA	<input type="checkbox"/>	<input type="checkbox"/>

	<b>Hour/Minute</b> 24 hour clock	<b>Date</b> dd/mm/yyyy
<b>Time of treatment onset</b> (local time)	___/___	___/___/___
<b>Time of angiogram:</b> _____	___/___	___/___/___

Associated therapies	Start date dd/mm/yy	End date dd/mm/yy
Glycerol IV	___/___/___	___/___/___
Mannitol IV	___/___/___	___/___/___
Furosemide IV	___/___/___	___/___/___
Labetalol IV	___/___/___	___/___/___
Nitroprusside IV	___/___/___	___/___/___
Low dose heparin/heparinoid (aPTT <input type="checkbox"/> 1.2 fold normal)	___/___/___	___/___/___
Full dose unfractionated heparin (aPTT > 1.2 fold normal)	___/___/___	___/___/___
Full dose oral anticoagulants (INR > 1.5)	___/___/___	___/___/___
Any aspirin	___/___/___	___/___/___
Any antiplatelet other than aspirin	___/___/___	___/___/___

**Use of:**

(please tick (√) one box on each line)

	<b>Yes</b>	<b>No</b>
Antiplatelet within 12 hours	<input type="checkbox"/>	<input type="checkbox"/>
Angioplasty	<input type="checkbox"/>	<input type="checkbox"/>

**2<sup>nd</sup> CT scan:** date \_\_\_/\_\_\_/\_\_\_ (please tick (√) one box)

<input type="checkbox"/> Normal	<input type="checkbox"/> Hemorrhagic infarct	<input type="checkbox"/> Intracerebral hemorrhage
<input type="checkbox"/> Infarct	<input type="checkbox"/> Other hemorrhages	<input type="checkbox"/> Other

**Final diagnosis of initial randomizing event** (using all clinical and/or imaging information available to you)



	<b>Yes</b>	<b>No</b>			
Definite ischemic stroke	<input type="checkbox"/>	<input type="checkbox"/>	If <b>Yes</b> state:		
			location in	Cerebral hemisphere <input type="checkbox"/>	Posterior circulation <input type="checkbox"/>
Definite or probable hemorrhagic stroke	<input type="checkbox"/>	<input type="checkbox"/>			
Non-stroke cause	<input type="checkbox"/>	<input type="checkbox"/>	If <b>Yes</b> was it due to:	Cerebral tumor <input type="checkbox"/>	Migraine <input type="checkbox"/>
				Epilepsy <input type="checkbox"/>	Other please say <input type="checkbox"/> _____

**Etiologic diagnosis of definite ischemic stroke:** (please tick (√) one box)

- Large-artery atherosclerosis     Cardioembolism     Dissection     Other     Unknown

<b>EVENTS in hospital after randomization</b> (please tick (√) <u>one</u> box on <u>each</u> line)	<b>Yes</b>	<b>No</b>	<b>Date</b> dd/mm/yy
Intra-angiographic complications (if Yes please say)	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Groin hematoma	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Limb ischemia	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Symptomatic intracranial hemorrhage	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Mild extracranial bleeding	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Severe extracranial bleeding	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
New ischemic stroke	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Cerebral edema	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
New stroke	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Myocardial infarction	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Anaphylactic shock	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___
Death	<input type="checkbox"/>	<input type="checkbox"/>	_/_/___



**Likely cause of death** (tick (√) one box only)

- Neuro-damage from initial stroke with no evidence of intracranial hemorrhage
- Recurrent stroke – type unknown -
- Intracranial hemorrhage
- Extracranial hemorrhage
- Ischemic heart disease
- Pulmonary embolism
- Pneumonia
- Other cause of death (please specify)

**If the patient is alive please complete the following:**

**Current Neurological deficit (NIHSS score):** \_\_\_\_\_

**Patient's full postal address on discharge:**

\_\_\_\_\_

\_\_\_\_\_

Postcode \_\_\_\_\_ Telephone \_\_\_\_\_

**Family doctor's details**

Name of family doctor: \_\_\_\_\_

Address \_\_\_\_\_ of \_\_\_\_\_ family \_\_\_\_\_ doctor:

\_\_\_\_\_

Postcode \_\_\_\_\_ Telephone \_\_\_\_\_

**Please give the name of a reliable contact below:**

Contact name: \_\_\_\_\_

Relationship to patient: \_\_\_\_\_

Address: \_\_\_\_\_

Postcode \_\_\_\_\_ Telephone \_\_\_\_\_

Form completed by \_\_\_\_\_ Today's date (Day/Month/Year) \_\_\_/\_\_\_/\_\_\_

Now please photocopy this form (for your own records) and send the ORIGINAL to the SYNTHESIS Trial Coordinating Center, Stroke Unit, Ospedale Niguarda Ca' Granda, Piazza Ospedale Maggiore 3, 20162 Milano, Italy, or Fax on ++39 02 64442819



**Neurological deficit** (please score each item)

<b>NIH STROKE SCALE ITEM</b>	<b>Scoring Definitions</b>	<b>Score</b>
1a. Level of Consciousness (LOC)	0=alert and responsive 1=arousable to minor stimulation 2=arousable only to painful stimulation 3=reflex responses or unarousable	
1b. LOC Questions--Ask pt's age and month. Must be exact.	0=Both correct 1=One correct (or dysarthria, intubated, foreign lang) 2=Neither correct	
1c. Commands--open/close eyes, grip and release non-paretic hand, (Other 1-step commands or mimic ok)	0=Both correct (ok if impaired by weakness) 1=One correct 2=Neither correct	
2. Best Gaze--Horizontal EOM by voluntary or Doll's.	0=Normal 1=partial gaze palsy; abnl gaze in 1 or both eyes 2=Forced eye deviation or total paresis which cannot be overcome by Doll's.	
3. Visual Field--Use visual threat if nec. If monocular, score field of good eye.	0=No visual loss 1=Partial hemianopia, quadrantanopia, extinction 2=Complete hemianopia 3=Bilateral hemianopia or blindness	
4. Facial Palsy--If stuporous, check symmetry of grimace to pain.	0=Normal 1=minor paralysis, flat nasolabial fold, asymm smile 2=partial paralysis (lower face=UMN) 3=complete paralysis (upper & lower face)	
5. Motor Arm--arms outstretched 90 deg (sitting) or 45 deg (supine) for 10 secs. Encourage best effort. Circle paretic arm in score box	0=No drift x 10 secs 1=Drift but doesn't hit bed 2=Some antigravity effort, but can't sustain 3=No antigravity effort, but even minimal mvt counts 4=No movement at all X=unable to assess due to amputation, fusion, fx, etc.	L or R
6. Motor Leg--raise leg to 30 deg supine x 5 secs.	0=No drift x 5 secs 1=Drift but doesn't hit bed 2=Some antigravity effort, but can't sustain 3=No antigravity effort, but even minimal mvt counts 4=No movement at all X=unable to assess due to amputation, fusion, fx, etc.	L or R
7. Limb Ataxia--check finger-nose-finger ; heel-shin; and score only if out of proportion to paralysis	0=No ataxia (or aphasic, hemiplegic) 1=ataxia in upper or lower extremity 2= ataxia in upper AND lower extremity X=unable to assess due to amputation, fusion, fx, etc.	L or R
8. Sensory--Use safety pin. Check grimace or withdrawal if stuporous. Score only stroke-related losses.	0=Normal 1=mild-mod unilateral loss but pt aware of touch (or aphasic, confused) 2=Total loss, pt unaware of touch. Coma, bilateral loss	
9. Best Language--Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis	0=Normal 1=mild-mod aphasia; (diff but partly comprehensible) 2=severe aphasia; (almost no info exchanged) 3=mute, global aphasia, coma. No 1 step commands	
10. Dysarthria--read list of words	0=Normal 1=mild-mod; slurred but intelligible 2=severe; unintelligible or mute X=intubation or mech barrier	
11. Extinction/Neglect-- simultaneously touch patient on both hands, show fingers in both vis fields, ask about deficit, left hand.	0=Normal, none detected. (vis loss alone) 1=Neglects or extinguishes to double simult stimulation in any modality (vis, aud, sens, spatial, body parts) 2=profound neglect in more than one modality	

Date (dd/mm/yy) \_\_\_/\_\_\_/\_\_\_

**TOTAL=**

## 10.2 Long-term assessment

Patient's clinical condition will be evaluated by a telephone call after 90 days from randomization by trained examiners, blinded to treatment allocation. The following aspects will be examined:

### Disability and death

Using the modified Rankin score, in 6 categories:

0. *No symptoms*

1. *No significant disability despite symptoms*: able to carry out all usual duties and activities.

2. *Slight disability*: unable to carry out previous activities but able to look after own affairs without resistance.

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. *Death*

The interobserver agreement for differences of 2 grades on the modified Rankin scale is 0.91<sup>17</sup> and its use by telephone instead of direct examination appears reliable<sup>18</sup>.

### New vascular episodes

Recurrence of stroke, myocardial infarction, defining the diagnosis with the available clinical information.

### Cause of death.

Data of follow-up will be obtained through a telephone interview by a limited number of interviewer per country, appropriately trained and blind to the treatment assignment. The interviewer will use a checklist of activities of daily living as a guide in questioning the patient<sup>17,18</sup>. In case of unavailability of patient, a proxy will be interviewed.

## **11. SAMPLE SIZE**

The sample size estimation for the primary outcome is based on a standard two sample test for differences in binomial proportions (two tailed), with  $\alpha=5\%$  and a power probability of 80%. The study is powered to detect or disprove an absolute difference of about 15% between the treatment groups in the percentage of patients with a favorable outcome. At least 172 valuable patients per arm would be required, assuming that 40% of IV rt-PA treated patients (estimation based on rt-PA treated patients in the NINDS trial) would have a favorable outcome.

## **12. STUDY DURATION**

In the case of participation of 10 centers, recruiting at least 2 patients per month, two years of recruitment will be needed. If the patients' number will be higher the study duration will be briefer.

## **13. STUDY ORGANIZATION**

The Scientific Group of the study consists of the following groups:

### **13.1 Steering and Organizing Committee**

This committee is responsible for the design of the protocol and it reviews periodically the progress of the study at operational level. Moreover it deals with all relevant aspects concerned with the progress and status of the study, and is responsible for coordination of clinical work as well as for collecting and processing all data received from the participating centers.

### **13.2 Participating Centers**

They are responsible for recruitment and treatment of the patients and collection of the study data.

### **13.3 Data Management Office**

It has the overall responsibility for the design and the implementation of the computerized data, data entry, quality control and statistical analysis.

### **13.4 Neuroradiologic Reviewing Committee**

All CT scans and angiograms-will be reviewed centrally according to pre-established standards by at least two members of the neuroradiologic committee.

### **13.5 Data monitoring Committee**

This committee consists of permanent members who are experienced neurologists and epidemiologists not associated with the operation of the trial. The members of this group approve the final protocol, periodically review the safety reports on intra hospital events and conduct the interim analyses. They will make relevant recommendations for the conduct of the study to the Steering and Organizing Committee.

## **14. ANALYSES**

“Intention to treat “ analyses will be used throughout.

### **14.1 Primary analysis**

The protocol will include two separate analyses. These will evaluate: 1. the effect of LIA rt-PA, as compared to IV rt-PA, on 3-month survival and autonomy. The primary analysis will be a comparison of the proportion of patients with modified Rankin Scale score 0 or 1 at 3 month. The analysis will be performed with standard statistical tests.

### **14.2 Secondary analysis**

Secondary analyses will include:

1. The proportion of patients reaching an NIHSS score of 6 or less at day 7 in the two treatment groups
2. Symptomatic intracranial hemorrhages, fatal and non-fatal strokes, death from any cause, neurological deterioration.

3. Subgroups analyses will be conducted according to main baseline prognostic variables (age, neurological deficit, time to randomization from stroke onset, CT, scan, and diagnosis) using a multifactorial model.

### **14.3 Safety and interim analysis**

The Safety and Monitoring Committee will receive clinical data about assessment during hospital stay and long-term assessment monthly from the coordinating investigators. Interim analyses are required for every 3 symptomatic intracranial hemorrhages and after every 10 deaths. During the period of recruitment two interim analyses are planned: the first after the first 100 patients randomized and the second after the second 100. The Safety and Monitoring Committee will suspend the study if a statistical and a clinical imbalance in the risk to benefit ratio is found. The Safety and Monitoring Committee may suggest at any time an interim analysis if this is needed.

### **15. SOURCE OF SUPPORT**

The trial has been designed independently of any commercial organization and will be coordinated, managed and analyzed independently.

## 16. APPENDIX A

### GLOSSARY

#### CT SCAN

**Hemorrhage** Presence of hyperdensity areas due to presence of blood.

**Infarct** Hypodense areas due to recent ischemic lesion congruous with neurological deficit

**Hemorrhagic infarct** Presence of one or more hyperdensity areas due to presence of blood with speckled or mottled appearance and with indistinct margins in the context of area of low attenuation representing infarction or edema

**Intracerebral hemorrhage** Very dense, homogeneous region of increased density with distinct margins with or without mass effect including all or the major part of the infarcted lesion

**Other hemorrhages** Intraparenchymal hemorrhage not related to the previous infarct or subdural hematoma or subarachnoid hemorrhage

#### ETIOLOGIC DIAGNOSIS

- **Cardioembolism:** the arterial occlusion is presumably due to an embolus arising in the heart when there is one of the following high-risk cardiac source of embolism: mechanical prosthetic valve, atrial fibrillation with or without valvular heart disease, rheumatic mitral stenosis, atrial appendage thrombus, dilated cardiomyopathy, atrial mixoma, recent myocardial infarction with anterior wall infarction and/or akinetic segment and/or intraventricular thrombus. Diagnostic studies should exclude dissection as a possible cause of stroke.
- **Dissection:** angiographic appearance of elongated and tapering stenosis, possibly with complete occlusion of the lumen and/or signs of intimal flap, a pseudoaneurism (i.e. an aneurismal bulging of the adventitial wall to the false lumen) or a double lumen.
- **Large -artery atherosclerosis:** angiographic findings of >50% stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. A history of intermittent claudication, transient ischemic attacks in the same vascular territory, diminished pulses helps support the clinical diagnosis. Diagnostic studies should exclude potential high-risk sources of cardiogenic embolism, dissection and other causes of stroke.
- **Other:** diagnostic studies identify other etiology such as non-atherosclerotic vasculopathies, hypercoagulable states and hematological disorders. Diagnostic studies should exclude cardioembolism and dissection as possible cause of stroke.
- **Unknown:** diagnostic studies exclude atherosclerotic, high-risk cardiac sources, dissection and other causes of thrombo-embolism.

## EVENTS

**Symptomatic intracranial hemorrhage** Sudden neurological worsening after a period of stable condition or recovery, with documented intracranial hemorrhage (CT scan or autopsy). Neurological worsening is defined by one or more of the following:

1. any major change in the level of consciousness
2. any substantial change in degree of motor deficit
3. new deficits that are clinically significant and persistent

**Extracranial bleeding** It is classified as mild if bleeding did not require blood replacement, or as severe if requiring blood replacement.

**New ischemic stroke** Sudden neurological worsening (see Intracranial hemorrhage) after a period of recovery or stable condition without documented intracranial hemorrhage or cerebral edema from the previous ischemic lesion.

**Cerebral edema** Sudden neurological worsening, as defined above, after a period of stable condition or recovery, due to the development of significant mass effect of the recent lesion, with midline shift.

**New stroke** Unknown if hemorrhagic or ischemic.

**Myocardial infarction** At least two of the following: typical history, new appearance of abnormal Q waves on ECG, peak enzymes levels exceeding twice the upper limit of normal.

**Anaphylactic shock** Sudden respiratory distress with urticaria or angioedema followed by arterial hypotension (SBP < 90 mmHg) and oliguria (< 20 ml/hr) for more than one hour, and within 12 hours of treatment

## MODIFIED RANKIN SCALE

0. *No symptoms*

1. *No significant disability despite symptoms*: able to carry out all usual duties and activities.

2. *Slight disability*: unable to carry out previous activities but able to look after own affairs without resistance.

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. *Death*

## **17. APPENDIX B**

### **MANAGEMENT DURING THE FIRST 7 DAYS**

#### **17.1 Components of care after admission into the Hospital**

- Bed rest progressing to full activity as tolerated:
  - Care of bedridden patients
  - Skin and joint care
  - Bronchopulmonary care
  - Watch for neurological worsening or hypotension during mobilization
- Measure vital signs and neurological checks:
  - Neurological worsening
  - Fever
  - Hypertension or hypotension
- Cardiac monitoring during first 24 hours
- Assess swallowing before starting oral intake of fluids or solids; advance diet as tolerated
- Intravenous fluids to avoid dehydration
- Nasogastric tube feedings for patients who can not swallow
- Avoid indwelling bladder catheter if possible
- Symptomatic treatment of pain, nausea, agitation
- Treat medical or neurological complications
- Treat heart disease and other comorbid diseases
- Prophylaxis against deep-vein thrombosis

#### **17.2 Acute treatment of hypertension**

- Treat anxiety, pain, nausea, vomiting
  - Treat increased intracranial pressure
  - Do not acutely treat an elevated blood pressure
  - If possible, give oral agents or reinstitute medications given before the stroke
  - Gradually lower the blood pressure
  - Monitor blood pressure at least every 30 minutes for two hours:
1. If systolic blood pressure is  $> 180$  mmHg and/or diastolic blood pressure is 105 to 140 mmHg for two or more readings 5 to 10 minutes apart:
    - Give intravenous labetalol, 10 mg over 1 to 2 minutes. The dose may be repeated or doubled every 10 to 20 minutes up a total dose of 150 mg.
    - Monitor blood pressure every 15 minutes during labetalol treatment and observe for development of hypotension.

- The dose may be repeated or doubled every 10 to 20 minutes, up to 150 mg
2. If diastolic blood pressure is  $> 140$  mmHg for two or more readings 5 to 10 minutes apart or if the preceding treatment did not give satisfactory response
- Infuse sodium nitroprusside (0.5 to 10  $\mu\text{g}/\text{Kg}/\text{min}$ )
  - Monitor blood pressure every 15 minutes during infusion of sodium nitroprusside and observe for development of hypotension.

If systolic blood pressure is  $\square 180$  and/or diastolic blood pressure is  $\square 105$  aggressive management of hypertension is discouraged. Conversely, hemorrhagic transformation requires a treatment of high blood pressure more aggressive than that outlined above because of the risk of continued bleeding or recurrent hemorrhage

### 17.3 Acute anticoagulant therapy

- Possible indications: high-risk source of embolism (e.g. mechanical prosthetic valve), pulmonary embolism, and "overt" deep vein thrombosis.
- Do not treat with full-dose oral anticoagulants or unfractionated heparin (e.g. to PT, INR  $> 1.5$  with oral anticoagulant; to aPTT 1.2 fold normal with unfractionated heparin) if patient presents with ischemic lesion detectable by CT scan that is  $> 33\%$  of the MCA territory, or any type of intracranial hemorrhage, unless the patient has a life-threatening condition (e.g. pulmonary embolus).
- Patients at high risk of deep venous thrombosis (e.g. plegia, obesity and obligated bed rest) should be placed on low dose unfractionated heparin (5000 units subcutaneous every 8 or 12 hours) or low molecular heparin (preferably) at prophylactic doses. Otherwise physical prevention (e.g. pressure stockings and mobilization) is recommended.
- Intravenous unfractionated heparin should be initiated with weight based bolus infusion, and adjusted according to the weight-based nomogram<sup>19,20</sup> when a therapeutic level (according to the aPTT) is reached.
- Acute anticoagulant treatment with unfractionated heparin usually requires an initial bolus injection of 5000-10,000 units followed by a *continuous* infusion of about 900 units/h or 10-15 units/Kg/h to maintain the PTT at 2-2.5 times that of the control time.

### 17.4 Treatment of increased intracranial pressure (brain edema, mass effect, hydrocephalus)

#### *General prophylaxis*

- Control fever, agitation, nausea and vomiting, hypoxia, hypercapnia
- Modest fluid restriction (approximately 1.5 L to 2 L/day)
- Avoid potential hypo-osmolar IV fluids



- Elevate the head of the bed to augment venous drainage

*Acute interventions*

- Mannitol 0.5 g/Kg given in a 18-20% solution over 20 to 30 minutes:
- Can repeat 0.25 g/Kg every 6 hours as needed
- Usual maximal daily dose is 2g/Kg
- Replace lost fluids
- Furosemide 20 to 40 mg given IV

**17.5 Treatment of intracranial hemorrhage following thrombolysis**

- Stop any thrombolytic, anticoagulant or antiplatelet therapy.
- Check hemoglobin, hematocrit, PT, aPTT, platelet count and fibrinogen
- Type and cross match 4 units of blood
- Give 4 to 6 units of cryoprecipitate to rise fibrinogen level to > 150 mg/dl
- Recheck fibrinogen level every 4 hours and transfuse with cryoprecipitate to maintain fibrinogen level > 150 mg/dl
- The hemostatic defect must be corrected before any surgery can be performed
- The blood pressure will need aggressive treatment because of the risk of continued bleeding or recurrent hemorrhage

## 18. REFERENCES

1. Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. Clinical and instrumental evaluation of patients with ischemic stroke within the first 6 hours. *J Neurol Sci* 1989; 91:311-321
2. del Zoppo GJ, Poeck, K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992; 32: 78-86
3. Wardlaw JM, Yamaguchi T, del Zoppo G. Thrombolytic therapy versus control in acute ischaemic stroke. Stroke module of the Cochrane Database of Systematic Reviews. Available in the Cochrane Library (database on disk and CDROM). Oxford: Update software, 2001.
4. Norris JW, Buchan A, Cote R, Hachinski V, Phillips SJ, Shuaib A, et al. Canadian Guidelines for Intravenous Thrombolytic Treatment in Acute Stroke: A consensus statement of the Canadian Stroke Consortium. *Can J Neurol Sci* 1998; 25:257-259.
5. Adams HP, Jr., Brott TG, Furlan AJ, Gomez CR, Grotta J, Helgason CM, et al. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation* 1996; 94:1167-1174.
6. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581-1587
7. Alberts MJ. tPA in acute ischemic stroke: United States experience and issues for the future. *Neurology* 1998; 51(suppl 3):S53-S55
8. Zeumer H, Freitag HJ, Knopse V. Intravascular thrombolysis in central nervous system cerebrovascular disease. *Neuroimaging Clin N Am* 1992;2:359-369
9. Sullivan KL, Gardiner GA Jr, Shapiro MJ, Bonn J, Levin DC. Acceleration of thrombolysis with a high dose transthorbus bolus technique. *Radiology* 1989;173:805-808
10. Zeumer H, Freitag HJ, Zanella F, Thie A, Arning C. Local intra-arterial fibrinolytic therapy in patients with stroke: urokinase versus recombinant tissue plasminogen activator (r-tPA). *Neuroradiology* 1993; 35:159-162
11. Del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *Stroke*. 1998;29:4-11
12. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F, for the PROACT Investigators. Intra-arterial Prourokinase for Acute IschemicStroke. The PROACT II Study: A Randomized Controlled Trial *JAMA* 1999;282:2003-2011
13. Lewandowski CA, Frankel M, Tomsick TA, Broderick J, Frey J, Clark W, Starkman S, Grotta J, Spilker J, Khoury J, Brott T. Combined intravenous and intra-arterial r-TPA versus intra-arterial

- therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. *Stroke*. 30(12):2598-605, 1999
14. Wichman A, Sandler AL. Research involving critically ill subjects in emergency circumstances: New regulations, new challenges. *Neurology* 1997; 48:1151-1155
  15. Goldstein LB, Bertels C, Davis JN. Interrater reliability of NIH Stroke Scale. *Arch Neurol* 1989;46:660-662
  16. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;20:864-870
  17. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 19(5):604-7, 1988
  18. Candelise L, Pinaridi G, Aritzu E, Musicco M. Telephone interview for stroke outcome assessment. *Cerebrovasc Dis* 1994;4:341-343
  19. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med* 1993;119:874-81
  20. Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. *Ann Intern Med*. 1993;119:104-9

## **19. Contributions and conflict of interest**

Alfonso Ciccone conceived and wrote this protocol.

No funding source had a role in the preparation of this protocol.