

STATEMENT OF THE RICORS COORDINATOR

RICORS CODE
RD21/0006

Thematic area: CEREBROVASCULAR DISEASES (STROKE)

RICORS Leader: IGNACIO LIZASOAIN

RICORS STRUCTURE AND OBJETIVES

Importance and scope of the RICORS at national and international levels.

Max. 1 page

Stroke is a cerebrovascular disease that has traditionally been defined clinically as a sudden onset of loss of focal neurological function due to infarction or haemorrhage in the brain, retina, or spinal cord. More recently, this definition has been revised to include time, imaging and pathologic criteria (acute episode of focal dysfunction lasting longer than 24h or any duration if imaging findings on CR or MRI; autopsy showing focal infarction or haemorrhage) to distinguish it from transient ischaemic attack (TIA). "Stroke" itself encompasses a heterogeneous group of conditions. Among them, **ischaemic stroke** is the most prevalent, accounting for 86% of cases (Hanhey, Lancet. 2017).

Stroke affects 13.7 million people **globally** per year and is the **second leading cause of death**, with 5.5 million deaths per year, according to the Global Burden of Disease 1990-2016 data (GBD 2019 Risk Factors Collaborators, Lancet Neurol. 2019). An estimated 1 in 4 adults will experience a stroke in their lifetime and there are over 80 million survivors of stroke globally. In 2016, 116.4 million DALYs (disability-adjusted lost years) lost due to stroke, making the present entity the **second leading cause of DALYs** lost worldwide. Despite descending incidence and mortality rates, absolute numbers keep increasing, due to population growth and ageing resulting in a greater number of people with stroke.

In the **European Union**, stroke also represents the **second most common cause of death**, the **first leading cause of adult disability** and **second cause of dementia** after Alzheimer's disease. In 2017, there were 1.1 million incident strokes in the European Union, 9.5 million stroke survivors, 0.4 million deaths, and 7.0 million DALYs lost because of stroke. By 2047, we estimated an additional 40.000 incident strokes (+3%) and 2.5 million prevalent cases (+27%) (Wafa et al., Stroke. 2020).

In **Spain**, as per 2018 data retrieved from INE (Instituto Nacional de Estadística, 2018), stroke is the **first cause of mortality in women** (14.985 deaths in 2018) and the **second in men** (11.435 deaths). The IBERICTUS study estimated that the age-standardized annual incidence rate of first stroke was 187/100.000 (95% CI 169-182), being the incidence in men higher than that of women (190/100.000 vs 159/100.000)(Díaz-Guzmán et al., Cerebrovasc Dis. 2012).

Globally, **12% of patients with stroke die within the first 24 hours**, 15% at 1 month, 25% at 1 year (55% in intracerebral haemorrhage -ICH-) and 50% at 5 years (75% in ICH). About 40% of stroke survivors are disabled. Beyond vital prognosis, stroke patients are also at increased risk of poor outcome at 1 year including re-hospitalisation (33%), recurrent event (7-13%; 25% at 5 years), **dementia** (7-23%), **mild cognitive impairment -MCI-** (35-47%), **depression** (30-50%), and **fatigue** (35-92%); all of them contributing to affect health related quality of life (Hankey, Lancet. 2017; Béjot et al., Presse Med. 2016).

SUMMARY

2nd cause of death (first in women in Spain)

2nd cause of DALYs lost

2nd cause of dementia, 1st cause of adult disability

Re-hospitalization in 33%

Dementia (7-23%) and MCI (35-47%)

Depression (30-50%) and fatigue (35-92%)

In terms of **socioeconomic burden**, it is estimated that stroke uses up to 3-4% of health care spending in high-income countries. The first year following the event comprises 76% of the direct health care costs, mostly represented by hospital costs. It has been published that those with **higher post-stroke disability** (measured by 3-month modified Rankin Scale -mRS-) had the highest costs: patients with an **mRS score** of 4 had 5 times greater the annual health care costs (\$279,188 USD) than those with an mRS score of 0 (\$53,578 USD) (Kim et al., Neurology. 2020).

In the light of the foregoing, exhaustive research on improved diagnostics and therapeutic strategies is pressing to combat the epidemic of stroke and its devastating consequences our society is facing.

The proposal to structure **RICORS-ICTUS** network arises from **23 research units** (from 11 autonomous regions) that have devoted most of their efforts to generate knowledge on basic and clinical aspects of cerebrovascular disease in recent years, and **9 associated clinical groups** who provided additional information in the healthcare field and facilitate the transfer of results of the network. Most of them, have been cooperating in the last years through the previous networks (INVICTUS+, INVICTUS, RENEVAS) demonstrating the added value of coordinated and synergic work among different research groups.

The GENERAL OBJECTIVE of the RICORS-ICTUS will be "**TO IMPROVE THE PROGNOSIS OF STROKE PATIENTS**" by studying 5 specific objectives: **1)** Biomarkers for identification of stroke and its recovery; **2)** Acute-phase treatment; **3)** Cerebroprotection; **4)** Brain repair and functional recovery; **5)** Secondary prevention (for details see Scientific Proposal and Impact).

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POTENTIAL IMPACT

Describe the dissemination plan and the strategy for the transference and exploitation of results to the society.
Describe the potential impact on patient-based health outcomes and National Health System (portfolio of services, national cohesion)...

Describe the contribution of the RICORS to national and international standards Max. 2 pages (10,700 characters)

IMPACT. As we have commented, stroke is **first cause of death** in women in Spain (second in men), **first cause of adult disability**, **second cause of dementia** and **second cause of DALYs lost**. Therefore, stroke represents a massive clinical, social, and economic burden for Spanish society, yet we have very limited effective therapies to treat it. This inadequacy is despite intensive research efforts and numerous failed clinical trials. Leading Spanish stroke researchers with a track record of established cooperation will share their complementary expertise that should facilitate a better integration and increase of the collaborative cerebrovascular research efforts in our country and a measurable improvement of its quality and international competitiveness. Remarkably, **survival after stroke** is not associated with full recovery, as up to 90% of patients who survive have different types of sequelae. About 40% of stroke survivors are **disabled**, 33% need **re-hospitalisation**, 25% have a **recurrent event** at 5 years, almost 50% of stroke survivors have different degrees of **cognitive impairment** including **dementia**, 50% have **depression** (30-50%), and between 35-92% have chronic **fatigue**; all of them contributing to be the **second cause of DALYs lost**.

Based on a thorough re-examination of the failures and bottlenecks of previous attempts to improve effective therapies for stroke, the RICORS-ICTUS Network proposes an integrative and innovative approach to improve patient prognosis. The GENERAL OBJECTIVE is "**TO IMPROVE THE PROGNOSIS OF STROKE PATIENTS**" which covers all the phases after a stroke and the processes that can prevent recurrent events. 5 specific objectives (for details see Scientific Proposal).

1) The identification of diagnostic and prognostic **BIOMARKERS** is perhaps one of the most important challenges in biomedicine. We will look for biomarkers to differentiate ischemic from hemorrhagic stroke and "mimics". Biomarkers of risk (unstable plaques and atrial fibrillation) and of reperfusion treatment complications (HT and non-reperfusion). We are also going to study biomarkers of functional recovery and cognitive deterioration to prevent these sequelae. This objective includes several clinical trials (BIO-FAST, BIOSHIP). The identification of these biomarkers will have a direct impact on a faster and more effective treatment (directly related to objective 2) improving the **prognosis** of patients and reducing the social and economic impact in our country.

2) **ACUTE PHASE OF TREATMENT.** It will involve improving reperfusion rates and patient selection and to increase the benefit/risk balance of iv thrombolysis vs thrombectomy. This is a key factor since, as previously mentioned, the percentage of patients who undergo reperfusion treatment is low (15-20% in the best of cases) and of these, up to 50% do not reperfuse. Achieving a higher rate of patients treated will mean not only a greater number of patients without sequelae but also a very important social and economic impact. It has been described that "**10-minute faster treatment** predicted a gain of about 40 days of disability-free life" for the patient and an incremental net monetary benefit of about \$10,000 for society (Kunz et al., Neurology 2020) and that mechanical thrombectomy produced over 101,327 additional **QALY** (quality-adjusted life years) and cost savings of \$1.7Billion in societal costs (Candio et al., Stroke 2021). We will also study **stroke-associated infections** and **COVID-19**. Again, the achievement of these objectives will lead to an improvement in the **prognosis** of stroke patients.

3) **CEREBROPROTECTION.** In this objective and based on the background of the different partners, we plan to validate the protective efficacy of those drugs or techniques developed from the previous cerebrovascular networks and to investigate new treatments and strategies to improve the **outcome and prognosis** of stroke patients. We will conduct different clinical trials to demonstrate the protective efficacy of uric acid (URICO-ICTUS); of lowering glutamate levels by using enzymes or by hemodialysis techniques (GOTIS, DIAGLUICTUS); of antagonists of immunity receptors such as TLR4 (APRIL) and of techniques such as ischemic preconditioning (REMOTE-CAT).

4) **BRAIN REPAIR AND FUNCTIONAL RECOVERY.** The main goals of this objective are the identification of markers of functional recovery and cognitive impairment. It has been published that those with **higher post-stroke disability** (measured by **modified Rankin Scale -mRS-**) had the highest costs: patients with an **mRS score** of 4 had 5 times greater the annual health care costs (\$279,188 USD) than those with an mRS score of 0 (\$53,578 USD) (Kim et al., Neurology 2020). Regarding post-stroke **dementia** and **cognitive impairment**, the Göteborg stroke study showed that patients with cognitive impairment spend significantly more time in the hospital and at readmissions and among them, the mean total cost (home assistance, assistive devices, house modifications, etc) was 35,287\$ as compared with 11,016\$ in patients with no cognitive impairment (Claesson et al., Stroke. 2000). This objective includes several clinical trials (TESLA, DULCINEA).

5) **SECONDARY PREVENTION.** Stroke prevention appears as the most effective strategy to reduce the stroke economical and logistic challenges. The general goal of this objective is to improve the **identification** of patients at the highest risk of **stroke recurrence** (unstable plaques and atrial fibrillation as examples), so that the recurrence risk profile can be individualized to establish the most effective **preventive strategy** for each patient.

DISSEMINATION. The impact of these contributions will be reflected in the increase the quality of care of stroke patients, offering new therapeutic options. Likewise, it is to tempt to postulate that these contributions will improve the prevention strategies and diagnostic tools for cerebrovascular diseases. This impact is measurable by quality indicators (see Impact Indicators). RICORS-ICTUS Network have an adequacy of the **dissemination plan and the transfer of technology strategy** for exploiting of results, mainly focused on articles, patents and clinical trials:

- 1) **Publication** of results in journals in our field (JCR; first decile and first quartile), among which we can mention: N Eng J Med, Lancet Neurol, Lancet, Ann Neurol, Neurology, Stroke, J Clin Invest, Circulation, J Neurosci, journals in which we have just published our results,
- 2) **Intergroup seminars.** On the first Monday of each bimester-trimester, we will set up translational research seminars (basic-clinical) telematically and with a duration of 2 hours (17:00-19:00). For this purpose, we will create a commission formed by a young postdoc and predoc from each group who will be in charge of the organization of these seminars.
- 3) Attendance at **national and international** meetings, such as European Stroke Conference, Brain, Annual meeting of the Neurosciences Society, International Stroke Conference.
- 4) Training for the preparation and presentation of **intergroup** and **international doctoral theses**
- 5) Main results will be protected by the corresponding **patents**.
- 6) **Preclinical studies** will allow the establishment of the conditions for the performance of Phase I and IIa clinical trials.
- 7) Follow-up and start-up of **clinical trials**.
- 8) Participation in **clinical practice guidelines** on stroke.

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ORGANIZATION AND MANAGEMENT

Max. 2 pages (10,700 characters)

In the coordinated project structure, we propose the combination of vertical and horizontal actions that facilitate decision-taking processes, the follow up of the progress of the project and its efficient management. The **COORDINATOR** (Ignacio Lizasoain) will act as contact point for this program, being also responsible for the submission of the technical and economical informs, and all the foreseen deliverables, in due time. Transversal actions related to communication and transfer of technology derived from them will also be responsible for RICORS-ICTUS coordinator (see figure in the RICORS Scientific Proposal document).

The **STEERING COMMITTEE (SC)** of the network will be composed by 12 members to comply with the regulation of being formed by at least 50% of the groups (6 women and 6 men). The members are: Ángeles Almeida, Francisco Campos, Mar Castellanos, Exuperio Díez-Tejedor, Mar Freijó, Ignacio Lizasoain, Joan Martí, Joan Montaner, Ana Morales, Natalia Pérez de la Ossa, Anna Rosell, Tomás Segura. The SC is the **executive committee** responsible for decision making. The SC will also support the Coordinator and will be responsible for establishing good communication and assist work among the groups that form the network and the implementation of the objectives. The SC will hold **working meetings**, at least, twice per year. During the months of January and February of each year, a face-to-face meeting shall be held with the following structure: i) Study and approval, if applicable, of the previous minutes; ii) Report of the Network Coordinator; iii) Study and approval, if appropriate, of the annual budget for income and expenses for the previous and the current year; iv) Study and approval, if applicable, of the dissemination and training plan for the current year; v) requests and questions. In addition to the face-to-face meetings, this committee will be in contact via telematic means, as often as necessary. All the information shared in those meetings will be registered in the corresponding **minutes**, which will be stored on the website's intranet with restricted access for IPs.

In the second level of the organizational structure are the **LEAD PARTNERS** of the **objectives**. The coordinators are specialists in each of the programs described, who will supervise the coordinated implementation of scientific actions, and communication of the results of the activities. To execute the project, the coordinators of the objectives will prepare reports including the detailed status of the programmed works, including the percentage of execution of the objectives, the expected timeframe for its complete consecution and the bottlenecks found in the progression of the scientific research. All this information will be used by the coordinator for discussion with the SC, for further decision taking. The lead partners are:

Objective 1. Biomarkers for identification of stroke and its recovery: Ana Rosell and Joan Montaner.

Objective 2. Acute-phase treatment: Natalia Pérez de la Ossa and Joan Martí

Objective 3. Cerebroprotection: Angeles Almeida and Francisco Campos

Objective 4. Brain repair and functional recovery: Mar Freijó and Exuperio Díez-Tejedor

Objective 5. Secondary prevention: Mar Castellanos and Tomás Segura.

Finally, there will be a **PRINCIPAL INVESTIGATOR (PI)** for each of the **research groups** involved in the Project. The PIs will be responsible for the organization and supervision of the research activities developed by their research groups in the different objectives and work packages, and to exploit the synergies among the different research groups. All of them (23) represent groups of 11 autonomous communities. The principal investigators of the research groups of the Network are:

1. Francisco Campos Pérez. Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS)

2. Maria del Mar Castellanos Rodrigo. Instituto de Investigación Biomédica A Coruña.

3. Jordi Jiménez Conde. Instituto Hospital del Mar de Investigaciones Medicas (IMIM)

4. Joaquín Serena Leal. Instituto Investigación Dr. Josep Trueta (IDIBGI)

5. Joan Martí Fàbregas. Instituto de Investigación Sant Pau

6. Ángel Chamorro Sánchez. Fundacio Clinic per la Recerca Biomedica (FCRB)

7. Francisco Purroy García. Instituto Investigación Biomédica de Lleida.

8. Monica Millán. Instituto de Investigación Germans Trias i Pujol

9. Anna Rosell Novel. Instituto de Investigación Hospital Vall D'Hebron

10. Blanca Fuentes. Instituto de Investigación Hospital Universitario La Paz (IdIPAZ)

11. Alberto Alcázar. Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS)

12. Ignacio Lizasoain. Instituto de investigación Sanitaria 12 de Octubre (IMAS12)

13. Jose Aurelio Vivancos Mora. Instituto Investigación Hospital La Princesa

14. María del Mar Freijo. Instituto Investigación Biocruces-Bizkaia

15. Juan Bautista Salom Sanvalero. Instituto de Investigación Sanitaria Hospital La Fe

16. Tomás Segura Martín. Complejo Hospital General de Albacete (SESCAM)

17. Joan Montaner Villalonga. Instituto de Biomedicina de Sevilla (IBIS)

18. Patricia Martínez. Fundación Investigación Biomédica Andalucía Oriental (FIBAO)

19. Ángeles Almeida Parra. Instituto de Investigación Biomédica de Salamanca (IBSAL)

20. Juan Francisco Arenillas Lara. Hospital Clínico Universitario de Valladolid

21. Maria Teresa Mendioroz Iriarte. Instituto Investigación Sanitaria Navarra (IDISNA)

22. Elena López-Cancio. Instituto Investigación Sanitaria Principado Asturias (HUCA)

23. Cristofol Vives-Bauzá. Instituto Investigación Sanitaria Islas Baleares (IDISBA).

Moreover, the **PI** for each **ASSOCIATED CLINICAL GROUPS**, who provided additional information in the healthcare field and facilitate the transfer of results of the network. All of them (9) represent groups of geographical areas of the rest of Spanish autonomous communities. Therefore, all the autonomous communities are represented in RICORS-ICTUS network. The principal investigators of the clinical associated groups of the Network are:

1. Manuel Gomez-Choco. Hospital de Sant Joan Despí Moisès Broggi.
2. Joaquín Carneado. Hospital Puerta de Hierro.
3. Carlos de la Cruz. Hospital Virgen de la Victoria de Málaga.
4. Enrique J Palacio. Hospital Universitario Marqués de Valdecilla (IDIVAL)
5. Jose María Ramirez Moreno. Hospital Universitario de Badajoz.
6. Juan Carlos López Fernández. Hospital Dr. Negrín La Palma Gran Canaria.
7. Ana Morales. Hospital Virgen de La Arrixaca.
8. Javier Marta. Hospital Universitario Miguel Servet.
9. Francisco Villaverde. Hospital San Pedro. Logroño.

The PI of all groups will form a **Consultive Committee** on the network, which will directly address the **RICORS-ICTUS ASSEMBLY** that will meet once a year, during the annual Conference to be organized by the Steering Committee.

RICORS-ICTUS also has an **EXTERNAL SCIENTIFIC ADVISORY COMMITTEE**, which is composed of four members including renowned scientists from the basic scope and include clinical setting. The committee will issue an annual written report on the activities of the network. They will meet with the groups of the network at least once a year. This committee will be composed by:

1. Diana Aguiar de Sousa. Hospital de Santa Maria. University of Lisbon. Portugal.
2. Sean Savitz. Institute for Stroke and Cerebrovascular Disease. Texas University USA.
3. Valeria Caso. Stroke Unit, Santa Maria della Misericordia Hospital University of Perugia. Italy.
4. Eng H Lo. Department of Radiology, Massachusetts General Hospital, Harvard Medical School, USA.

Additionally, an open **WEBSITE** will be created to share information from all research units and where all events and information of the network will be published. All the administrative work necessary to keep RICORS-ICTUS running will be developed by a **PROJECT MANAGER** (secretary) of the network.

The sequence of decisions that the new **RICORS-ICTUS** has been taking is, in summary, as follows:

- January 28, 2021. The new **Steering Committee (SC)** is elected, formed by 11 members that later (April 15) was increased with one more member to comply with the regulation of being formed by at least 50% of the groups. The SC, finally, is formed by 12 PIs, 6 women and 6 men.
- February 18, 2021. The functions of the **SC as the executive committee** of the network are established.
- March 4, 2021. Study by the SC of the different research groups and associated clinical groups.
- March 11, 2021. **Approval** of the **definitive list of research groups** (23 groups from 11 autonomous communities) and **associated clinical groups** (9 groups, prioritizing those communities not represented). All the autonomous communities are represented in the network.
- March 18, 2021. **Classification of research groups (RG)** for budgeting purposes. The SC approves this classification. To establish the budgets for each of the RG, the SC decided that the groups themselves should carry out a self-assessment of their scientific-technical profile of the last 5 years, according to the scales (with some modifications) used by the Carlos III Health Institute for contracting the Rio Hortega personnel. Scientific production (70/100), projects (20/100) and patents (10/100) were evaluated. According to the self-evaluations of the groups (which were checked by the SC) 3 categories of groups were established: category A with a budget of 77,000 euros/year plus indirect costs (representing 5.3% of the total budget); category B with a budget of 62,000 euros/year plus indirect costs (4.3%) and category C with a budget of 42,000 euros/year plus indirect costs (2.9%). Category A is made up of 9 RGs, category B of 8 RGs and category C of 6 RGs.
- March 25, 2021. The **general objective** of the RICORS-ICTUS and the **5 specific objectives** are approved, and the coordinators are nominated. An expression of interest document is requested from each of the research groups, to prepare the final research report with the corresponding work-packages. The associated research groups express their interest to collaborate in the different objectives.
- April 8, 2021. The first **general assembly** of the new RICORS-ICTUS is held via telematics with the participation of more than 50 researchers (PIs of the groups and other members of the groups). The coordinator informs the participants of the different steps taken by the SC.
- April 15, 2021. The SC approves the **final budget** of the research groups and the coordination budget.

The SC has met every Thursday since its creation, via telematic from 9.30-10.30 a.m. to prepare the application. All the minutes approved by the SC have been sent to all PIs to maintain a fluid and continuous information and a transparent management.

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IMPACT, INNOVATION, TRANSFER AND DISSEMINATION

Describe the potential impact of the programme and the expected scientific and technological contributions; detail the adequacy of the dissemination plan and the strategy for the technology transfer.

This section should include: potential impact on health outcomes for patients and for the backbone of the National Health System; for the scientific community (clinical guidelines or other contributions to national and international standards); patents.

Max. 3 pages (17,500 characters)

IMPACT.

As we have commented, stroke is **first cause of death** in women in Spain (second in men), **first cause of adult disability**, **second cause of dementia** and **second cause of DALYs lost**. Therefore, stroke represents a massive clinical, social, and economic burden for Spanish society, yet we have very limited effective therapies to treat it. This inadequacy is despite intensive research efforts and numerous failed clinical trials. Leading Spanish stroke researchers with a track record of established cooperation will share their complementary expertise that should facilitate a better integration and increase of the collaborative cerebrovascular research efforts in our country and a measurable improvement of its quality and international competitiveness. Remarkably, **survival after stroke** is not associated with full recovery, as up to 90% of patients who survive have different types of sequelae. About 40% of stroke survivors are **disabled**, 33% need **re-hospitalisation**, 25% have a **recurrent event** at 5 years, almost 50% of stroke survivors have different degrees of **cognitive impairment** including **dementia**, 50% have **depression** (30-50%), and between 35-92% have chronic **fatigue**; all of them contributing to be the **second cause of DALYs lost**.

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2) **ACUTE PHASE OF TREATMENT**. It will involve improving reperfusion rates and patient selection and to increase the benefit/risk balance of iv thrombolysis vs thrombectomy. This is a key factor since, as previously mentioned, the percentage of patients who undergo reperfusion treatment is low (15-20% in the best of cases) and of these, up to 50% do not reperfuse. Achieving a higher rate of patients treated will mean not only a greater number of patients without sequelae but also a very important social and economic impact. It has been described that "**10-minute faster treatment** predicted a gain of about 40 days of disability-free life" for the patient and an incremental net monetary benefit of about \$10,000 for society (Kunz et al., Neurology 2020) and that mechanical thrombectomy produced over 101,327 additional **QALY** (quality-adjusted life years) and cost savings of \$1.7Billion in societal costs (Candio et al., Stroke 2021). We will also study **stroke-associated infections** and **COVID-19**. Again, the achievement of these objectives will lead to an improvement in the **prognosis** of stroke patients.

3) **CEREBROPROTECTION**. In this objective and based on the background of the different partners, we plan to validate the protective efficacy of those drugs or techniques developed from the previous cerebrovascular networks and to investigate new treatments and strategies to improve the **outcome and prognosis** of stroke patients. We will conduct different clinical trials to demonstrate the protective efficacy of uric acid (URICO-ICTUS); of lowering glutamate levels by using enzymes or by hemodialysis techniques (GOTIS, DIAGLUICTUS); of antagonists of immunity receptors such as TLR4 (APRIL) and of techniques such as ischemic preconditioning (REMOTE-CAT).

4) **BRAIN REPAIR AND FUNCTIONAL RECOVERY**. The main goals of this objective are the identification of markers of functional recovery and cognitive impairment. It has been published that those with **higher post-stroke disability** (measured by **modified Rankin Scale -mRS-**) had the highest costs: patients with an **mRS score** of 4 had 5 times greater the annual health care costs (\$279,188 USD) than those with an mRS score of 0 (\$53,578 USD) (Kim et al., Neurology 2020). Regarding post-stroke **dementia and cognitive impairment**, the Göteborg stroke study showed that patients with cognitive impairment spend significantly more time in the hospital and at readmissions and among them, the mean total cost (home assistance, assistive devices, house modifications, etc) was 35,287\$ as compared with 11,016\$ in patients with no cognitive impairment (Claesson et al., Stroke. 2000). This objective includes several clinical trials (TESLA, DULCINEA).

5) **SECONDARY PREVENTION**. Stroke prevention appears as the most effective strategy to reduce the stroke economical and logistic challenges. The general goal of this objective is to improve the **identification** of patients at the highest risk of **stroke**

recurrence (unstable plaques and atrial fibrillation as examples), so that the recurrence risk profile can be individualized to establish the most effective **preventive strategy** for each patient.

Our innovative proposal is expected to have a profound scientific/technological impact at several levels:

- **Conceptually**, our study expands current knowledge on stroke focusing on 5 aspects (biomarkers, acute-phase treatment, cerebroprotection, brain repair and secondary prevention), which is expected to reveal key advances to improve the **prognosis** of stroke patients

- At the **diagnostic** and **therapeutic** levels, this proposal will provide a framework ideally suited to identify appropriate non-invasive, sensitive and specific biomarkers of the different stroke subtypes and to design specific therapies for each of the nosological entities involved, with an evident therapeutic and diagnostic potential.

- Impact on **employability and innovation**: In this very active field with a clear need for well-trained scientists, this proposal will enhance the career perspectives and employability of the trained fellows in cerebrovascular science R&D. We are mainly requesting a budget for personnel (more than 75% of the total budget; 3,629,801,13 euros/years). Specifically, The RICORS-ICTUS intends to hire 37 full-time researchers during the 3 years, in particular, 16 Predoctoral researchers (5 of them with Master degree), 10 technicians and 11 postdoctoral researchers. (See Budget justification).

- At the **academic level**, we expect that the importance and novelty of the results obtained will be attractive in high-impact journals and meetings (please see Diffusion Plan below).

- Last but not least, at the level of **innovation**, the information obtained is liable to be patented, thus promoting collaborative research with the industrial sector (please see next section "Added value and Management of the intellectual property").

DISSEMINATION.

The impact of these contributions will be reflected in the increase the quality of care of stroke patients, offering new therapeutic options. Likewise, it is to tempt to postulate that these contributions will improve the prevention strategies and diagnostic tools for cerebrovascular diseases. This impact is measurable by quality indicators (see Impact Indicators). RICORS-ICTUS Network have an adequacy of the **dissemination plan and the transfer of technology strategy** for exploiting of results, mainly focused on articles, patents and clinical trials:

1) **Publication** of results. Prior to publication, all data generated by the network will be considered for protection and, if applicable, appropriate steps will be taken towards industrial exploitation of the knowledge. Once IPR protection has been arranged, scientific results will be made available to the scientific community via high-ranking peer-reviewed scientific journals in our field (JCR; first decile and first quartile), among which we can mention: N Eng J Med, Lancet Neurol, Lancet, Ann Neurol, Neurology, Stroke, J Clin Invest, Circulation, J Neurosci, journals in which we have just published our results,

2) **Intergroup seminars**. On the first Monday of each bimester-trimester, we will set up translational research seminars (basic-clinical) telematically and with a duration of 2 hours (17:00-19:00). For this purpose, we will create a commission formed by a young postdoc and predoc from each group who will be in charge of the organization of these seminars.

3) Attendance at **national and international** meetings, such as European Stroke Conference, Brain, Annual meeting of the Neurosciences Society, International Stroke Conference.

4) Training for the preparation and presentation of **intergroup** and **international doctoral theses**

5) Main results will be protected by the corresponding **patents**.

6) **Preclinical studies** will allow the establishment of the conditions for the performance of Phase I and IIa clinical trials.

7) Follow-up and start-up of **clinical trials**.

8) Participation in **clinical practice guidelines** on stroke.

9) Dissemination plan also includes the design of a **web page** describing the lines of work of our network. Thus, information will be made available to the general public through the public domain of the website.

PATIENTS.

The **European Parliament** in June 2003 addressed the urgency of tackling the prevention of stroke at EU level; in the 10-point action plan a key goal was to set up a European Patient Group for Stroke Prevention. In October 2004, 20 patient groups from across Europe joined forces and formed **SAFE**, the **Stroke Alliance For Europe**. SAFE is a non-profit-making organization that represents a range of stroke support organizations from across Europe. With the goal of driving stroke prevention up the European political agenda and preventing the incidence of stroke through education. SAFE is included in several of the European projects from Horizon 2020 in which some members from RICORS-ICTUS are participating. That is a great link to have SAFE experience, participation and advice included in our network amplifying the voice of patients in and out RICORS-ICTUS.

In **Spain**, our relationship with **patient organizations** will be to organize dissemination days on the disease, present the objectives and achievements of the research network (to the population, media, authorities), to facilitate contact with patients and families, to know their opinion on the prioritization of lines of work and objectives. To this purpose we will have a direct communication with them, and the different associations will be invited to the **annual congress** of the network. In fact, we have foreseen the corresponding expenses (see budget justification).

The main patient associations are:

- Federación española de ictus: <https://ictusfederacion.es/fei-home/asociaciones/>

- Fundación freno al ictus: <https://www.frenoalictus.org/>

- Fundació Ictus: <https://www.fundacioictus.com/es>

- FEDACE: <https://fedace.org/>
- Fundación Alberto Contador: <http://fundacionalbertocontador.com/ictus/>
- ATECE: <http://atecebizkaia.org/>
- ADACEN: <https://www.adacen.org/>

TRAINING PROGRAM

One of the goals of the network is to provide research training and clinical neurologists in general and specific issues related to the design and conduct of research, development and innovation. To achieve these objectives, we have developed a training program based on previous experience, as well as for the expertise of RICORS-ICTUS researchers in other training programs such as EU grants.

The specific objectives are:

1. To improve the technical and knowledge training for PhD and postdoc students of RICORS-ICTUS teams.
2. To create a network of young researchers working in Cerebrovascular research.
3. To improve research skills for clinical neurologists collaborating with RICORS-ICTUS in topics related with translational research for Cerebrovascular diseases.
4. To promote and facilitate collaboration, interaction, and constant updating of the members of the Network through presentational and virtual activities.
5. Activities and dissemination of research results network.

Training activities are going to be advertised through RICORS-ICTUS website as well as during the meetings of the network and to be based in the following actions:

1. **Short-stays** in other RICORS-ICTUS labs/stroke units or in international centers of excellence in Cerebrovascular research. This activity is mainly dedicated to PhD and postdoc researchers but also is going to be offer to residents in neurology and young neurologists interested in developing their skills in Cerebrovascular research. Such stages will be designed in order to transfer knowledge and technical expertise within teams in relation with the WP and specific subprojects of RICORS-ICTUS. Moreover, we could establish new collaborations with the centers of excellence, favoring the production of our network.
2. **Intergroup seminars** will be organized. On the first Monday of each bimester-trimester, we will set up translational research seminars (basic-clinical) telematically and with a duration of 2 hours (17:00-19:00). For this purpose, we will create a commission formed by a young postdoc and predoc from each group who will be in charge of the organization of these seminars.
3. **Training courses.** IRCORS-ICTUS will organize training courses focused on different topics of interest in Cerebrovascular research such as proteomics, genomics, cellular and animal models of disease, neuroimaging, etc. Such courses are open to all RICORS-ICTUS researchers as well as the network of clinical collaborators. These training courses could include lectures, training cases to be solved by teamwork and in lab training if available.
4. Organization of **scientific symposiums** with the presence of important scientists, about topical issues in the field of cerebrovascular diseases.
5. Participation in **external training courses** that may have a strategic interest for the network, in order to train scientists in new techniques or new specialties.
6. **Grants** to attend national and international conferences in the field of neurosciences, to disseminate the results of the network and to be updated on new scientific advances.
7. Organization of an **annual conference** aimed at all researchers of the Network, Here the results of the works will be presented by the participating members, and the participation of young researchers will be encouraged. In addition, this meeting will be to finalize the new works and setting goals.
8. Direction and co-direction of **theses** related to the objectives of the programs and WP.

RICORS Code: RD21/0006

ADDED VALUE OF SCIENTIFIC COLLABORATION AMONG THE DIFFERENT RESEARCH GROUPS AND MANAGEMENT OF THE INTELLECTUAL PROPERTY

Functional structure of the programme: describe the extension of the synergies and the added value to be obtained from the cooperative structure.

Scientific relationship between the different research groups in the proposed research topics: describe the ongoing scientific collaboration between different groups of the programme on the proposed objectives.

Describe the management of the intellectual property, in terms of previous knowledge, access rights, knowledge generated within the project and exploitation agreements.

Max. 2 pages (10,700 characters)

Establishing research networks and collaborations provides the necessary flexibility to adapt to a wide spectrum of arising challenges, and the establishment of synergies to develop extensive studies. It enables develop extensive studies and share learning, new research opportunities, establishing new research projects, joint applications for funds, and technology transfer, that individually would not be possible. In the **RICORS-ICTUS** network, researchers from different institutions and regions work together as consortia focused on stroke research aiming **to improve the prognosis of stroke patients**. Our network is especially valuable for the Spanish health system because they offer interdisciplinary expertise and allow recruitment of stroke patients in different settings and scenarios. Moreover, the network consists of multidisciplinary groups, making it even more attractive for progress in the subject area, because the contact existing between translational and clinical groups would be very difficult to develop without this program.

The proposal to structure **RICORS-ICTUS** network arises from 23 research units (from 11 autonomous regions) that have devoted most of their efforts to generate new knowledge on translational and clinical aspects of the cerebrovascular disease in recent years, and 9 associated clinical groups who provided additional information in the healthcare field and facilitate the transfer of results generated in the network to the Spanish health system. Most of groups have been cooperating in the last years, through previous research networks (INVICTUS PLUS, INVICTUS and RENEVAS) demonstrating the added value of coordinated and synergic work among different research groups. In this new edition, new groups have been added, from other regions of Spain (in fact, all the autonomous regions of Spain are including whether we consider research and associated clinical groups), to optimize and strengthen the study of stroke, then complementing the weakest points of the previous network.

The **Coordinator** of the RICORS-ICTUS network has participated in the prior research networks on Cerebrovascular Diseases, playing a prominent role as a member of the Executive Steering Committee and WP leader. Then, this previous experience on management has been very positive and represents an added value to this proposal. In fact, 18 of the groups that are part of the scientific program of this new network have already participated in the past program of INVICTUS-PLUS network, funded by the Spanish Health Institute Carlos III (ISCIII) in 2016. The results of the network are highly satisfactory. In addition, many of these groups were already involved in the previous RENEVAS and INVICTUS networks. Therefore, the networking of most of the groups is fully consolidated, as they have been working and collaborating as a network for around 14 years (from 2007 to the present). Moreover, the proposal incorporates new groups, especially clinicians, which will provide added value to get the objectives for the large clinical studies.

In relation to **ongoing scientific collaboration**, members of this network have achieved funding from international competitive calls for the development of research projects in collaboration, with more than one network group and with another international reference centers. In this context, RICORS-ICTUS groups participate in the project "Regenerative Stem cell therapy for stroke in Europe - RESSTORE" the Horizon 2020 program, or the PANA project "Promoting active ageing: functional nanostructures for Alzheimer's disease at ultra-early stages", in the Horizon 2020 program, along with other European centers. The ongoing collaboration between different groups on the proposed objectives is also evident in the number of high-quality publications that groups have in common in the field of stroke.

Regarding the **management of intellectual property**:

Results are owned by the Party that generates them.

1. Joint ownership

a) Jointly Results will belong to those Parties involved in its development. The Parties agree that two or more Parties own results jointly if: (1) they have jointly generated them and (2) it is not possible to: (i) establish the respective contribution of each partner, or (ii) separate them for the purpose of applying for obtaining, or maintaining, their protection. The joint owners must agree (in writing) on the allocation and terms of exercise of their joint ownership (joint ownership agreement), to ensure compliance with their obligations.

Every Party involved in the development of such jointly Results, will retain a share on that Results according to the Intellectual and Economic Contribution made in the development of such Results. Economic Contribution shall refer to RTD and IP protection expenses, related to the jointly Foreground, born by each Party. Activities such as manufacturing scaling-up, regulatory advice, GMP implementation or business development advice shall not be considered as Economic Contribution. Any RTD and IP protection expenses not directly related to the jointly foreground shall be not considered as Economic Contribution to Foreground.

Each of the joint Parties shall be entitled to inform other Parties and the Coordinator about any discrepancies in the calculation of their share of the Jointly Results. Any discrepancies that might be risen will be discussed and settled within the Executive Steering Committee.

b) Each of the joint owners shall be entitled to use their jointly owned Results for non-commercial research activities on a royalty-free basis, and without requiring the prior consent of the other joint owner(s).

c) Unless otherwise agreed in the joint ownership agreement, each joint owner shall be entitled to exploit the jointly owned results and to grant non-exclusive licenses to third parties (without any right to sub-license), if the other joint owner/s are given:

i) at least 45 calendar days advance notice; and ii) fair and reasonable compensation.

2. Transfer of Results

a) Each Party may transfer ownership of its own Results.

b) It may identify specific third parties it intends to transfer the ownership of its Results. The other Parties hereby waive their right to prior notice and their right to object to a transfer to listed third parties.

c) The transferring Party shall, however, at the time of the transfer, inform the other Parties of such transfer and shall ensure that the rights of the other Parties will not be affected by such transfer.

d) The Parties recognize that in the framework of a merger or an acquisition of an important part of its assets, it may be impossible under applicable EU and national laws on mergers and acquisitions for a Party to give the full 45 calendar days prior notice for the transfer.

e) The obligations above apply only for as long as other Parties still have - or still may request - Access Rights to the Results.



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