

## Editorial

Cooperative Research in Biomedicine. Spain's Cardiovascular Network, *Red de Investigación Cardiovascular*

## Investigación cooperativa en biomedicina. La Red de Investigación Cardiovascular

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## INTRODUCTION

Cardiovascular disease remains the leading cause of death and disability in Spain.<sup>1,2</sup> Nevertheless, its impact has steadily declined in recent years, which may be partly due to the promotion of biomedical research. Setting up and running cooperative research networks are the most important of the actions undertaken by the Spanish authorities to promote research.

In 2002, the *Instituto de Salud Carlos III* (ISCIII)<sup>3</sup> created the Thematic Networks for Cooperative Research (*Redes Temáticas de Investigación Cooperativa* [RETIC]).<sup>4</sup> These were based on the idea of an association between different multidisciplinary research centers and groups and the ISCIII. The research centers or groups could be publicly or privately funded with at least 4 autonomous regions represented in each network. The aim was to promote collaboration between research groups within the National Health System. In the cardiovascular area, calls in 2002 and 2006 led to the creation of 3 networks<sup>4</sup> (HERACLES,<sup>5</sup> REDINSCOR,<sup>6</sup> and RECAVA<sup>5–7</sup>). The last call (RETIC 2012) included a proposal for a single cardiovascular network and resulted in the integration of the 3 research networks into one project, the *Red de Investigación Cardiovascular* (RIC, Cardiovascular Research Network), which is described below.

## THE NETWORK

## Objectives, Strategic Design, and Organization

As mandated in the last call,<sup>8</sup> the aim of the RIC is to reduce the impact of cardiovascular disease on survival and quality of life in Spain by promoting biomedical research and translating the results into daily clinical practice. The training of researchers is also an important part of the mandate. The RIC is organized as a single network<sup>5–7</sup> and incorporates a system of solid and

representative governance. It includes a training program and uses a matrix structure of longitudinal actions for scientific development in combination with cross-sectional measures to facilitate those actions. The 2012 call established a requirement for priority research programs in each network (Table). The overall network coordinators were responsible for identifying those programs and selecting individuals to lead them. Together, they then established specific research projects and decided on the most appropriate groups to carry them out. Research groups that had participated in the 3 previous cardiovascular networks were invited to participate as well as other groups that had not participated in the earlier networks but were considered necessary for the new project. The appropriateness and budgets of the invited groups were subjected to a process of external and anonymous evaluation. The final version of the RIC includes more than 800 researchers from all regions of Spain, organized in 64 research groups (Fig. 1).<sup>9</sup>

The organizational structure of the RIC (Fig. 2) ensures maximum representation of all groups and is made up of the following elements: *a*) the General Assembly, which includes all groups; *b*) the Governing Council, which is composed of program coordinators, members of the subcommittees (scientific, training, and communication), the Executive Committee, and the head of the Technical Secretariat; *c*) an executive body, the Executive Committee, which, through the General Coordinator, is responsible for the overall coordination and operative functioning of the RIC, and *d*) an External Scientific Committee, which advises the network and ensures a measure of external control.

## Overall Scientific Design

The network is organized into 7 major programs focusing on the main cardiovascular diseases.<sup>10</sup> Each program is required to develop a 4-year research project,<sup>9</sup> which is evaluated by international experts. The projects focus on specific issues using planned work packages and involving several coordinated groups. Objectives are specified and project implementation is defined in

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**Table**

## Research Activity Programs

Myocardial remodeling in heart disease
Atherothrombosis. Myocardial ischemia
Diseases of the heart valves and the great vessels
Family and congenital heart disease
Cardiac arrhythmias
Clinical and translational heart failure
Cardiovascular prevention and mechanisms of hypertension

terms of milestones and deliverables, thereby allowing evaluation of progress.

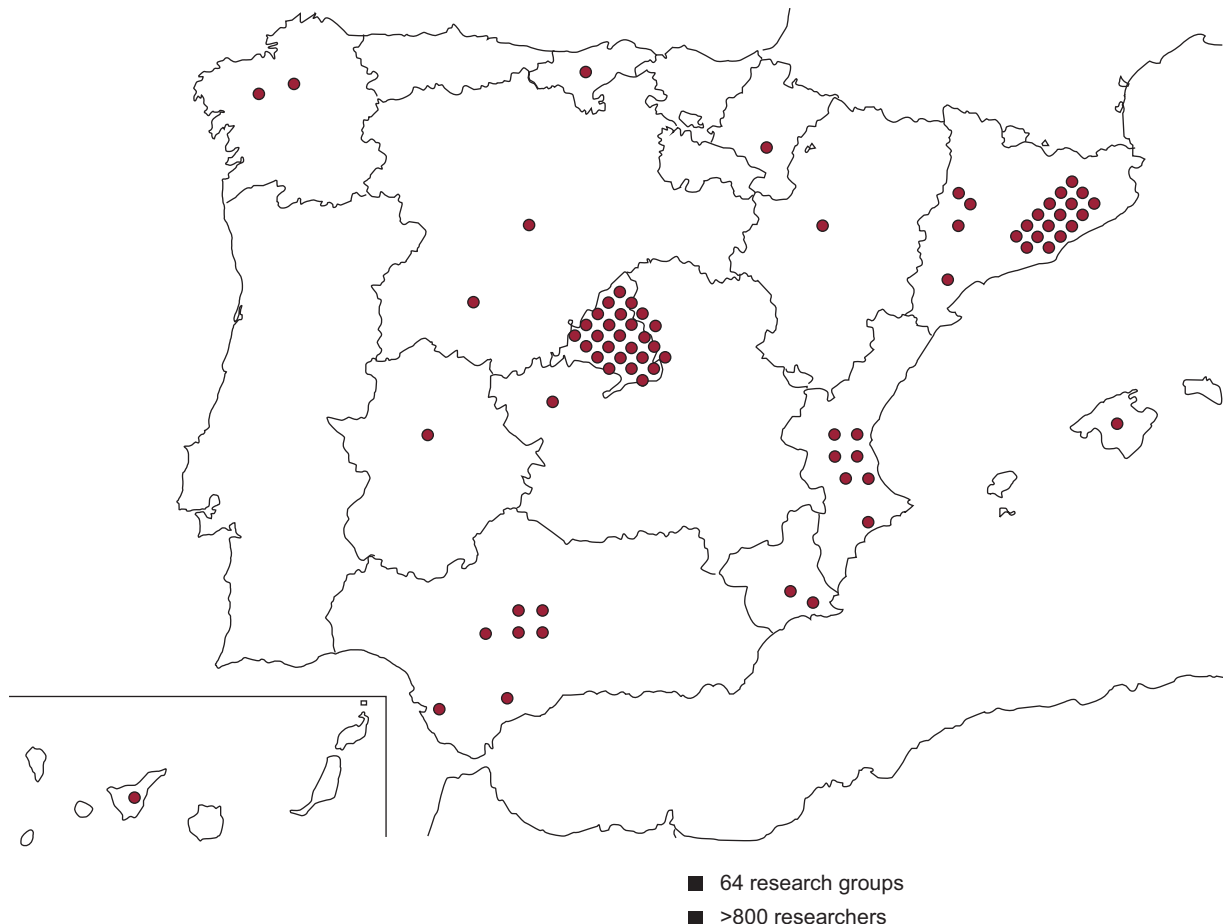
One of the strategic directives of the RIC is to generate a comprehensive, explicit, and evaluable scientific program that goes beyond a simple summation of the 7 projects comprising the different programs. There are compelling reasons for this. First, the spirit of the ISCIII call was clearly to integrate the preexisting cardiovascular networks into a single organizational structure, rather than 7 different structures. Second, there was a need to ensure cooperation between the groups in the different programs. Finally, it was considered essential to have a single, common scientific platform, with high strategic value. The 3 hypotheses underlying the RIC are: *a*) that there are molecular mechanisms that are common to different cardiovascular diseases; *b*) that knowledge of distinct cardiovascular diseases and syndromes is scattered across different specialist areas and that communication between those areas is less than ideal, and *c*) that tackling many

cardiovascular research objectives requires a large critical mass and a high number of patients.

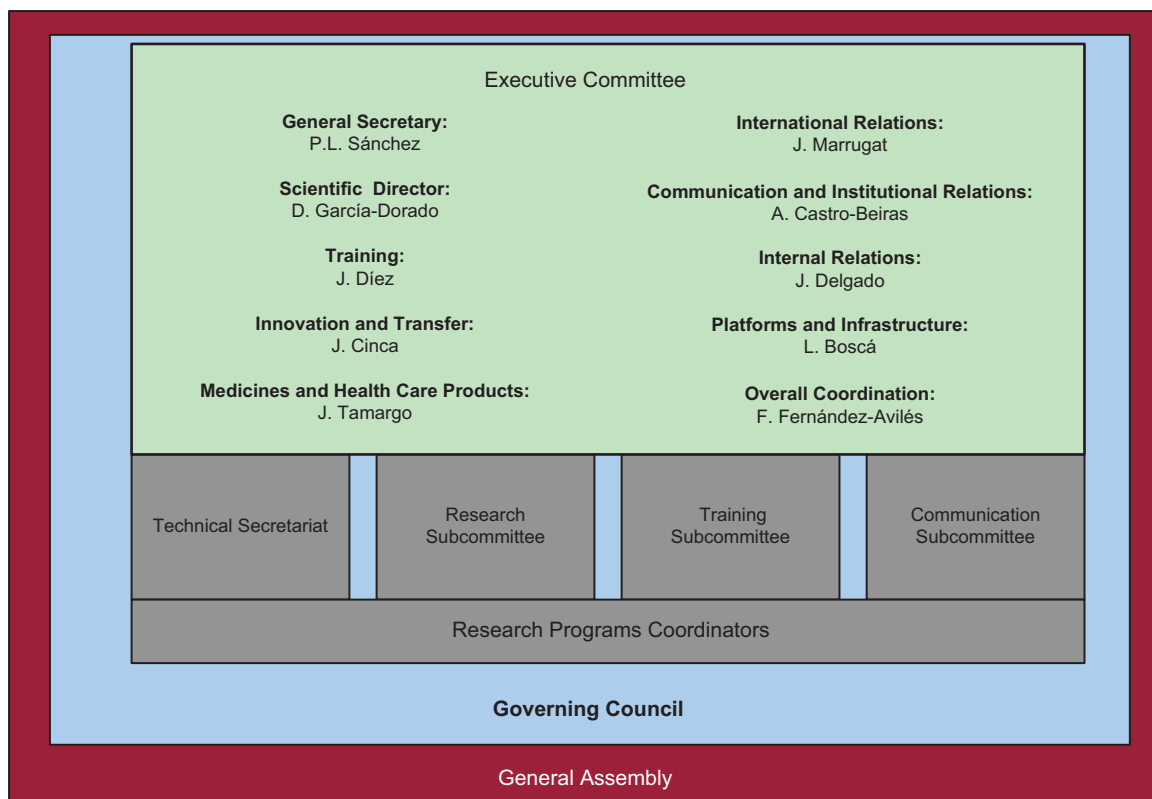
Consequently, the scientific focus of the network for the next 4 years will be very much on solving the problems associated with coronary disease in all its forms (programs 1, 2, 5, 6, and 7), on cardiovascular risk factors, with special attention to high blood pressure and diabetes mellitus (programs 2 and 7), on nonischemic myocardial disease (programs 1, 4, 6, and 7), diseases of the aorta (program 3), and on familial heart diseases (programs 3 and 4). As regards the creation and promotion of research tools, the objectives of the scientific program are: *a*) to create a large collection of commonly used samples, which will be stored in biobanks at the different participating centers and which be accessible to different groups and network programs; *b*) to build a stronger base of unique technology platforms with high strategic value; *c*) to create a resource base for laboratory research (including genetically modified models); *d*) to organize a platform to support clinical research, and *e*) to establish lines of communication and cooperation among groups involved in laboratory and clinical research. Objectives in the comprehensive scientific program of the RIC are designed to be met according to a preset schedule. The implementation of the network's overall scientific program will be evaluated annually in terms of how well it has met its objectives and the amount of cooperative activity generated at all levels.

### Training Program in Translational Research

Given that advances generated by basic cardiovascular research are clearly not being adequately transferred to the health care system and the population,<sup>11</sup> one of the general objectives of the



**Figure 1.** Map of the 74 centers corresponding to the 64 research groups that compose the *Red de Investigación Cardiovascular*.



**Figure 2.** Organizational governance of the Cardiovascular Research Network.

RIC is to provide scientists with training in the methodology, implementation, and management of research, the aim being to facilitate translation from basic knowledge to advances in social and health care.<sup>12–14</sup>

The training program is designed to: *a*) provide basic researchers with the knowledge and skills to carry out research intended to convert basic discoveries into new models or clinical paradigms; *b*) provide clinical investigators with the knowledge and skills to transform new models or paradigms into diagnostic and therapeutic advances that will help renew clinical practice; *c*) provide epidemiological researchers with the knowledge and skills to orient diagnostic and therapeutic advances toward prevention and the preservation of population health, and *d*) equip scientific managers with the knowledge and skills to ensure that advances in health and clinical care generate social wealth in its broadest sense.

The 3 tools used to implement this aspect of the RIC are: *a*) classroom academic courses; *b*) virtual interactive meetings, and *c*) a scientist exchange program. The academic element consists of 2 courses per year on “Advances in Translational Research” and “Biomedical Research Management”. All members of the network centers participate in these courses, which are organized in collaboration with scientific societies such as the Spanish Society of Cardiology and the Spanish Arteriosclerosis Society and/or national research centers such as the National Cardiovascular Research Center. The courses are held at a single venue. A second group of face-to-face academic courses are held in the respective headquarters of the individual centers within the RIC and take into account the teaching plans of the institutions involved. The number and frequency of these courses varies. The program of virtual interactive meetings aims to maintain a steady flow of information and training between RIC centers, using various types of audiovisual communication.

The scientist exchange program is the main instrument within the training strand of the RIC and is based on movement of RIC

researchers among centers. Scientists can spend time at RIC centers other than their own to work on cooperative projects that involve both their own and the receiving center, or they can spend time at a centers with a RIC platform, in order to learn how they work and how they are used in research. A third option is to spend time at centers external to the RIC. These centers may be domestic or foreign and the objective is to acquire a methodology that is not available in any of the RIC centers but which is required for the development of projects within the RIC research agenda. The management training program is overseen by a subcommittee responsible for the approval and dissemination of the various plans, the allocation of funds necessary for their implementation, and the evaluation of results.

#### **Other Strategic Actions: Platforms, Foundation, Communication**

Organization, scientific productivity, and training will be fundamental in determining the future performance of the RIC, but its success will also depend on other strategic actions.

Such actions include the enhancement of platforms used across the research groups, ie: *a*) computing resources and databases; *b*) biobanks and collections; *c*) proteomics; *d*) genomics; *e*) metabolomics; *f*) cardiac electrophysiology; *g*) extraction and normalization of DNA and other proteins; *h*) imaging data assessment laboratory, and *i*) an animal facility for the use of genetically modified animals. One of the key tools for the sustainability and development of the RIC is the Foundation for Network Research in Cardiovascular Disease (*Fundación para la Investigación en Red en enfermedades CardioVasculares* [FIRCAVA]), which was established to promote and observe the RIC under the rules of the RETIC<sup>15</sup> and with the agreement of the ISCIII. Through its legal status and agile management, FIRCAVA is intended to facilitate research and

training, and to raise funds beyond those that can be obtained in public calls. FIRCAVA already provides several services, including an academic CRO (contract research organisation). It is also accredited by the European Union and acts as a research center with the ability to apply, develop, coordinate, implement, and manage European research projects in which RIC research centers can participate via FIRCAVA.

The network is further supported by an interactive web portal that allows the dissemination and exchange of information and provides shared computing resources for the coordination and management of cooperative research.<sup>9</sup> The RIC also has a press and communications office whose brief is to disseminate the results of research and training to the scientific community, and to society more generally.

## THE 2013-2017 SCIENTIFIC PROGRAMS

The 7 current scientific projects at RIC are as follows:

1. *Adverse ventricular remodeling.* The objectives of this program are to: a) explore the molecular and cellular mechanisms involved in its pathophysiology; b) develop and test new biochemical and imaging biomarkers which are able to identify, diagnose, and monitor response to treatment and clinical events in patients with adverse ventricular remodeling; c) develop new treatment targets; d) conduct clinical trials to prevent or reverse adverse ventricular remodeling, and e) develop biotechnology and innovation in the field. The program coordinator is Francisco Fernández-Avilés, and 15 research groups will undertake the different work packages.
2. *Reduction of myocardial damage secondary to coronary artery disease.* The objectives of this project are to: a) gain a deeper understanding of the mechanisms of ischemia-reperfusion and the genetic and environmental factors that modulate them, as well as to develop safe and effective treatments for patients with myocardial infarction; b) to better understand the molecular mechanisms underlying the progression and destabilization of atherosclerotic plaque and intracoronary thrombosis in order to facilitate the development of new therapeutic strategies, and c) use epidemiological tools to investigate methods to identify patients at risk for adverse ischemic cardiovascular processes, plaque instability, and poor clinical outcome in the management of patients with acute coronary syndrome. The program coordinator is David García-Dorado, and 15 research groups will be involved in the different work packages.
3. *Aortic aneurysm: from molecular mechanisms to new diagnostic and therapeutic tools.* The objectives of this program are to: a) investigate the role of genetics, hemodynamics, and risk factors in the development of aortic aneurysms; b) identify the molecular and biological mechanisms involved in vascular wall dilation, and c) develop new guided therapeutic strategies and biomechanical genetic markers in the clinical management of the disease. The program coordinator is Arturo Evangelista, and 15 research groups are involved in the different work packages.
4. *Familial heart disease.* The objectives of this project are to: a) improve the diagnosis, clinical management, treatment, and risk stratification of individuals with familial heart disease, and to prevent sudden death and improve quality of life; b) promote the creation of large databases that include the study of families and which can provide sufficient information to researchers and clinicians to help answer existing clinical questions, and c) integrate basic and clinical research activities in order to improve clinical and scientific efficiency in this disease. The program coordinator is Alfonso Castro-Beiras, and 11 research groups will develop the different work packages.

5. *Identification and characterization of the processes involved in the development of arrhythmic substrate myocardial scarring.* The objectives of this program are to: a) organize a platform to study the development and characteristics of heterogeneous myocardial tissue in patients with structural heart disease and ventricular tachycardia; b) develop experimental postinfarct and ventricular tachycardia models to allow the characteristics of the arrhythmogenic substrate and progression to be studied over time; c) identify the mechanisms that determine the occurrence of ventricular tachycardia substrate and the changes that occur over time in the scar tissue; d) develop imaging techniques to characterize and identify arrhythmogenic substrates and stratify arrhythmic risk; e) identify biomarkers that monitor the extent and progression of arrhythmogenic myocardial tissue; f) develop experimental models to explore therapies to prevent and treat arrhythmic progression, and g) design clinical trials to meet the objective described in point f). The program coordinator is Ángel Arenal, and 11 research groups will develop the different work packages.

6. *Translational and clinical heart failure.* The objectives of this program are to: a) improve understanding, prognosis, care, and cost-effectiveness in heart failure and heart transplantation; b) organize a horizontal scientific and technology platform for the performance of clinical trials and translational research in heart failure and cardiac transplantation; c) gain greater understanding of the pathophysiology and treatment of heart failure, pulmonary hypertension and graft rejection using a joint clinical, biochemical, and genetic approach; d) identify the most appropriate candidates for complex and expensive treatments in order to improve prognosis and cost-benefit ratios, and e) explore new proinflammatory cellular activation mechanisms, nuclear-cytoplasmic derangement, and calcium management in cardiac tissue from patients with heart failure. The program coordinator is Juan Cinca, and 13 research groups will develop the different work packages.

7. *Prevention of cardiovascular disease and research into hypertension.* The objectives of this program are to: a) improve the predictive power of cardiovascular risk functions used in primary prevention; b) develop mathematical functions to predict prognosis in acute coronary syndrome, stroke, and heart failure, and c) study hypertensive molecular and metabolic mechanisms in the development of atherosclerosis and cardiovascular disease. The program coordinator is Jaume Marrugat, and 13 research groups will develop the different work packages.

## FINAL THOUGHTS

Network research has been and remains an effective tool for translational research in cardiovascular disease in Spain. It has created synergies between groups and has increased information exchange between scientists involved in basic, clinical, and epidemiological research. The benefits are beginning to become apparent, with a decrease in morbidity and mortality from cardiovascular disease in Spain in recent years. The new network call means that cardiovascular research in Spain is now concentrated within a single grid project. In addition, during a time of austerity politics and severe cuts in financing for R+D+I, the RIC will receive a similar amount of funding as that provided to the RECAVA, HERACLES, and REDINSCOR networks in the last years of their existence. This, perhaps more than anything, underlines the commitment of our science and health authorities to supporting the RIC and its role as an essential tool to boost research and investigator training in cardiovascular diseases throughout Spain. Noblesse oblige.

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## CONFLICTS OF INTEREST

None declared.

## REFERENCES

1. Instituto Nacional de Estadística. Defunciones según causa de muerte [accessed 2013 Jun 16]. Available at: <http://www.ine.es/jaxi/menu.do?type=pcaxis&path=/t15/p417&file=inebase&L=0>
2. Instituto Nacional de Estadística. Encuesta de morbilidad hospitalaria [accessed 2013 Jun 16]. Available at: <http://www.ine.es/jaxi/menu.do?type=pcaxis&path=/t15/p414&file=inebase&L=0>
3. Instituto de Salud Carlos III [accessed 2013 Jun 16]. Available at: [www.isciii.es](http://www.isciii.es)
4. Sánchez PL, Fernández-Baza A, Fernández-Avilés F. ¿Qué son las redes temáticas de investigación cooperativa en salud (RETICS)? *Cardiocr.* 2011;46:131–5.
5. Marrugat J, López-López JR, Heras M, Tamargo J, Valverde M. Red cardiovascular HERACLES. *Rev Esp Cardiol.* 2008;61:66–75.
6. Alonso-Pulpón L, Borrás X, Brugada J, Cinca J, Fernández Cruz A, González Juanatey JR, et al. Red de investigación clínica y básica en insuficiencia cardíaca (REDINSCOR). Redes temáticas de investigación cooperativa del Instituto de Salud Carlos III. *Rev Esp Cardiol.* 2008;61:76–81.
7. García-Dorado D, Castro-Beiras A, Díez J, Gabriel R, Gimeno-Blanes JR, Ortiz de Landazuri M, et al. Red Temática de Investigación Cooperativa en Enfermedades Cardiovasculares (RECAVA). *Rev Esp Cardiol.* 2008;61:58–65.
8. Ministerio de Economía y Competitividad. Resolución de 8 de Feb de 2012, del Instituto de Salud Carlos III, por la que se aprueba la convocatoria de ayudas de la Acción Estratégica de Salud, en el marco del Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2008–2011. Boletín Oficial del Estado, 2 de marzo 2012, núm. 53. Sec. III [accessed 2013 Jun 16]. Available at: <http://www.boe.es/boe/dias/2012/03/02/pdfs/BOE-A-2012-3035.pdf>
9. Red de Investigación Cardiovascular [accessed 2013 Jun 10]. Available at: [www.redinvestigacioncardiovascular.es](http://www.redinvestigacioncardiovascular.es)
10. Sipido KR, Tedgui A, Kristensen SD, Pasterkamp G, Schunkert H, Wehling M, et al. Identifying needs and opportunities for advancing translational research in cardiovascular disease. *Cardiovasc Res.* 2009;83:425–35.
11. Nieuwlaet R, Schwalm JD, Khatib R, Yusuf S. Why are we failing to implement effective therapies in cardiovascular disease? *Eur Heart J.* 2013;34:1262–9.
12. Lauer MS, Skarlatos S. Translational research for cardiovascular diseases at the National Heart, Lung, and Blood Institute: moving from bench to bedside and from bedside to community. *Circulation.* 2010;121:929–33.
13. Lauer MS. Advancing cardiovascular research. *Chest.* 2012;141:500–5.
14. Dégano IR, Elosua R, Marrugat J. Epidemiología del síndrome coronario agudo en España: estimación del número de casos y la tendencia de 2005 a 2049. *Rev Esp Cardiol.* 2013;66:472–81.
15. Ministerio de Sanidad y Consumo. Resolución de 13 de junio de 2006, del Instituto de Salud Carlos III, por la que se convocan ayudas destinadas a financiar estructuras estables de Investigación Cooperativa, en el área de biomedicina y ciencias de la salud, mediante la participación en Redes Temáticas de Investigación Cooperativa en Salud. Boletín Oficial del Estado, 19 de junio de 2006, n° 145 [accessed 2013 Jun 16]. Available at: <http://www.boe.es/boe/dias/2006/06/19/pdfs/A23296-23301.pdf>