ECRIN SPANISH REPORT

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Contents:

1. LEGISLATION

On May 1st. the new 2001/20/EC Directive has entered into force. In Spain, the Directive has been transposed in February 2004; by the *Real Decreto 223/2004*. The new law regulates randomised clinical trials (RCTs) with investigational medicinal products, different from observational studies (studies defined as those in which every investigation, diagnostic, therapeutic and follow-up procedure strictly corresponds to the usual practice), and has only minor changes from the previous law (*Real Decreto 561/1993*). It further develops the Medicines law (*Ley 25/1990 del Medicamento*), and it is being applied also to medical devices. Another important law is the *Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Caracter Personal*, the law protecting the use of personal data.

The *Real Decreto 223/2004* is a very close translation to the Directive, being very broad and still is awaiting implementation texts as well as application procedures. The Spanish Competent Authority are defined as the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMyPS) and the *Comités Éticos de Investigación Clínica* (CEICs), the Research Ethics Committees (RECs). Although the general requirements for conducting RCT depend on this law, the accreditation criteria for RECs are depending on local governments.

The law increases the requirements for sponsoring clinical trials, especially for multicenter trials in different domains: liability and accountability, SUSARs notification, providing IMP (including active control drugs and placebos) free of charge, drug labelling and insurance coverage. These requirements have raised great concerns within academia and clinical investigators. Since the last decade some Scientific Societies (mainly in the areas of Oncology, Cardiology, Transplantation, and Infections Diseases/AIDS) have been acting as public clinical trials sponsors, trying to cover areas not developed by the pharmaceutical industry. However, traditionally public funding of clinical trials has been very scarce in Spain.

2. FINANCING AND SPONSORING

Between 500 to 600 RCT are being performed every year in Spain; more than 80% of those are sponsored by the pharmaceutical industry. Individual investigators, cooperative groups and Scientific Societies take into account for the rest of RCT. Madrid and Barcelona enrol more than 50% of all RCT participants.

The *Fondo de Investigaciones Sanitarias* (FIS), derived from the *Instituto de Salud Carlos III*, depending from the Ministry of Health, is the main source of funding for biomedical research in Spain. FIS provides funds through national calls and peer review process on a yearly basis. It has been reluctant to provide funding for clinical trials, being more prone to fund pathophisiological or epidemiological studies than randomized clinical trials. Regional agencies also provide some financial support, but with similar criteria as FIS does.

Investigators believe than pharmaceutical industry and CROs have the necessary resources and investments to fund their trials, but they are usually drug-oriented and addressed to regulatory purposes, and very seldom problem-oriented. These situation should be counterbalanced by a strong political commitment to fund RCT in many neglected areas. Effectiveness studies, comparisons within different usual care patterns and real life strategies, as well as orphan diseases are poorly developed. However these studies are needed for care providers and public agencies to provide the best evidence-based medicine.

The *Instituto de Salud Carlos III* has driven a change in its policy by promoting networking throughout the country. During 2004, and within this framework, the *Red de Centros en Epidemiología y Salud Pública* (RCESP) has been implemented to provide support for collaboration and

communication between centres devoted to epidemiological and clinical research, within Spain and also to collaborate with European networks. Inside the RCESP two working task forces have been initiated. The main division line between the two is methodological; one supporting observational epidemiological studies and the second one, the SCReN, the Spanish Clinical Research Network, devoted to coordinate RCT within the public domain.

3. CENTERS AND NETWORKING

The *Sociedad Española de Farmacologia Clinica* (SEFC) is the Scientific Society that integrates all the Clinical Pharmacology Services (CPhS) working within the Spanish public University Hospitals. Some of the main aims of CPhS are as follows: promoting a more rationale use of drugs, improving drug efficiency and providing tools for academic research within the public Hospitals Network, on a problem-oriented framework rather than a drug-driven strategy. In the main public hospitals, CPhS play an important role conducting RCTs and giving support to individual clinicians or Scientific Societies interested in promoting RCTs. They also support different Clinical Research Centres and Clinical Trials Units that undertake phase I to phase IV RCTs.

These Units and Scientific Societies perform the majority of publicly sponsored RCT in Spain. The new 2001/20/EC Directive should be a challenge and an opportunity to provide a framework for implementing a network of public University hospitals and Scientific Societies to provide the tools needed to undertake publicly oriented RCTs.

On 31st January 2004 an informal meeting was held at the Hospital Clinic, Barcelona. The main objectives and structure of ECRIN was explained to participants. Participants were as follows: Dr. Jacques Demotes (ECRIN chairman), Dra. Mariantonia Serrano from the *Agencia Española del Medicamento y Productos Sanitarios* (AEMyPS), Dr. Josep Torrent-Farnell (Committee of Orphan Drugs, EMEA), Dr. Gerard Urrutia and Dra. MJ Martínez from Cochrane-Iberoamerica and different representatives from Clinical Pharmacology Services from Madrid and Barcelona: Dr. JMª Arnau (Hospital Universitari Vall d'Hebron) Dr. Joan Costa (Hospital Universitari germans Trias i Pujol, Badalona), Dr. Manel Barbanoj (Hospital de Sant Pau, Barcelona), Dr. Antonio Portolés (Hospital Clínico San Carlos, Madrid), Dr. Antonio Carcas (Hospital La Paz, Madrid), Dra. Cristina Avendaño (Hospital Puerta de Hierro, Madrid), and Drs. Joan-Albert Arnaiz and Dr. Xavier Carné (Hospital Clínic, Barcelona and members of

the RCESP). Overall these hospitals represent the public centres with the greatest number of RCTs performed in Spain.

A permanent secretariat of the SCReN group was decided. Its members are as follows: Mariantonia Serrano, Cristina Avendaño, Manel Barbanoj and Xavier Carné who will be the SCReN correspondent to ECRIN in Spain.

The ECRIN-España group (SCReN) Spanish Clinical Research Network, has been presented at the Annual meeting of the *Sociedad Española de Farmacologia Clinica* (SEFC) that was held in Santander on 27-28 October 2004. The project was presented to all Spanish Clinical Pharmacologists who work in Public Hospitals, where the great majority of public-sponsored RCTs are been performed in Spain.

In this meeting a Round Table about ECRIN networking was presented: "*Redes multicéntricas y multinacionales de investigación clínica. Ensayos Multicéntricos en indicaciones huérfanas*". The participants were as follows:

- Xavier Carné (SCReN-correspondent)
- Josep Torrent (EMEA-Orphan Drugs Committee)
- Miguel Martín (Grupo GEICAM –Grupo Español en Investigación Clínica del Cáncer de Mama) Spanish group to study breast cancer
- Carmen Cabezas (Fundación Jordi Gol i Gurina, Barcelona), a Foundation devoted to promote RCT in primary care.
- Chairman: Fernando de Andrés (Former Spanish member of de CHMP of the EMEA).

Prof. Silvio Garattini (Istituto Mario Negri from Milano) was the guest speaker. His lecture was entitled: "Bias in Clinical Trials".

During the roundtable, the objectives and structure of ECRIN were discussed, and all the participants from the different CPhS from Spain willing to participate in ECRIN were invited.

The SEFC secretariat fully supports the initiative and has offered its website (www.se-fc.org) to provide general information about SCReN and a link to the ECRIN website (www.ecrin.org). Within SEFC, different working groups have been implemented devoted to different topics. At present, two main working groups are in operation. One is preparing a unified inform consent sheet, and a second one, dealing with

methodological designs in RCT, has been preparing a draft about "Non-inferiority designs".

Other Scientific Societies; *Sociedad Española de Cardiología,* GEICAM (*Grupo Español en Investigación del Cáncer de Mama*) *de la Sociedad Española de Oncología*, or the *Grupo Español para el estudio del SIDA* (GESIDA), are more focused on specific disease entities, with one of their main activities being to conduct RCT in their specific areas. SCReN, being an interdisciplinary network considers them as strong cooperation partners, with the aim at creating a fluent bi-directional information to connect these Scientific Societies with ECRIN.

4. ETHICS AND INSURANCE

At present, Spain has 129 *Comités Éticos de Investigación Clínica* (CEICS-RECs). Nine RECs are related to different Autonomous Communities: Andalucia, Aragon, Baleares, Cantabria, Asturias, Galicia, la Rioja, Madrid and Navarra. The rest belong mainly to University Hospitals.

An Autonomous Community (local government) is an official state level, which is responsible (among others) for providing and financing the population health care. Public health care provision covers more than 99% of population. Almost 95% of RCTs are being implemented within the National Health Care System. In the remaining 8 Autonomous Communities RECs are mainly located in Hospital settings, and a few in primary care facilities. The Autonomous Communities are responsible for the accreditation of RECs, and for their auditing. The Autonomous Communities' RECs review all trials that are going to be performed in its area of influence.

Spanish RECs meet monthly, they have a median of 14 members, and request a median of 9 copies of the protocol and the Investigator´s Brochure. 65% of them request for payment fees, with a mean of 388 € per protocol (range 0-1.500).

Approximately 80% of all RCTs are multi-centre, and 60% are multi-centre and international. Until first of May 2004 all multi-centre RCT were reviewed by all RECs responsible for each of the participating centres. There was a great heterogeneity among different RECs procedures, some being faster and more efficient that others. The median nº days between submission and approval or disapproval was 62 days (range 27-120 days).

The RD 223/2004 states that the Reference REC for a multi-centre trial should take into account all the implicated REC opinions, and that its final opinion must be reasoned, especially if they are different opinions among different RECs. A REC coordination centre (CC) is responsible for coordinating the different participating RECs, but, at present, this CC is not in operation, nor a uniform documentation form for application has been implemented. Both are urgently needed.

Meanwhile, two different positions have arisen: (1) accepting the mutual recognition procedure, with the final decision of the Reference REC being accepted by all other REC implicated (except for local issues); and (2) a situation where the Reference REC being a simple intermediary between implicated RECs. At present the second option is prevailing.

In order to facilitate the consultation between different RECs and exchange information, a communication system has been implemented through the web. The SIC-CEIC system (*Sistema Informativo de conexión de CEIC*). In order to coordinate the RCT evaluation by the different implicated RECs, all protocols must be submitted between the first and the fifth of every month. The 15th of this month, the implicated RECs must accept the evaluation of the protocol.

With this procedure laid down by the requirements derived from RD 223/2004, almost all REC request for supplementary information or clarification comments, and, thus, almost always the period lay down in paragraph 5 of 2001/20/EC Directive is suspended. As a consequence, at present, the median nº of days between submission and reception of the RECs decision has increased from 62 days to 123 days. The number of amendments has also increased. RECs should also take care of adverse events notification, new facts modifying the benefit-risk ratio and the annual security reports. All these represent an important burden for RECs and many are overwhelmed.

In Spain, any RCT with medicinal products requires an insurance covering for the sponsor responsibilities. He or she is liable unless it can prove that the alleged damage is unrelated to the study. There is one exception; if investigational drugs have been previously registered in Spain, the trial is performed according to SpC, and RECs do not require insurance. However, even in these circumstances, some RECs demand for a insurance coverage. Insurance compensation must be 250.000 € per subject and 3.000.000 € per study. Insurance premium are important and poorly related to the benefit/risk ratio. For instance, a phase IV RCT comparing primary angioplasty vs. thrombolytic treatment in 600 patients

older than 75 years, during the first 6h. after a myocardial infarction has a premium of 72.000 €.

5. PHARMACOVIGILANCE

Pharmacovigilance includes the activities aimed to the identification and quantification of the risk of unwanted effects produced by medicines as well as the assessment of factors and features associated to a higher risk. Its main focus is the assessment of adverse drug reactions once the drugs reach the market. The main objective of pharmacovigilance is to provide continuously the best possible information on the safety of medicinal products, thus enabling the adoption of the appropriate measures and ensuring that the medicinal products available in the market have a favourable benefit-risk ratio for the population under the authorised conditions of use. Pharmacovigilance is a responsibility shared by the regulatory authorities, the marketing authorization holders and health professionals.

Pharmacovigilance has four basic objectives:

1) identify new adverse effects not previously known.
2) quantify the risk
3) propose public health measures aimed to reduce the incidence a
4) provide information to prescriptors, other health professionals, health authorities and the citizens.

Spain joined the WHO International Drug Monitoring Programme in 1984, and the Clinical Pharmacology Units, some of them integrated within the SCReN played a key role in the development of the Spanish system of pharmacovigilance.

The national policy on Pharmacovigilance follows the WHO recommendations to ensure a safe and effective pharmacotherapy and promote the rational use of drugs:

1. The establishment of a national pharmacovigilance system with 17 regional centres and a coordinating centre linked to the pharmacoepidemiology and pharmacovigilance unit at the Division of Human Medicines of the Spanish Medicines Agency.

   The functions of the Spanish Medicines Agency include:
   a) To plan, co-ordinate, assess and develop the Spanish Pharmacovigilance System for medicinal products for human use

and also the tasks of its Technical Committee, in accordance with the "Good Pharmacovigilance Practices of the Spanish Pharmacovigilance System» drawn up by this Committee and published by the Ministry of Health and Consumer Affairs.
b) To establish, in collaboration with the Autonomous Communities, a data processing network which provides computer access to all information collected by the Spanish Pharmacovigilance System.
c) To manage the database of the Spanish Pharmacovigilance System of medicinal products for human use.
d) To act as a reference centre of the Spanish Pharmacovigilance System with the marketing authorization holders of medicinal products.
e) To make available to the marketing authorization holders the reports on suspected serious adverse reactions occurring in Spain and where medicinal products of which they are holders are involved.
f) To notify to the European Agency for the Evaluation of Medicinal Products and the Member States the reports on suspected serious adverse reactions occurring in Spain. This should be made through the data processing network established by the European Agency for the Evaluation of Medicinal Products in collaboration with the Member States and the European Commission.
g) To promote the creation of computerised health databases to be used as a source of information for performing pharmacoepidemiologic studies.

2. The continuing education and information on adverse drug reactions to professionals through different specific publications and bulletins on pharmacovigilance.

3. The development of legislation for drug monitoring.

The Royal Decree 711/2002, of 19 july 2002, regulating pharmacovigilance of medicinal products for human use lays down the matters related to pharmacovigilance and considers the Spanish Pharmacovigilance System as a decentralised scheme integrating the activities of Health Administrations in this matter and co-ordinated by the Ministry of Health and Consumer Affairs. It also establishes the obligation of health professionals to collaborate with this System and regulates the obligations of the marketing authorization holder.

Even though case reports remain the key source for interventions on drug safety, the development of specific pharmacovigilance programs, several well-designed and conducted case-control studies and the use of large

databases are important tools for the assessment of drug safety. The inclusion of safety endpoints in large public-sponsored clinical trials is a key issue to be implemented in ECRIN.

Regarding drugs within RCT, Spain follows EU rules; definition of expected and unexpected events according to Investigator's Brochure, expedite notification of events (7 days for serious ad 15 days for others), MeDRA coding, declaration of SUSARs on the Eudravigilance database by the sponsor, communication of safety report on a annual basis and detail explanation of changes on the benefit/risk ratio to both RECs and to AEMyPS.

6. DATA MANAGEMENT, QUALITY MANAGEMENT SOPs AND AUDITS

Within SCReN a wide range of methodological support is to be found. Activities being offered include: assistance in drafting the protocol and the case report form (CRF), organising data monitoring, data management and data analysis, and assistance in drafting the study report and scientific publication. At present, there is a great variability of practice regarding data management, within different centres. Each centre has its own SOPs, and very few audits have been performed. A lot of work should be done in order to achieve adequate harmonization.

7. DRUG DISPENSATION

According to *Real Decreto* 1564/1992 the Investigational Medicinal Product (IMP) manufacturer must be authorised by the competent authority. The pharmacy service within a public hospital can provide IMP conditioning. Pharmacists play a major role in the control of study drugs, control of administrative documents about the drug cycle and control of Good Manufactory Practice (GMP). Other tasks of the pharmacist are: receiving drug packages and control of drug labelling which should display the name of sponsor, code of the trial, reference of the IMP, batch number, stability period, storage conditions, and expiry date, and the statement*: "Muestra para investigación clínica"*. During the conduct of the trial, the pharmacist is responsible for the storage, dispatching and traceability of the IMP. Also he/she should guarantee the destruction of the remaining unused drugs. Compliance with GMPs may not be possible for many hospital pharmacists that are preparing placebos for non-commercial clinical trials with authorised medications.

8. COMMUNICATION AND PARTNERSHIP

Many Scientific Societies believe that in the new Directive the definition of sponsor is too rigid, and does not take into account public-private partnerships, that many non-commercial trials tend to follow. Many public funding bodies or sponsors are not able to afford some costs (i.e. to provide all investigational drugs free of charge, labelling, and insurance), and some responsibilities (Pharmacovigilance i.e. SUSARs notification) within a pan-European scale. With authorised medicinal products (within effectiveness trials) some of these requirements are excessive.

The possibility of co-sponsorship, by sharing the different sponsor responsibilities among different partners is seen as not possible under the new Directive. If it would be possible, some of the problems above could be solved.

Combination therapies with authorised drugs or strategy studies (i.e. in oncology or AIDS) are the most clear examples of trials very difficult to be implemented with the new Directive. In this situation a combination therapy used outside a trial is being paid by the Social Security System, but within the context of a clinical trial it must be paid by the sponsor. (Article 19 of the Directive: "investigational medicinal products shall be made available free of charge by the sponsor"). Similarly, the requirement for an investigator's brochure even when the study drug is on the market makes the public sponsor dependent on the pharmaceutical companies.

Given the increase in workload and complexity (data monitoring, purchase of study drugs...) of public sponsored trials, there is also a need for increased levels of funding for clinical research, either at the national level when a study is performed in a single member state, or at the EU level for pan-European studies.

The accountability of sponsors performing trials at different European countries needs a network of public institutions (Hospitals, National funding bodies, Universities) ready to provide transnational support for data monitoring, regulatory affairs, management of Pharmacovigilance data, etc. The European Clinical Research Infrastructure Network (ECRIN) programme recently has received funding from the European Union (Support Specific Action in priority 1). ECRIN represents the first step of an Europe-wide infrastructure for publicly-funded clinical research based on the interconnection of different national networks.

9. STUDY REGISTER

The ICMJE statement that RCT registration will be required, as a condition of consideration for publication before the onset of patient enrolment has open an intense debate in Spain. Many investigators believe that promoting transparency for clinical trials is an ethic principle that traditionally has not been fulfilled. According to the *Real Decreto* 223/2004 (article 41) information regarding the RCT title, the sponsor, trial sites, disease and population recruited must be made publicly available through the Web, unless the sponsor states the contrary in the application. The implementation of this article raises practical problems as no such tool exists in Spain, and at present it has not been carried out.

10. EDUCATION AND TRAINING

In Spain there are generally few institutionalised educational programmes in the area of RCT. Many Universities have pregraduate teaching on clinical research and clinical trials methodology, but very few postgraduate courses are offered by Universities. The *Universitat Autonoma de Barcelona* offers a 2-year Master course on Pharmacoepidemiology that incorporates different disciplines and knowledge needed to undertake RCT.

Some other SCReN groups provide postgraduate courses on Good Clinical Practices, Clinical Pharmacology, Epidemiology and Clinical Trials Monitoring and Coordination addressed to physicians, biologists, pharmacists and nurses. Also a wide range of seminars, workshops are regularly offered by a wide range of suppliers. There is a big need of coordinating such activities.

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APPENDIX 1: List of Spanish SCReN centres.

APPENDIX 1

Unit	Personnel	Ongoing studies	Randomized studies	Therapeutic trials	Industry sponsored	Remarks/selected fields
H Clinic CTU Barcelona	16	9	100%	100%	66%	AIDS
St Pau CIM Barcelona	32	13	NA	0%	92%	Neurosciences, PK-PD modeling
Vall d'Hebron FICF, Barcelona	35	23	9%	NA	35%	Neurosciences, cardiovascular Pharmacoepidemiology, Drug safety
C. Farmacología Clínica UAM Madrid	18	15	NA	7%	100%	Cancer, AIDS
HU Puerta de Hierro UIF, Madrid	6	17	82%	76%	100%	Cardiovascular, cancer, metabolism
H Clínico S Carlos SFC, Madrid	30	12	NA	NA	NA	Neurosciences, metabolism, PK-PD
C Cochrane Iberoamericano, UAB, Barcelona	16	18	44%	39%	5%	Cardiovascular, cancer, devices Meta-A
HV Rocio, Sevilla	-	-	-	-	-	-
Total	143	107	-	-	-	-