Final Report Summary - ECRIN-PPI (European clinical research infrastructures network for clinical trials and biotherapy - preparatory phase for the infrastructure)

Executive summary:

Objectives

The European clinical research infrastructure network (ECRIN) was designed to facilitate multinational cooperation in investigator-driven clinical trials in Europe.

To achieve this goal, ECRIN acts as an infrastructure supporting investigators and sponsors in multinational clinical studies by provision of coordinated, high quality services on a not-for-profit basis for academic projects selected according to scientific excellence.

In addition, ECRIN contributes to the structuring of clinical research capacity both at the national and European levels through complementary approaches:

1. developing common standards and tools, increasing transparency and access to data
2. structuring the national clinical research infrastructures
3. reducing the fragmentation of clinical research, through active involvement towards better harmonisation of legislation and the development of pan-European training programmes in cooperation with the other European Strategy Forum for Research Infrastructures (ESFRI) biological and medical sciences (BMS) infrastructures.

In the ECRIN preparatory phase for the infrastructure (PPI) project both these structuring and operation aspects were addressed.

Structuring activities

1. the ECRIN project development board, composed of both ministry and scientific partners, selected the European Research Infrastructure Consortium (ERIC) model for its legal status during the operation phase. As a consequence a business plan was prepared as part of work package three (WP3) to calculate the requested national contribution, whereas the scientific and technical annex and the Statutes were drafted (WP2). Based on these documents, a memorandum of understanding was signed in September 2010 by four countries (Spain, Italy, Germany and France). The ERIC application was formally sent to the Commission in July 2011 by the host country (France). The feedback received in September resulted in changes in the statutes, requiring a new draft and additional negotiations between the four founding members. The second submission step will start when the legal services of these countries will give their formal agreement with the final version. The creation of the ECRIN-ERIC is expected for mid-2012.

2. an extension programme coupled to a capacity building activity helped expansion of the network in the present and future
3. core competences on ethics, regulation, adverse event reporting, monitoring, quality assurance were developed over the course of the project to refine the organisation in the provision of services, to establish the basic know-how needed for efficient support and was transposed into a repository used to develop training for the staff working in the infrastructure.

4. communication was developed first with patients and citizens to increase awareness and acceptability of clinical trials, second with the users to capture their expectations and needs and to make them understand the nature of support and services proposed by ECRIN, then with policymakers to promote the need for a sustainable support for clinical research infrastructure, the need for public funding to large-scale, multinational investigator-driven clinical trials and the need for a more efficient and risk-adapted regulation of trials.

5. finally, a data centre certification process was initiated and will be continued during the next step. This pilot experience allowed establish the criteria for certification and run a first batch of ECRIN certification for professional, not-for-profit data centres able to participate in multinational, ECRIN-supported trials.

Operation activities

1. WP11 was dedicated to the provision of support to pilot clinical trials, selected by the scientific board based on scientific excellence and medical relevance. This helped capture the expectation of users’ communities, to test the complex procedure of supporting multinational investigator-driven clinical trials, to refine the organisation and procedures and to provide hands-on training for the network of European correspondents. This pilot activity resulted among other in a change in the selection process (a two-step selection process was replaced by a single-step selection based on the full protocol), to better define the role of the European correspondents in the coordinating and non-coordinating countries, to understand which tools have to be developed in the near future (costing templates, framework contracts, e-services for information). In turn, the absence of a legal status raised major difficulties for ECRIN, which is currently not able to sign a single task delegation contract with the sponsor and to delegate tasks to the final service providers (i.e. clinical research centres in the partner countries). This is even more complicated for Seventh Framework Programme (FP7) funded projects and we expect all these problems to be solved when the ERIC statute will be given, as the ERIC will be linked by permanent contracts with its national partners that will act as final service providers and as third parties in FP7 funded projects.

2. in spite of these obstacles, a series of multinational clinical trials were selected by the scientific board and are currently being conducted with the support of ECRIN. The first one (a phase one vaccine trial using recombinant pertussis bacteria) is now successfully completed.

Impact and added value

In addition to preparing the next steps of ECRIN development, i.e. the ECRIN-ERIC to run the operations, but also the successful application to the FP7 ECRIN integrating activity project to further structure and expand the connections of ECRIN, this preparatory phase had a major impact of ECRIN and on its national partners.

First of all, it led to develop contacts in new countries to expand the network, with one additional country entering over the course of the project (Poland) and nine other entering during the next ECRIN integrated activities (IA) project, leading to 23 connected countries. It also helped strengthen the national infrastructure in already connected projects, the most salient example being Spain with the set-up and development of the Spanish clinical research network (CAIBER) coupled to a strong coordinating hub. Other countries also took advantage of this multinational benchmarking to upgrade their clinical research infrastructure, including France with the F-CRIN project funded as an infrastructure by the ‘investing for the future’ programme.

Secondly, the ECRIN PPI was a proof-of-concept for the operation phase, demonstrating the usefulness (confirmed by the user’s survey) and effectiveness of the services supporting multinational trials in Europe. This will open a new era where Europe will be regarded as a single area for clinical research, taking advantage of its patients’ population size and of its
medical and scientific expertise, avoiding duplication of parallel, underpowered and underfunded trials and enabling the conduct of large trials addressing major health issues, leading to evidence-based medical practice for the sake of Europe's citizens and healthcare systems. Interestingly, the DG research, health priority, decided in 2011 to fund multinational investigator-driven clinical trials in Europe.

Thirdly, ECRIN-PPI had a major impact on the discussion on the simplification and harmonisation of the regulation of clinical trials, not only through the debates on the European legislation and the need to revise the current clinical trial Directive (2001/20/EC), but also through its active involvement in the global discussion steered by the Organisation for Economic Cooperation and Development (OECD) global strategy forum (GSF) working group to facilitate multinational cooperation in non-commercial clinical trials. This ECRIN contribution to the promotion of a globally harmonised risk-based approach will be reflected in the next ECRIN-IA project (with a WP dedicated to the implementation of this recommendation on monitoring strategies) and also increases the global visibility of ECRIN, facilitating contacts with partner networks and institutions in other world regions.

Finally, ECRIN-PPI established a strong communication policy towards the policy makers, including a hearing and a dinner-debate at the European Parliament, towards the scientific community with a users? survey and users? meetings, numerous meetings with learned societies and collaborative groups and towards the general population and the patients through the annual celebration of the international clinical trials day (ICTD). It also promotes full transparency in clinical trials, particularly with the requirement, among the criteria for acceptance by the scientific board, to provide access to the raw anonymised data after completion of the trial, ensuring the quality of data and the credibility of analyses and building trust among patients and citizens.

Project context and objectives:

Clinical research involves testing new discoveries by carrying out carefully controlled investigations on patients. This includes testing not only new medicines, but also new therapies (e.g. radiation), devices, diagnostic techniques (e.g. imaging) and surgical procedures, as well as optimising existing medicinal products and procedures to promote better health and welfare. Many of these trials are non-commercial, usually driven by pressing public health needs and scientific questions.

Evaluating research outcomes requires multinational cooperation in clinical research for optimisation of treatment strategies and comparative effectiveness research, leading to evidence-based practice and healthcare cost containment.

However, fragmentation of the health and legislative systems and funding sources in Europe represent major bottlenecks to multinational collaboration and serious impediment to conducting international multi-centre trials, particularly for academic researchers who cannot rely on well-developed administrative support mechanisms and who lack expertise, infrastructures and resources. There is a clear deficit in multinational academic studies and less than 10 % are multinational, whereas more than 50 % of industry trials are multinational.

Such need for a pan-European infrastructure to support clinical trials has been recognised by the European Union by the award of significant resources to develop the process and to create the ECRIN, listed on the ESFRI roadmap in 2006 (http://www.ecrin.org) designed to make Europe a single area for clinical research.

ECRIN started in 2004 with a FP6 ECRIN reciprocal knowledge project (RKP), which lasted from 2004 to 2005, which helped identify the bottlenecks and define the strategy to improve situation. The second FP6 ECRIN transnational working groups (TWG) project (2006 to 2008) led to the development of generic tools and procedures for multinational clinical research.

ECRIN was developed to support investigators and sponsors in multinational clinical studies by provision of coordinated, high quality services on a not-for-profit basis for academic projects selected according to scientific excellence.
ECRIN currently covers 14 countries and is based on the connection of national networks composed of clinical trials units or clinical research centres and with a national coordinating hub acting as the single contact point for the coordination of services.

The ECRIN staff is composed of a core team plus European correspondents hosted in each national hub.

ECRIN contributes to the structuring of clinical research capacity both at the national and European levels through complementary approaches:

1. developing common standards and tools, increasing transparency and access to data
2. structuring the national clinical research infrastructures
3. reducing the fragmentation of clinical research, through active involvement towards better harmonisation of legislation and the development of pan-European training programmes in cooperation with the other ESFRI-BMS infrastructures.

The current ECRIN PPI project consisted of a transition from a network to the development of a sustainable distributed infrastructure able to provide support to multinational clinical projects. The key objectives of this preparatory phase were to:

1. define and set up the best appropriate legal structure and agree on a business plan to operate a distributed infrastructure
2. define the expansion strategy and criteria and expand to new countries with the support of the capacity building programme designed to structure and strengthen the non-profit clinical research capacity
3. develop the procedure and criteria to evaluate the scientific excellence of clinical projects
4. further develop the knowledge on regulatory and ethical requirements in the different countries and for the different categories of research and the corresponding generic tools and procedures for multinational clinical research
5. strengthen and develop the expertise of the network of European correspondents
6. define and develop the certification policy for the data centres able to support multinational clinical research
7. conduct a survey on existing resources in terms of good manufacturing practice (GMP) facilities for biotherapy and identify the needs
8. further develop the communication towards the scientific community and adapt the network and services provided to their identified needs.

Project results:

The main planned activities of the consortium during this preparatory phase were to develop the legal structure and operational strategy of the future distributed pan-European infrastructure while starting to support clinical projects, managing operational aspects and developing appropriate tools.

One of the key tasks of the WP2 and project development board was to select the most appropriate legal entity to support the distributed operation of ECRIN and provide support to multinational clinical research.

The decision of the network committee was to establish an ECRIN-ERIC for an unlimited period under the provision of European Community (EC) regulation No 723/2009 of 25 June 2009.

The ECRIN-ERIC is set up to operate a research infrastructure supporting multinational collaboration in clinical research, to make Europe a single area for clinical trials.

ECRIN-ERIC shall provide information, consultancy and services to clinical investigators and sponsors of multinational studies, as well as advice to national and European authorities and policymakers.
Information, consulting and services proposed by ECRIN-ERIC shall particularly cover support to clinical trial management, reducing the fragmentation of health and legislative systems in Europe: submissions to ethics committees and competent authorities, adverse event reporting, study monitoring, data management, support with insurance contracting.

ECRIN-ERIC shall pursue its principal task on a non-economic basis. ECRIN-ERIC has the objectives to provide consultancy and services to multinational clinical research, in any medical field and for any category of clinical research, observing high scientific, ethical and quality standards, in order to strengthen the capacity of the European Union to explore the determinants of diseases and to develop and optimize the use of diagnostic, prevention and treatment strategies. The values of the ECRIN-ERIC shall be to:

1. be a distributed infrastructure, based on the connection of existing national or regional clinical research networks
2. provide support to multicentre clinical studies involving at least two countries
3. be primarily accessible to investigator-initiated clinical research, but also open to industry-sponsored clinical research projects, originating from any country
4. encourage cooperation and harmonisation
5. promote common standards, tools and practice that will impact on the structuring of national networks
6. promote training of investigators and all categories of professionals and lay persons involved in clinical research
7. promote quality, transparency and optimal use of clinical research data; and
8. communicate with patients and citizens on the challenges and opportunities raised by clinical research.

The governance structure of the ECRIN-ERIC will be the assembly of members composed of representatives of members and observers and the director nominated by the assembly of members.

The assembly of members shall be the governing body of the ECRIN-ERIC and shall decide on the strategic plan, governance structure, annual or pluri-annual work plan and annual budget of the ECRIN-ERIC. The director shall be in charge of the overall management of the Infrastructure with the support of the management office and will function as the intermediary between the scientific partners, management office and the assembly of members.

The detailed description of the operation of the ECRIN-ERIC can be found in the business plan and technical annex. Both documents will be completed by the internal rules of procedures.

Currently, the final statutes were agreed by the European Commission and the four members having signed the memorandum of understanding. The host country, France, is preparing the official application of ECRIN-ERIC with an expected start date in the first semester of 2012.

The creation of the ERIC was expected at the end of 2011 to avoid a transition period between the end of the current preparatory phase and the ECRIN-ERIC creation. Business continuity and especially the follow-up of clinical projects will be ensured during this interim period. The management structure of ECRIN will be maintained as the same governance bodies are set up for the management of the ECRIN-ERIC and will continue to drive the support activities. In most of the countries, the European correspondents will be supported by their national network during the interim period and the ECRIN website will remain active and updated. Some of the networking activities will also be covered by the ECRIN IA starting in January 2012.

During this preparatory phase ECRIN also enters into real life and through the experience of support to multinational projects, has developed the tools and strategies to meet users' expectations and address the challenges created by the provision of services.

A procedure to access the infrastructure and evaluation of projects by the scientific board was defined. The criteria of the
scientific board and the evaluation process were revised in light of the first evaluations and are available to all the applicants on the ECRIN website (http://www.ecrin.org/index.php?id=105). To facilitate the communication flow among all the parties involved in the evaluation procedure, an online working area has been created. The ECRIN scientific board working area is a shared electronic repository aimed at facilitating the electronic submission of clinical trial protocols to the Scientific Board, the assessment procedure, communication and training on protocols submitted to ECRIN. The access to this online tool is secured to guarantee the confidentiality of the stored information.

The projects seeking for ECRIN support are evaluated by the core scientific board supported by external referees who are experts suggested by the national hubs. The evaluation is based on few mandatory acceptance criteria and completed by advice and recommendations on further methodological aspects of the study plan, conduct and analysis.

In that way, the contribution of the Scientific Board was viewed as having a strong impact on the methodological, scientific and medical soundness of the supported projects and this can be seen as the first service provided by ECRIN to the investigators. This may also drive the harmonisation of the methodological standards across Europe.

Specific tools and communication circuits were also set-up by the network of European correspondents to perform in parallel, the feasibility and logistical assessments and to evaluate with the ECRIN partners and final services providers the services requested in the different countries.

One of the challenges for ECRIN is to provide high quality support for the planning and conduct of clinical trials for partners taking into account the diversity of the national networks and individual final services providers and the expertise and knowledge already developed by those national networks.

The quality assurance system was developed to meet the regulatory requirements, the International Conference on Harmonisation (ICH) good clinical practice (GCP) and the quality standards expected by users. The current system is based on:

1. an internal level with ECRIN instructions that are quality standards for ECRIN staff, with the description of the processes, workflows within ECRIN as well as the cooperation and the role of the European correspondent
2. an external level with ECRIN policies which define minimum quality requirements for the provision of defined services for all member institutions, e.g. clinical research coordinators (CRCs) and clinical trial units (CTUs) as members of the national networks as well as the relevant small and medium sized enterprises (SMEs) third party providers. These policies are general standards and are completed by more detailed list of requirements developed for the different services with the support of experts in the field.

To ensure that the minimum requirements are fulfilled for defined services (regulatory submission, monitoring, pharmacovigilance), a self-assessment sheet has to be completed by the member institutions and centres that will provide services.

All quality documents currently in use (approved instructions and policies) are available on the ECRIN website (internal section) and revision is planned once the ECRIN-ERIC will be operational.

The quality assurance (QA) group also propose the quality strategy and audit strategy to be implemented in the operation phase founding a balance between the necessity to reinforce the quality standards and reach the ‘excellence’ level as an ECRIN’s objective and the pragmatic approach taking into account the current situation of the partners and make sure that the standards are achievable for most of the partners. The group proposed a progressive approach with self-check, internal audits and then independent audits based on criteria defined within ECRIN.

The fulfilment of quality standards can be one of the criteria for connection and alignment of new partners to ensure
consistency within the network and the 'excellence' of ECRIN infrastructure with high level of quality for services. Once the ECRIN-ERIC is operational, the framework agreements between ECRIN-ERIC and the national ECRIN scientific partners and final service providers will include the quality standards requested and described in the above section.

The groups representing different types of services such as data centres, monitoring and pharmacovigilance developed specific requirements and tools to be used for the operation phase.

The WP10 developed the standard requirements for GCP-compliant data management that were published in the Journal ‘Trials’ (Ohmann et al., Trials, 2011; 12:85). The standard is intended to provide an open and widely used set of requirements for GCP compliant data management and the accompanying information technologies (IT) infrastructure, particularly in academic trial units and to address the current lack of available standard. These requirements will be used as the basis for the certification of ECRIN data centres.

The infrastructure for certification was implemented, including an independent certification board (ICB) and ECRIN appointed auditors and a call for ECRIN prototype data centres was launched on 1 June 2011. The ICB ranked applications and selected two centres (in Germany and Sweden) for audit as part of the pilot phase. In both cases the units had met most but not all of the minimal requirements but there was an expectation that within four months the units could be re-audited and could then demonstrate all the minimal criteria and certified within ECRIN-ERIC.

The development of this certification process is a very important step towards the definition of common high quality standards and harmonisation of practices, standards of IT and data management in CTUs throughout the EU. This activity will be continued within the ECRIN-ERIC with the objective to provide effective, efficient and regulation compliant infrastructure for the running of ECRIN trials.

The strategy for the future of the certification process has been discussed by the ECRIN network committee and will be reviewed by the ECRIN-ERIC management structure. Future calls for certification will be annual and between 35 to 50 trials units should be accredited as ECRIN data centres, over five years. The decision to award certification or not to a unit will be taken by the ICB based solely on the technical evaluation of the unit's IT and data management systems, against the agreed ECRIN criteria and the certified units should sign a consortium agreement with ECRIN-ERIC to be able to define the framework of collaboration, including costs, links with monitoring activity, etc. and to appear as a third party in FP7 projects.

The monitoring group drafted a policy for monitoring, defining the responsibilities of ECRIN partners, ECRIN European correspondents and the sponsor towards the support given by ECRIN partners for monitoring clinical trials. It describes the prerequisites and minimal requirements for monitoring. This policy requires the use of a risk-based approach for monitoring activities, with initial risk assessment and the drafting of a risk-adapted monitoring plan and the group validated a guidance document for risk-assessment.

For pharmacovigilance, the group developed a policy document and a self-assessment sheet (SAS) according to QA objectives. In addition, a preliminary survey was designed and circulated as to know how many centres are willing and capable to act as reference pharmacovigilance centres for multinational clinical trials at this stage. Finally, a list of standard operating procedures (SOPs) were identified and agreed. A benchmarking exercise will be set-up within the group of centres willing and capable to act as reference centres.

The key goals of WP4 were to define the existing resources and needs in Europe, in terms of GMP facilities for the production of biopharmaceuticals, both for academic institutions and for biotechnology SMEs and to identify and evaluate solutions for satisfying the unmet needs.

The survey on resources resulted in a directory with the full list of the identified facilities with detailed information on the
facilities' features.

As a joint ECRIN European Advanced Translational Research Infrastructures (EATRIS) activity, the survey on needs was addressed to the European organisations/institutions engaged in the clinical and/or translational research in the biomedical field and therefore, universities, university-hospitals, clinical research centres and biotechnology SMEs, were the main target. However the unsatisfactory and insufficient response rate registered for both surveys make difficult to analyse the situation and provide final conclusions. Additional activities will be needed in order to obtain a comprehensive picture and then jointly build a roadmap as far as said facilities are concerned.

Education and training

The ECRIN European correspondents played a key role in ECRIN PPI, providing information, coordinating consultancy and service and their pivotal role increased during the course of the project.

The European correspondent was the bridge between ECRIN and each national network. In order to fulfil this central and important role, the European correspondents needed continuous training on ECRIN developed material from the different working parties, knowledge about the national networks, working procedures and expertise in teaching and management. This task demanded training sessions for the European correspondents, the ECRIN summer schools.

Material from these training sessions should be exploited to be integrated in the future training activities in ECRIN-ERIC and ECRIN-IA, preferably adapted to meet the needs of new member countries. The objective is to develop training modules on how to initiate and manage multinational trials, including the design, the methodology, the application process, the project management, the clinical trial management and supervision, e.g. ethical and regulatory submissions, adverse event reporting, monitoring, DSMB, data management, investigational medicinal products (IMP) management, biobanking, the transparency, the biostatistical analysis, the reporting. These modules should then be either stand-alone modules for the national staff (provided for instance through 'national summer schools'), or part of a more comprehensive curricula.

This activity takes also advantage of its synergy with the other ESFRI-BMS infrastructures through the IMI EMTrain project.

Support to clinical trials

Among the projects evaluated and accepted by the scientific board, five 'pilot' clinical research projects were initiated during the ECRIN preparatory phase and were supported by the network. Those clinical projects were considered as 'pilot' for ECRIN to assess the efficacy of the whole organisation, of the procedures and the collaboration and communication between participants within the network. This experience demonstrates the feasibility and helped to refine the procedures and make some recommendations for the operation phase of ECRIN-ERIC.

Of the five projects supported, four are clinical trials with medicinal products and one is a therapeutic procedure. The number of countries involved varies from 2 (the minimum to be supported by ECRIN) to 12 countries (including non-ECRIN countries) with a mean value of 6 countries.

For all the projects, the first support provided by ECRIN is information on the regulatory and ethics requirements and the practical processes to submit the clinical trial application, on insurance requirements and contact with the investigator sites including the national or local specificities for contracts and finances.

In this preparation phase of the project, the network of European correspondents supported by their national hub and their national partners was considered as efficient and reactive to provide timely information towards sponsors and investigators and the coordinating European correspondent.
The services requested in those pilot projects were the regulatory and ethical submission, the translation of study documents, the support with contracting, the on-site monitoring and the pharmacovigilance at the national level. In this phase of service provision, ECRIN act as coordinator and facilitator in establishing the organisation of the services using the national resources of each national hub.

Overall, this early experience with pilot clinical trials and the number of projects submitted to the scientific board as well as the number of applications to FP7 calls where ECRIN is involved demonstrate the added value of such infrastructure. This experience also resulted in some changes (for instance a new procedure for acceptance by the scientific board). This also helped refine the future organisation that will be put in place the ERIC, with two main senior positions: the operation manager, coordinating the activities of the network of European Correspondents and a quality assurance and core competence manager, in charge of updating the know-how and the procedures in the ‘back office’.

In order to increase the attractiveness of the infrastructure and allow all European citizens to access to clinical research, ECRIN has to expand the current capacities of the network to more European countries unlocking latent scientific potential and boosting European competitiveness in the global scene. The activity of the WP6 mainly focuses on the establishment of appropriate contacts with organisations/institutions in new countries to prepare a further connection to ECRIN, as based on defined criteria, whereas the capacity building WP is designed to help the new networks and potential new networks to bridge the gap between their existing capacities and the requirements for connection to ECRIN.

Expansion resulted in the connection of Poland, following the organisation of a platform for medical research based on a network of the 10 medical universities, coordinated by the Medical University of Warsaw. POLCRIN represents the country’s academic network and facilities enhancement of clinical research in Poland.

Contacts were also established in 14 new countries interested in participating in ECRIN. Nine of them (Czech Republic, Iceland, Luxembourg, Netherlands, Norway, Portugal, Romania, Serbia, Turkey) were included in the ECRIN IA project and will benefit from the financial support to the European correspondent and capacity building programme to structure or strengthen their national network in order to be able to provide support to multinational clinical research (see ECRIN IA paragraph).

The WP7, capacity building is designed to help the national network to structure through short-term mobility programmes built after diagnostic step identifying the strengths, weaknesses and needs at the national level. The key to success is cooperation and sharing experience and practice and overall these mobility programme activities have upgraded the reciprocal knowledge and skills of the involved parties, allowed the connection of a new country (Poland) and prepared the future connections. These are important steps to expand the network that will continue in the next project (ECRIN-IA) for the nine new networks to be involved.

Communication

The communication strategy was adapted to the preparatory phase with a stronger communication towards the national partners, the users, the science policymakers and EU parliament.

In particular, two meetings were organised with users and various stakeholders. A first one with different stakeholders (investigators? networks, clinical trials units/clinical research centres and public sponsors) and users of ECRIN allowed to reinforce the approach of ECRIN and confirmed that the services needed and the main users' expectations were already listed in the information, consultancy or services as proposed by ECRIN. A second one, with stakeholders and users community as well as regulatory and policy makers where ECRIN addressed the health and research challenges and how to make Europe a single area for clinical research organised within the Biovision meeting in Lyon.
ECRIN also participated with other ESFRI research infrastructures in a Hearing on 'Health-related research infrastructures and their contribution to the EU's grand challenge' at the European Parliament, Brussels on 26 October 2010. This Hearing was sponsored by Dr Paul Rübig MEP, Chairman of the science and technology options assessment (STOA) panel.

Another event at the European Parliament Brussels was the diner debate on 'clinical trials' organised at the initiative of Dr Peter Liese MEP and ECRIN together with 'Intelligence in science (ISC) on the challenges and perspectives for clinical research in Europe, with a focus on the need for improved legislation, for stronger national and multinational infrastructures, for appropriate funding for independent clinical trials and for full transparency and optimal use of clinical trial data.

The communication with patients is also a value promoted by ECRIN that organised every year since 2005 the ICTD, a communication event during which the main stakeholders involved in clinical research (patients, investigators, sponsors, ethics committees and competent authorities) discuss the challenges raised by clinical research. This is an opportunity to promote the active participation of patients in trials and to improve the awareness of citizens on the challenges raised by clinical research.

In 2008, the meeting was held in Brussels, Belgium and resulted in three articles In Nature Reviews Drug Discovery.

In 2009, the meeting was organised by the Mario Negri Institute at Milan, Italy and was followed by Italian clinical trials day conferences.

In 2010, the ICTD was hosted by Sweden and was coupled with all day, outdoor events in Kungsträdgården. The event attracted 40 000 visitors.

In 2011, Vienna was the city of the ICTD and the conference was opened by the Austrian Federal Minister for Science and Research. In addition to the international events the ICTD also resulted in national initiatives:

1. 2008 in Ireland, Dublin and Italy, Genova
2. 2009 in Sweden, Stockholm with a day-long event offering the visitors the opportunity to test the latest in medical inventions that, thanks to the performance of clinical trials, are used on a daily basis in patient care and to hear prominent researchers giving short lectures and news within their field of expertise
3. 2011 in Luxembourg.

The yearly celebrations of the ICTD have been a success and several organisations all over the globe have started to conduct similar celebrations.

ECRIN IA

ECRIN apply to FP7 Infrastructures (INFRA)-2011-1.1.5. facilities and resources for multinational clinical trials' in order to expand ECRIN partnerships and impact beyond the core activity of the ECRIN-ERIC.

Within the ECRIN IA project, the networking activities will promote pan-European expansion, capacity building and partnership with other world regions and address the funding issue (WP2). ECRIN-IA will develop e-services, education material to train professionals and patients associations and communication with users, patients, citizens and policymakers (WP3). It will support the structuring and connection to ECRIN of disease, technology, or product oriented investigation networks and hubs focussing on specific areas: rare diseases (WP4), medical device (WP5), nutrition (WP6).

Transnational access activities will support the cost of multinational extension of clinical trials on rare diseases, medical device
and nutrition selected by the ECRIN scientific board (WP7).

Joint research activities are designed to improve the efficiency of ECRIN services, through the development of tools for risk adapted monitoring (WP8) and the upgrade of the VISTA data management tool (WP9).

In the present project, we had to select a few pilot disease areas to implement such a model and we considered that the highest European added value for ECRIN and for the partner networks is the areas of rare diseases, medical device and nutrition. Access to patients is critical for rare diseases, usually out of scope of industry investment; the medical device community (both academic and SME) needs pan-European structuring to comply with the new requirements for clinical assessment of efficacy; and human nutrition research is a high priority for Europe, with the joint programming initiative healthy diet for a healthy life (HDHL). But this may later extend to other medical fields. ECRIN (with the ESFRI infrastructures) could thus act as a federator and develop strategic partnerships with the scientific communities that also represent their users.

This four-year ECRIN-IA project will therefore result in major changes in the structuring and activities of ECRIN, through expansion to new countries and partnership with other world regions, through the development of a common and de-fragmented culture and of common tools, through the development of investigation networks in three strategic areas and through the funding made available to multinational clinical research in the same areas (rare diseases, medical device, nutrition).

Potential impact:

ECRIN activity ‘support to individual multinational trials and structuring the clinical research capacity’ should have a significant direct and indirect impact on the competitiveness of Europe in this area.

For each member state, participating in ECRIN offers the capacity to initiate and to participate in multinational clinical studies, facilitating the access to EU funding for clinical research projects and leading to high impact scientific output. It also has a major impact on health and economy, fostering the development of innovative health products, promoting independent evaluation of healthcare strategies and hence contributing to cost containment.

The ECRIN expansion policy is to provide access to patients throughout Europe, as size matters for the access to patient populations. Since its onset, ECRIN progressively expands to other countries (from 6 in 2004 to 14 in 2010, now covering 80 % of the EU population), based on extension criteria (a single hub connected to a national infrastructures network, able to support any category of clinical research in any disease area).

Contacts were established in 14 countries and 9 new countries are involved in the ECRIN IA project (Czech Republic, Iceland, Luxembourg, Netherlands, Norway, Portugal, Romania, Serbia, Turkey) and will benefit from the financial support to the European correspondent and capacity building programme to structure or strengthen their national network in order to be able to provide support to clinical research.

Creating this single area for clinical research in Europe will therefore strengthen the competitiveness of Europe in clinical science, enabling high and rapid patient recruitment, with an impact on the statistical power and duration of trials, therefore boosting the robustness of results, the impact of publications and accelerating access to innovation for patients. It will unlock latent scientific potential and expertise, facilitating multinational studies initiated by investigators from any European country and providing access to resources developed by all the European countries (healthcare databases, genetic databases, etc.). It will also strengthen the attractiveness of Europe for industry trials through the creation or maintenance of national infrastructures sharing common tools, standards and procedures. In addition, structuring of European investigation networks will allow industry to directly access multiple investigation sites.
Acting as a single hub for Europe, ECRIN may also facilitate transcontinental cooperation, with either clinical studies (trials, cohorts) initiated in Europe and requiring global extension, or studies initiated in other world regions with implementation in Europe. ECRIN will foster systematic contacts with national infrastructures in other world regions. Agreements on common procedures for joint research, including ethical review, interaction with competent authorities, insurance, sponsorship, adverse event reporting, monitoring, data management, IMP management and export, circulation or analyses of human biological samples, will therefore be established.

Impact on structuring the national capacities and pan-European investigation networks

ECRIN, through the criteria defined for the connection of new countries contribute to the structuration of national networks. It also helped strengthen the national infrastructure in already connected projects, the most salient example being Spain with the set-up and development of the CAIBER network coupled to a strong coordinating hub (http://www.caiber.net/). Other countries also took advantage of this multinational benchmarking to upgrade their clinical research infrastructure, including France with the F-CRIN project funded as an infrastructure by the investing for the future? programme.

ECRIN also supports the structuring of disease oriented investigation networks coupled to a pan-European hub. ECRIN had a pilot experience in supporting cross-border connection of disease-oriented networks, through its participation in the FP7 European network of bipolar research expert centres (ENBREC) at http://www.enbrec.eu project, developing common standards and specific tools for cognitive, imaging and biomarker investigations, whereas ECRIN provides and adapts its generic tools and procedures for study management.

Expanding this strategy may lead clinical (and biomedical) research support structures in Europe that will act as strategic partners for a wide range of pan-European projects.

A capacity for investigation and some time for study management is already developed at the pan-European level in some areas, particularly in the field of cancer. However, such an organisation is still lacking in many areas and has to be developed to provide ECRIN with both multinational projects and with investigation networks.

Through the new project funded by the FP7 infrastructures programme (ECRIN-IA, 2012 to 2015) ECRIN now plans to support the structuring of networks in three strategic areas (rare diseases, medical devices and nutrition). ECRIN (with the ESFRI biomedical research infrastructures for translational research and biobanking ? EATRIS and Biobanks and Biomolecular Resources Infrastructure (BBMRI) could thus act as a federator and develop strategic partnerships with the scientific communities that also represent their users. Such a combination avoids duplication of resources and allows cross-fertilisation across disciplines, as generic tools and procedures for study management are made available to all the research communities, allowing them to focus on developing support which is specific for their own disease area.

Legislation

Having collected exhaustive information on national legislation on clinical trials in Europe, ECRIN plays a major role in the discussion on the revision of the 2001/20/EC Directive, through its involvement in the Impact on Clinical Research of European Legislation (ICREL) project (http://www.efgcp.be/icrel) assessing the impact of the Directive and in the academic initiatives such as the ‘Roadmap initiative for clinical research in Europe’ working on solutions to improve the situation (http://www.efgcp.be/Conference_details.asp?id=265&L1=10&L2=2&TimeRef=2).

Based on its European expertise and participation in different workshops, ECRIN recommended, a stratified approach for legislation purposes, with three categories depending on the status of the health product (non-marketed, marketed exploring a new indication, or marketed within the licensed indication) leading to risk based adaptations for most of the processes in clinical trial supervision and a personalised approach for monitoring, with a decision tree for risk assessment of each individual protocol, taking into account all the risk determinants including the hazard to data quality and to the reliability of results.

These recommendations are now discussed at the global level in the Organisation for Economic Cooperation and Development (OECD) working group to facilitate international cooperation in non-commercial clinical trials? (report o http://www.oecd.org/sti/gsf) and appears to be relevant in other world regions where the regulation differentiates between registration trials and non-registration studies.

This cooperation enlarges the connection network of ECRIN and increases its global visibility.

Education

ECRIN plays a central role in the Innovative Medicines Initiative (IMI) funded European Medicines Research Training Network (EMTrain, at http://www.emtrain.eu) project, coordinating at the pan-European level education and training contents and methodologies to create a new culture bridging the gaps between countries in Europe, between disciplines and between industry and academia. Particularly, the accreditation of harmonised and interoperable training modules and the promotion of mobility will result in a single market for students, for universities and for employers in Europe. This de-fragmentation of education systems is also a priority of the 'Europe Innovation 2020' agenda.

Communication 'transparency'

ECRIN has organised every year since 2005 the ICTD communication event during which the main stakeholders involved in clinical research (patients, investigators, sponsors, ethics committees and competent authorities) discuss the challenges raised by clinical research. This is an opportunity to promote the active participation of patients in trials and to improve the awareness of citizens on the challenges raised by clinical research.

ECRIN also promotes transparency in clinical research, not only through registration of study protocol and reporting of results, but also through the commitment of the investigator and sponsor to provide access to anonymised clinical trials data once the study is published, enabling re-analyses and meta-analyses, thus optimising the use of clinical trial data.

Funding

Availability of funding for multinational trials is a critical issue. The 2011 call of the FP7 health priority made a major breakthrough by opening seven calls for investigator-driven clinical trials. Clinical trials supported by the Innovative Medicines Initiative (IMI) mostly focus on biomarkers. Other mechanisms should be explored, including a wider coverage of disease areas by the FP7 health priority, the possibility to coordinate national funding through a European Research Area (ERA) net mechanism, either an ERA-net for clinical research, or a clinical research component in an ERA-net focussed on a disease area (on cancer, on neurosciences, on rare diseases, etc.). Joint programming initiatives appear to be a better opportunity, i.e. either thematic joint programming, or a joint programming initiative for clinical research.

Impact on public health, healthcare and health economy

Considering all these objectives, ECRIN is expected to have a major overall impact on the scientific competitiveness and attractiveness for industry of Europe and of the individual European countries. This will help Europe:
1. play a leading role in major research and innovation challenges (biopharmaceuticals, biotherapy, regenerative medicine), with an impact on biotechnology and pharmaceutical industries
2. develop new healthcare models (personalised and stratified medicine)
3. address health challenges (rare diseases, nutrition and health, ageing and health technology, with an impact on biotechnology, food and health technology industries)
4. translating clinical research into clinical practice (through treatment optimisation trials and comparative effectiveness research), including better use of medicines, appropriate use of behavioural and organisational interventions, health therapies and technologies, special attention being paid to patient safety (e.g. benchmarking of strategies or investigating outcomes of different interventions including medicines)
5. achieve healthcare cost containment
6. promote evidence-based medical practice and enhance health promotion and disease prevention, providing evidence for the best public health measures in terms of life styles and interventions, covering different levels and different contexts, including mental health issues
7. thus reduce health inequalities in Europe and promoting quality, solidarity and sustainability of health systems, by developing a basis for countries to adapt their health systems, taking into account national contexts and population characteristics, such as organisational, financial and regulatory aspects, implementation of best practice, outcomes such as effectiveness, efficiency and equity with special attention on investment issues and human resources
8. and allow patients and citizens to further impact on health and clinical research challenges.

This will require commitment from investigators and administrators across Europe in order to achieve the goals of pan-European funding and of optimising the delivery of healthcare to European citizens and take forward the relevant investigator-driven clinical trials.

The development of a pan-European infrastructure providing generic tools and services is, however, not sufficient to achieve the single European area for clinical research. The ECRIN initiative should be extended through incentives to further strengthen the national clinical research infrastructures, the partner of ECRIN in each country and to expand the network throughout Europe with connections in other world regions. Funding should be available for multinational clinical research projects; although some topics can now be funded through FP7 Health Priority, funding multinational trials is a major challenge for Europe. A common pan-European culture should be developed among the clinical research professionals and patient communities; this requires training and communication policies to build common awareness for a new generation of clinical research professionals. Multinational cooperation in clinical trials requires not only generic tools to support study management, but also common procedures and standards to support investigation, specific for each disease area. It is therefore crucial to support the cross-border connection of disease-specific investigation networks, enabling them to efficiently design and conduct multinational studies.

List of websites:

http://www.ecrin.org/

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2, Rue d’Alésia