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A European perspective – the European clinical research infrastructures network

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Evaluating research outcomes requires multinational cooperation in clinical research for optimization of treatment strategies and comparative effectiveness research, leading to evidence-based practice and healthcare cost containment. The European Clinical Research Infrastructures Network (ECRIN) is a distributed ESFRI (European Strategy Forum on Research Infrastructures) roadmap pan-European infrastructure designed to support multinational clinical research, making Europe a single area for clinical studies, taking advantage of its population size to access patients, and unlocking latent scientific potential. Servicing multinational trials started during its preparatory phase, and ECRIN will now apply for an ERIC (European Research Infrastructures Consortium) status by 2011. By creating a single area for clinical research in Europe, this achievement will contribute to the implementation of the Europe flagship initiative 2020 'Innovation Union', whose objectives include defragmentation of the research and education capacity, tackling the major societal challenges starting with the area of healthy ageing, and removing barriers to bring ideas to the market.

introduction

Fragmentation of the health and legislative systems and funding sources in Europe represent major bottlenecks to multinational collaboration. Support is therefore needed to enable Europe to take advantage of its population size to access patients, and to unlock latent scientific potential and clinical expertise [1]. Such need for a pan-European infrastructure to support clinical trials has been recognized by the European Union by the award of significant resources to develop the process and to create the European Clinical Research Infrastructures Network (ECRIN), listed on the European Strategy Forum on Research Infrastructures (ESFRI) roadmap in 2006 (www.ecrin.org), designed to make Europe a single area for clinical research. ECRIN is based on the connection of national clinical research infrastructures, hubs and networks, composed of Clinical Trial Units (CTU) or Clinical Research Centres (CRC). It currently covers 14 countries in Europe. The ECRIN staff is composed of a core team plus a network of European Correspondents (EC) hosted in each national hub.

The sixth Framework Programme (FP6) ECRIN-RKP project (Reciprocal Knowledge Programme, 2004–2005), helped identify the bottlenecks and define a strategy [2]. The FP6 ECRIN-TWG (Transnational Working Groups, 2006–2008) led to the development of generic tools and procedures for multinational clinical research. ECRIN was listed on the first edition of the ESFRI roadmap, and is now in its FP7-funded preparatory phase (ECRIN-PPI, Preparatory Phase for the Infrastructure, 2008–2011), designed to further structure the distributed infrastructure, and to start provision of support to 'pilot' multinational clinical research projects through information and services, to test the organization and the procedures. ECRIN is currently applying to obtain European Research Infrastructure Consortium (ERIC) legal status by 2011, whose sustainability will be secured by the contribution of member states. In addition, a new FP7-funded project (ECRIN-IA, Integrating Activity, 2011–2015) will help ECRIN expand and structure its users' communities.

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.

building a sustainable infrastructure for multinational trials

ECRIN is a pan-European, distributed infrastructure based on the connection of national networks composed of CTU or

CRC, and a coordinating national hub acting as the single contact point for the coordination of services. It currently covers 14 countries in Europe, and the ECRIN staff is composed of a core team plus a network of EC hosted in each national hub (Figure 1).

ECRIN supports multinational clinical studies through services provided by multiple national partners to a single study, with a single EudraCT number, a single protocol, a single sponsor, and a single database. ECRIN coordinates the provision of services (and also provides information and consulting during the preparation of the study), and a single assessment of the study protocol by the ECRIN scientific board provides access to the services.

ECRIN is currently an FP7 project whose participants are bound by a consortium agreement. ECRIN is applying for an ERIC status by 2011, at the end of the preparatory phase. This ERIC status will allow ECRIN, defined as the core team plus the European Correspondents (EC), to act as a single international legal entity, will provide with the capacity to propose a single task delegation contract with the sponsor of the clinical trial, and to be bound by framework contracts to its national partners, specifying the cost of services and the quality assurance.

ECRIN developed its knowledge base during the FP6 ECRIN-TWG (2006–2008) and FP7 ECRIN-PPI (2008–2011) projects, with a comprehensive description of the national ethical and regulatory framework [3–7], with the development of procedures for adverse event reporting and monitoring, with a certification policy for data centres, and with a quality assurance system composed of instructions binding for the ECRIN team and quality policies specifying the quality requirements for the CTUs and CRCs in the partner national networks.

support to multinational clinical studies in Europe

During its FP7 preparatory phase (ECRIN-PPI), ECRIN started providing support to a few pilot projects. The ECRIN scientific board has received about 20 multinational clinical research projects, and 6 of them were accepted and have started enrolment of patients. As there is a clear deficit in multinational academic studies (less than 10% are multinational, whereas more than 50% of industry trials are multinational) the ECRIN business plan expects a progressive expansion of its activity.

Information, consultancy and services (Table 1) are coordinated by the network of EC. Before the full protocol is finalized, the EC provide information and consulting. The protocol is assessed by the ECRIN scientific board, whereas feasibility and logistical aspects are examined by the network of EC. Once the protocol is accepted, services to support the conduct of the studies are proposed at a not-for-profit cost, provided by the ECRIN partners and coordinated by the ECRIN EC.

ECRIN provides access to clinical studies requiring multinational cooperation in Europe, in any medical area, and for any category of clinical study: clinical trials on medicinal products, on medical devices, non drug trials (surgery, radiotherapy, etc.), diagnostic studies, nutrition studies, studies on the mechanism of disease, and observational studies. ECRIN is primarily designed to support academic sponsors, but is also open to a restricted number of industry-sponsored trials, particularly for small- and medium-sized enterprises (SME) who often lack the capacity to act as a sponsor and to design the trial.

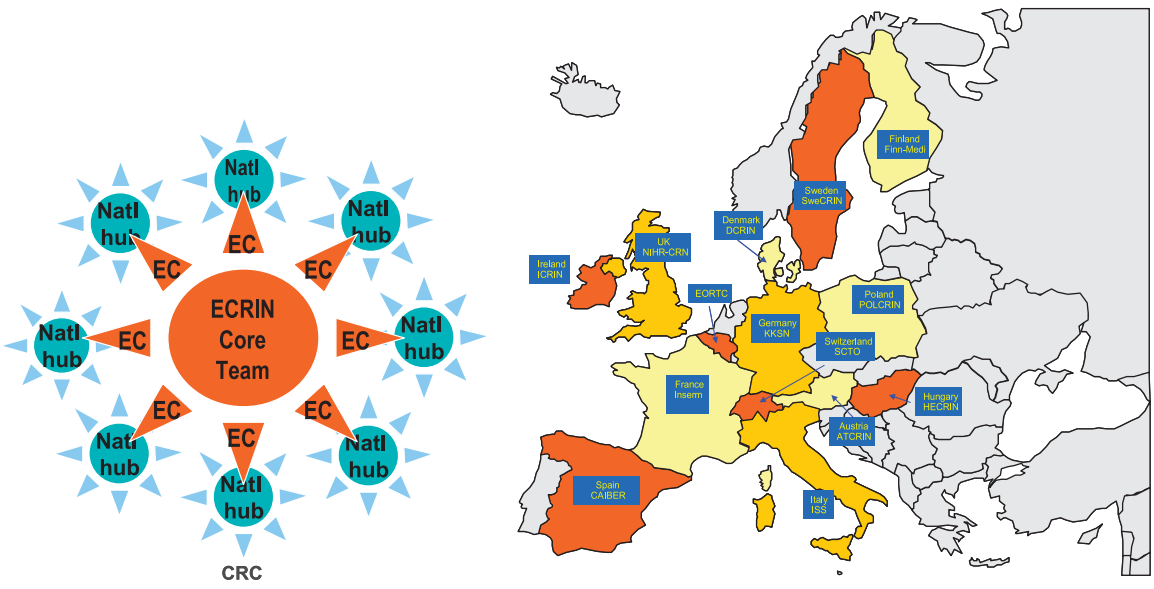

Figure 1. ECRIN is composed of a core team and national contact persons (the European Correspondents, EC) embedded in the national hub coordinating the national partner network. These national partners are represented by their coordinating hubs: France, INSERM (for the CIC network), Paris; Germany, KKSN (KKS network), Cologne; Italy, ISS (Istituto Superiore di Sanità), Rome; Spain, CAIBER, Madrid; UK, University of Leeds for the NIHR-CRN; Ireland, Molecular Medicine Ireland for ICRIN, Dublin;Sweden, Karolinska University Hospital for SweCRIN, Stockholm; Denmark, Rigshopsitalet for DCRIN, Copenhagen; Finland, FinnMedi, Tampere; Switzerland, SCTO Swiss Clinical Trial Organisation, Basel; Austria, Medical University of Vienna for AtCRIN, Vienna; Belgium, EORTC, Brussels; Hungary, HECRIN, Budapest; Poland, Medical University of Warsaw for PolCRIN.

structuring pan-European investigation networks

There are two main categories among clinical research infrastructures, as support to clinical research covers two distinct roles (Figure 2):

- support to investigation, including hospital-based clinical research facilities for early phase trials and experimental medicine, and investigator networks supporting both industry-driven and academic trials;
- support to study management and to sponsors for academic trials (also open to SME, which is particularly relevant for biotechnology, medical device or nutrition studies): clinical trial units for the study design and management, monitoring, vigilance, interaction with ethics committees and competent authorities, insurance, contracting; and data centres.

Table 1. Information and services proposed to multinational clinical studies

Core set of information and consulting items during the preparation of the project (before submission to the Scientific Board)	Core set of services provided during the conduct of the clinical research project (after acceptance of the full protocol by the Scientific Board)
Adaptation of protocol to local context	Submission to, and interaction with, competent authorities and ethics committees
Information on regulatory and ethical requirements	Support with insurance contracting
Information on clinical trial sites and participant recruitment	Adverse event reporting
	Monitoring
Information on clinical trails units	Data management
	Training of study personnel
Information on insurance	Investigational medicinal product (IMP) management
Information on cost evaluation and funding opportunities	Blood and tissue sample management
Information on contracting	

Depending on the country, various models for clinical research infrastructures were developed in Europe. National networks were developed to foster multicentre trials and to share procedures and tools for study management. Similarly, ECRIN provides support across countries regarding study management capacity.

This is, however, insufficient to achieve the single area for clinical research, as additional competencies are still required to support cross-border investigation: these should be based on common standards, procedures and tools for patient investigation, and require a disease-specific instead of a generic approach. For this reason, ECRIN 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, 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 (Figure 3). 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. For instance the EORTC (European Organization for Research on Treatment of Cancer) is a member of the ECRIN consortium, and ECRIN

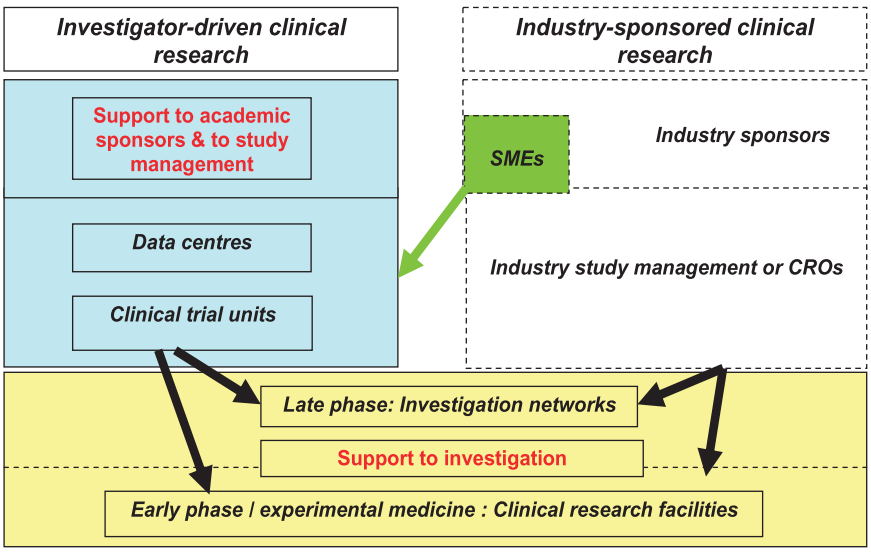

Figure 2. Infrastructures for investigation (yellow: clinical research facilities, investigation networks) develop disease-specific tools and procedures, and support both industry-sponsored and investigator-driven trials. In turn, infrastructures for study management (blue: CTU, data centres, support to sponsors) rather develop generic tools and mostly support academic studies. Industry has either in-house study management capacity, or use external CRO, however SME without capacity for trial and data management may benefit from public CTU.

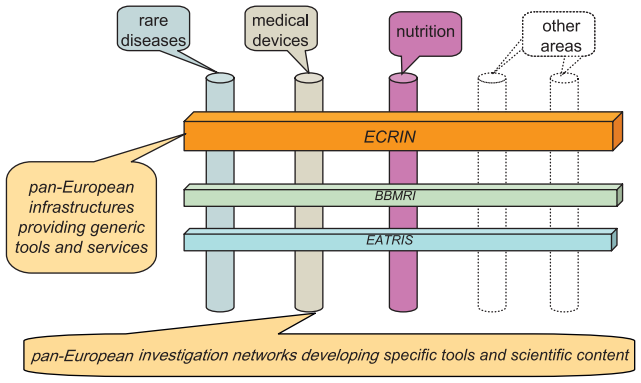

Figure 3. Model for an organisation of biomedical research in Europe, with generic infrastructures providing technical support, whereas investigation networks develop disease-oriented procedures, standards and tools, and design the scientific content.

benefits from its experience and from already developed tools and procedures. However, such an organization 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, 2011–2015) 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 (European Advanced Translational Research Infrastructures) and BBMRI (Biobanks and Biomolecular Resources Infrastructure)] 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-fertilization 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.

impact

The 'Innovation Union 2020' strategy [8] states that 'by 2015, Member States together with the Commission should have completed or launched the construction of 60% of the priority European research infrastructures currently identified by the ESFRI. The potential for innovation of these infrastructures should be increased. The Member States are invited to review their Operational Programmes to facilitate the use of cohesion policy money for this purpose.' In line with these principles core 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.

legislation

Having collected exhaustive information on national legislation on clinical trials in Europe [3–7], ECRIN plays a major role in the discussion on the revision of the 2001/20/EC Directive, and in proposals for a risk-based approach to clinical research legislation, through its involvement in the Impact on Clinical Research of European Legislation (ICREL) project (www.efgcp.be/icrel) assessing the impact of the Directive, and in academic initiatives to propose solutions [10]. This led ECRIN to recommend [11] the following points.

- 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.
- A personalized 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 Organization for Economic Cooperation and Development (OECD) 'Working Group to Facilitate International Cooperation in Non-Commercial Clinical Trials', and appears to be relevant in other world regions where the regulation differentiates between registration trials and non-registration studies.

expansion and worldwide connections

The ECRIN expansion policy is to provide access to patients throughout Europe, as size matters for the access to patient populations. The 14 countries currently participating in ECRIN (Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Poland, Spain, Sweden, Switzerland, United Kingdom) represent 400 millions citizens, and 9 additional countries (Czech Republic, Iceland, Luxembourg, Netherlands, Norway, Portugal, Romania, Serbia, Turkey) are about to join in the ECRIN-IA project. Even if China and India have a greater population size, the heterogeneity of their health systems will not allow, over the next decades, development of an equivalent clinical research infrastructure.

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.

education

ECRIN organizes training sessions for its staff, focussing on multinational clinical studies to create a common culture among professionals. However ECRIN has broader perspectives, with the objective of creating a new generation of clinical research professionals in Europe through:

- training modules for investigators, in the national context;
- training modules for the coordinating investigators, in a multinational context;
- and comprehensive training programmes for clinical research professionals, both academic and industry, in a European perspective.

For this reason ECRIN plays a central role in the Innovative Medicines Initiative (IMI)-funded European Medicines Research Training Network (EMTrain, 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 harmonized 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 International Clinical Trials' Day (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.

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 anonymized clinical trials data once the study is published, enabling re-analyses and meta-analyses, thus optimizing 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 an ERA-net mechanism, either an ERA-net for clinical research, or a clinical research component in an ERA-net focused on a disease area (on cancer, on neurosciences, on rare diseases, etc.). Joint programming initiatives appear to be a better opportunity – either thematic joint programming, or a joint programming initiative for clinical research.

Availability of multinational funding sources will also have an indirect impact on the national clinical research infrastructure: investigators and countries will compete to access such funding, which is expected to act as an incentive for investing in the national infrastructure. This should make policymakers aware that investing in high-quality clinical research leads to a major return on investment [9] through value generated by health innovation, by healthcare optimization, and by healthcare cost containment.

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:

- play a leading role in major research and innovation challenges (biopharmaceuticals, biotherapy, regenerative medicine), with an impact on biotechnology and pharmaceutical industries;
- develop new healthcare models (personalized [12] and stratified medicine);
- address health challenges (rare diseases, nutrition and health, ageing and health technology, with an impact on biotechnology, food and health technology industries);
- translating clinical research into clinical practice (through treatment optimisation trials and comparative effectiveness research [13]), 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; investigating outcomes of different interventions including medicines);
- achieve healthcare cost containment;
- 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;
- 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:
    - organizational, financial and regulatory aspects
    - implementation of best practice
    - outcomes – effectiveness, efficiency and equity
    - with special attention on investment issues and human resources

- and allow patients and citizens to further impact on health and clinical research challenges.

Achievements of these objectives 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'.

disclosures

The authors have not declared any conflicts of interest.

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