

Translational Research in Ophthalmology – A European Perspective

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Abstract

Loss of vision is a major threat for the ageing European society as its incidence quickly increases with age. While cataract is handled well by microsurgery, other blinding conditions such as age-related macular degeneration, retinal dystrophies, glaucoma and diabetic retinopathy cannot be treated well. On the other hand, knowledge about endogenous and exogenous factors increases rapidly in basic research, opening new pathways to therapy. It will be increasingly important to foster translational research to bring such new strategies in genetics, proteomics, metabolomics and new drug delivery systems for neuroprotection, stem cell research and optogenetics from bench to bedside. Adequate funding for this translational research has to be ensured. These goals are strongly supported by the European Vision Institute (EVI) and by the European Vision Institute Clinical Research Network (EVICR.net), a clinical research network that comprises more than 70 certified sites to perform clinical studies in the field of ophthalmology and by the European Clinical Research Infrastructures Network (ECRIN). These developments, their aims and accomplishments are described here.

Keywords

Ophthalmology, translational research, clinical studies, European Vision Institute (EVI), Clinical Research Network (EVICR.net), European Clinical Research Infrastructures Network (ECRIN)

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Blindness is one of the most feared health hazards in our present society; millions of Europeans are threatened by blinding, untreatable eye diseases producing costs of several billion Euros. The European Vision Institute (EVI) (www.europeanvisioninstitute.org) aims at devising and implementing programmes and projects for new therapeutic strategies for eye diseases that are difficult or impossible to be treated presently.¹ EVI's approach will incorporate the most recent scientific developments of the post-genomic area.

However, the explosion of technological advances, scientific efforts and opportunities to disseminate new knowledge in the last decade is placing healthcare professionals in a challenging position to keep abreast of current developments in science. Therefore, EVI should be of enormous strategic importance for the future and is targeted towards more immediate policy objectives of improving the visibility and competitiveness of European Vision Research (www.vision-research.eu). EVI integrates, conducts and supports research that helps to prevent and treat eye diseases and other disorders of vision. This research leads to sight-saving treatments, reduces visual impairment and blindness and improves the quality of life for people of all ages.²

To implement these targets it is necessary to accelerate and strengthen the clinical research process and to establish the infrastructure and organisation necessary to translate basic laboratory discoveries into the reality of improved patient care. This necessary process will indirectly increase the quality of life for many people in the EU. Therefore, it

is mandatory to create the basis for more efficient and effective translational research, characterise clinical research policies among countries within the EU and harmonise and validate objective tests of disease progression and patient-reported outcomes.

There are several successful initiatives to foster clinical research in Europe. For example, the European Clinical Research Infrastructures Network (ECRIN) (www.ecrin.org) is a European network dedicated to improving the health of patients and citizens worldwide through clinical research. It supports, services, co-ordinates and manages high-quality, independent and fully transparent multinational clinical research. ECRIN synergises the capacities and capabilities of national clinical research and strives for harmonisation of European clinical research.

More specifically in the field of ophthalmology, the European Vision Institute Clinical Research Network (www.EVICR.net) – a network of European Ophthalmology clinical research sites as an own legal entity – is dedicated to performing clinical research in ophthalmology with the highest standards of quality. EVICR.net is already carrying out investigator-driven clinical trials (IDCT) following the European and international directives for clinical trial research (Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice [ICH-GCP] Guidelines, clinical directive EU and local legislations).

Translational research – usually called bench to bedside – applies discoveries generated through basic research to the development and

testing of preventative and treatment interventions (i.e. services, programmes, practices and products) and vice versa. It may be seen as a five-phase model of interventional research that is commonly used to describe the continuum of biomedical research, from basic to applied science and vice versa.

Translational research is patient-orientated and implicates an approach to health research where there is a permanent interchange between basic and applied science. Excellence in clinical research is, therefore, a fundamental component of good translational research. To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin at 'the bench' with basic research – in which scientists study disease at a molecular or cellular level – then progress to the clinical level, or the patient's bedside. However, questions raised at the bedside need also to be presented to molecular scientists. A stronger clinical research infrastructure is necessary to strengthen and accelerate this critical part of the clinical research enterprise. It is fundamental to create the right conditions for an even more successful process of translational research in the EU. The EU-funded project 'Eurovisionet' (Visual Impairment and Degeneration: a Road-map for Vision Research within Europe' [www.eurovisionet.eu]) has developed a white paper, which includes recommendations on how to foster translational research in the vision sciences in the EU. Some of the recommendations are described below. Clinical and translational research centres are needed to support research of clinical and translational science and the needs of its researchers. They should be encouraged to propose novel concepts, methodologies and approaches to be integrated into comprehensive, effective and efficient researcher-, trainee- and participant-orientated programmes and develop their own list of the major functions and components of the centre. Relevant topics include:

- pilot and collaborative translational and clinical studies;
- development of communication pathways;
- implementation of IDCT;
- centralised support for research design, epidemiology, biostatistics and clinical research ethics;
- EU institutions;
- regulatory knowledge; and
- research education, training and career development.

Each centre should have clinical research resources, training programmes and access to basic laboratory research. Research projects involving multiple aspects of health promotion, disease prevention and treatment should be performed in active collaboration with other centres in the same area of scientific interest, e.g. ophthalmology and vision healthcare. One or more co-ordinating core centres must be set up and receive regular funding in order to facilitate co-ordination between centres. The centres are encouraged to make alliances and create partnerships with foundations, industry and community organisations as appropriate, with all partners agreeing to follow EU policies in terms of listing clinical trials at ClinicalTrials.gov, sharing of resources, data sharing and public access and establishing policies in support of investigator academic independence.

Pilot and Collaborative Translational and Clinical Studies

New resources are generally required to determine whether the clinical potential of a promising laboratory finding can be realised. Such funds must be available promptly and be accompanied by

an organisational structure that allows full compliance with regulatory requirements. Each centre or network of centres should be able to request support for pilot and collaborative clinical research projects that:

- allow clinical and translational trainees or researchers to generate preliminary data for submission of a research grant application;
- address clinical trial design, novel biostatistics approaches, informatics and regulatory pathways; and
- develop new technologies.

These pilot and collaborative projects should, in general, be of sufficient scope to qualify as a stand-alone research effort and should be well integrated into the activities of the centre.

Development of Communication Pathways

Biomedical informatics is the cornerstone of communication within centres and with all collaborating organisations. The centres should consider both internal, intra-institutional and external interoperability to allow for communication between centres and the necessary research partners of clinical and translational investigators (e.g. government, clinical research networks, pharmaceutical companies, commercial vendors, laboratories and equipment manufacturers). Biomedical informatics support in one or more centralised facilities is considered fundamental and must be innovative, taking into account that interoperability, security, workflow, usability and standards are essential areas of work. The dissemination of knowledge concerning the role of translational research may be augmented through the launch of online forums for free communication and exchange of ideas and through a dedicated journal of translational ophthalmic research for the publication of related articles, letters and reviews.

Implementation of Investigator-driven Clinical Trials

It is well accepted that improving conditions for better IDCT and clinical research will translate into better patient care and health worldwide. The top five recommendations to strengthen IDCT in Europe as ranked by a recent consensus conference as follows:

- to improve the education, training and career structure and opportunities for scientists involved in patient-orientated clinical research;
- to increase levels of funding for IDCT;
- to adopt a 'risk-based' approach to the regulation of IDCT;
- to streamline procedures for obtaining authorisation for IDCT; and
- to ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered'.

These directions are considered a fundamental step towards effective translational research and they include the need for one or more centralised facilities to support and co-ordinate the activities of transnational IDCT.

Centralised Support for Research Design, Epidemiology, Biostatistics and Clinical Research Ethics

Centralised support in trial design, biostatistics and clinical research ethics is necessary to co-ordinate and support interactions between the individual research centres. Topics for research involving this

centralised facility may include, for example, limiting risk to participants, preventing bias, improving recruitment and retention, developing innovative methods of enhancing the power of studies, capturing appropriate data, developing design and analysis plans for studies of unique or vulnerable populations or very small numbers of subjects, informed consent and factors in diseases with limited treatment options.

EU Institutions

A major goal of this initiative is to develop a transnational Consortium of Clinical and Translational Centres that will co-operate together to address impediments to clinical and translational science and will work towards adopting and implementing agreed-on best practices, policies, procedures and other measures to advance collaborative clinical and translational research and to reduce burden on individual investigators at all institutions. EVICR.net exists to bring together 75 clinical research centres in ophthalmology from 16 European countries, which could serve as an appropriate basis to promote and develop translational networking in ophthalmology and vision sciences across the EU.

Clinical Research Networks

Because of the vast number of therapies, diagnostics and treatments that must be evaluated through clinical trials, many clinical research networks operate simultaneously, but independently, of each other. As a result, researchers must sometimes duplicate data that already exist because they are unaware of, or do not have access to, the data. Standardising data reporting would enable seamless data- and sample-sharing across studies. By enhancing the efficiency of clinical research networks through informatics and other technologies, researchers will be able to more easily broaden the scope of their research. Reduced duplication of studies will leave more time and funds to address additional research questions.

Clinical Research Network Inventory

The goal of this effort is to determine best practices in clinical research networks by conducting an inventory of existing national networks. This project examines organisational and management structures of existing networks and evaluates the types and volume of studies being conducted. Other parameters to be analysed include network performance, informatics infrastructure and training procedures.

Integrating Clinical Research Networks

This initiative will test the feasibility of integrating and expanding existing clinical research networks. A particular focus is on assessing the capacity for interoperability among networks. This will broaden the kinds of research questions that can be addressed and will enhance the efficiency of clinical research. The long-range goals are to develop networks that are based on common infrastructure elements, such as informatics, governance and common language.

Clinical Research Training

One of the most important factors determining the health and vitality of the clinical research enterprise is the scientific workforce. It is necessary to find ways to expand and diversify the clinical research workforce by optimising training and career development programmes for the many

necessary players required to conduct successful clinical investigations. These players include physicians, nurses, dieticians, epidemiologists, biostatisticians and informatics specialists. Tomorrow's clinician must be trained to work in the interdisciplinary, team-orientated environments that characterise today's emerging research efforts.

Ophthalmology residents should be trained in translational research and translational research projects. Visits of resident ophthalmologists or fellows at basic research centres should be encouraged or even financed. Similarly, visits of basic scientists to ophthalmic departments and eye hospitals should also be encouraged. The clinical research workforce must be large enough to catalyse the translation of discoveries during research to patient care at the community level.

Co-ordinating Infrastructure

EVICR.net is a network of European ophthalmological clinical research centres dedicated to performing multinational clinical research trials with the highest standards of quality, following European and international directives for clinical trial research. Currently, EVICR.net has 75 centres members from 16 European countries.^{3,4} This network should serve as the basis for promoting and consolidating clinical research networking in the EU. Furthermore, most of the proposed centres that were identified as having the necessary requirements to become a clinical and translational research centre in ophthalmology and vision sciences are already part of this network. Therefore, EVICR.net could serve as the nucleus for innovative re-engineering of clinical research in ophthalmology and vision sciences within the EU.

A major initial step involves a complete inventory of the different participating centres, their resources in personnel and equipment, their scientific productivity and their internationalisation by partnerships with other similar institutions in the world. This inventory will help identify the available resources, how they could be synergised and the weaknesses that should be corrected.

EVICR.net offers an established basis for further development of improved organisational management structures. It has organisational standard operating procedures (SOPs) and independent procedures for certification and quality control of the participating centres.

EVICR.net has already established a co-ordinating infrastructure at the Association for Innovation and Biomedical Research on Light and Image (AIBILI), in Coimbra, Portugal, to support IDCT, functioning as a not-for-profit contract organisation and creating the necessary conditions for efficient academic led trials. Appropriate recognition and funding is needed to consolidate this type of co-ordinating infrastructure.

A major final goal is to extend these networking activities to affiliated centres in each EU region, thus contributing progressively to spreading harmonised information, governance, scientific language and training activities. This extension of networking in the different European regions will create a major organisation that will produce a volume of scientific response expected to compete favourably with any other region of the world and would certainly contribute to strengthen the EU health industry and innovation. ■

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