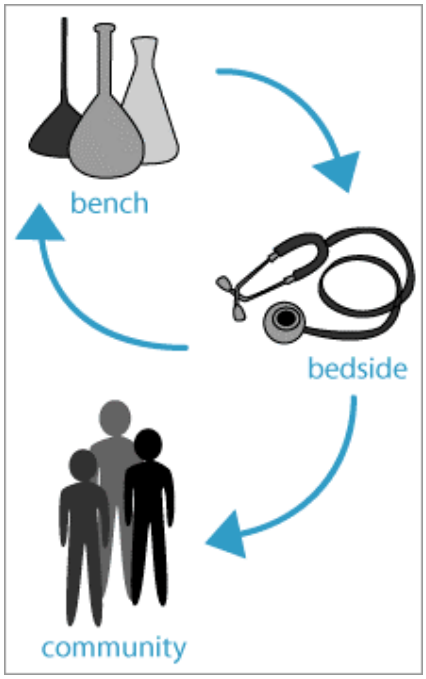
WHITE PAPER ON

TRANSLATIONAL RESEARCH

IN OPHTHALMOLOGY AND VISION SCIENCES

IN THE EUROPEAN UNION



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This White Paper is a deliverable of the Workpackage 5 “Re-engineering of clinical research, including clinical trials, in the field of vision sciences” of the project “Visual Impairment and Degeneration: A Road-map for Vision Research within Europe – EuroVisionNet” funded by the 7th Framework Programme of the European Union.

This White Paper emerged from a group of European Centres with active programs integrating Laboratory Research and dedicated Clinical Research Facilities in Vision and Ophthalmology.

The Centers were invited to participate in a Network “Translational Research Centres in Ophthalmology and Vision Sciences” within the European Union. The purpose of this Network is to stimulate the process for translational research between them and to synergize multidisciplinary and interdisciplinary clinical and translational research.

1. Definition

Translational research, usually called “bench to bedside”, applies discoveries generated through basic science research to the development and testing of preventive and treatment interventions (i.e., services, programs, practices and products) and vice versa.

Translational research may be seen as a five-phase model of intervention research that is commonly used to describe the continuum of biomedical research, from basic to applied science and vice versa. Translational research is patient-oriented and implicates an approach to health research where there is a permanent interchange between basic and applied science. Excellence in clinical research is a fundamental component of good translational research. Clinical research raises the questions and tests the proposed solutions.

The five phases of research, as applied to preventive intervention research across its life cycle, include:

- epidemiology (identification of the problem or disorder and review of information to determine its extent),
- disease-onset and disease progression (identification of risk and protective biomarkers for the problem or disorder as potential targets for preventive intervention),
- intervention design, pilot testing, efficacy trials,
- effectiveness trials,
- dissemination trials.

The translation process and communication between the different partners must be an integral part of all phases of research.

2. Justification

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.

Scientists are increasingly aware that this bench-to-bedside approach to translational research is really a two-way street. Basic scientists provide clinicians with new tools for use in patients and for assessment of their impact, and clinical researchers make novel observations about the nature and progression of disease that should stimulate basic research.

Translational research has proven to be a powerful process that drives the clinical research engine. However, a stronger clinical research infrastructure is necessary to strengthen and accelerate this critical part of the clinical research enterprise. It is fundamental to create in the European Union the right conditions for an even more successful process of translational research.

3. Clinical and Translational Research Institutions

Clinical and Translational 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 that can be integrated into a comprehensive, effective, and efficient researcher-, trainee-, and participant-centered program and develop their own list of key functions and components of the Center.

Potential topics include:

- Development of Novel Clinical and Translational Methodologies
- Pilot and Collaborative Translational and Clinical Studies
- Development of Communication Pathways
- Implementation of Investigator-Driven Clinical Trials
- Centralized Support for Research Design, Epidemiology, Biostatistics and Clinical Research Ethics
- Regulatory Knowledge
- Research Education, Training and Career Development
- European Union Institutions

Each Centre should have clinical research resources, training programmes and regular 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 Centers in the same area of scientific interest, e.g., Ophthalmology and Vision Health Care.
One or more Central Coordinating Core Centres must be set up and receive regular funding in order to facilitate coordination between the individual centres.
The Centres are encouraged to make alliances and create partnerships with foundations, industry and community organizations as appropriate, with all partners agreeing to follow European Union policies with respect to 1) listing clinical trials at ClinicalTrials.gov; 2) sharing of resources; 3) data sharing and public access and 4) establishing policies in support of investigator academic independence.

<u>Development of Novel Clinical and Translational Methodologies</u>
Original research on novel methodologies and approaches for translational and clinical sciences will be needed if a Centre is to build an environment that sustains intellectual innovation. Areas in which faculty should pursue funded research include new translational methodologies, methods for more objective and quantifiable biomarkers or phenotyping, determining cost effectiveness, research into clinical trial designs, clinical informatics for longitudinal studies, home based research devices and methods, predictive toxicology in human populations and ethics research specific to populations.

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 realized. Such funds must be available promptly and be accompanied by an organizational 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;
- 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 organizations. The Centres should consider both internal, intra-institution and external interoperability to allow for communication among 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 centralized facilities is considered fundamental and must be innovative taking into account 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 on-line 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 investigator-driven clinical trials and clinical research will translate into better patient care and health worldwide.

The top five recommendations to strengthen Investigator-Driven Clinical Trials (IDCT) in Europe as ranked by a recent consensus conference were as follows:

1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research
2. To increase levels of funding for IDCT
3. To adopt a ‘risk-based’ approach to the regulation of IDCT
4. To streamline procedures for obtaining authorisation for IDCT

5. 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 centralized facilities to support and coordinate the activities of transnational investigator-driven clinical trials.

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

Centralized support in trial design, biostatistics and clinical research ethics is necessary to coordinate and support interactions between the individual Research Centres. Topics for research involving this centralized facility might 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 issues in diseases with limited treatment options.

Regulatory Knowledge

Regulatory support for research teams will promote the protection of human subjects and facilitate regulatory compliance. The Centres are encouraged to be innovative at all levels of clinical research regulation including, for example, the provision of integrated training, services, or tools for protocol and informed consent authoring and translation, adverse event reporting, safety and regulatory management and compliance, etc. Centres could develop best practices that reduce or remove institutional impediments to clinical and translational research and, through dissemination and sharing, could enhance inter-institutional collaborations.

Communications with European Regulatory Authorities such as EMEA is considered an important step forward by strengthen cooperation between Centres and the Central Office of EMEA.

Research Education, Training and Research Career Development

A key component of a Clinical and Translational Centre will be one or more graduate degree-granting and post graduate programs in clinical and translational science that include a knowledge base for clinical and translational researchers, irrespective of their primary interest, degree or discipline. In response to the emergence of interdisciplinary, team-oriented environments, Centres should be encouraged to train investigators from diverse disciplines as well as study coordinators, project managers, and other key clinical research personnel in a range of topics relevant to clinical and translational science (e.g., clinical research design, epidemiology, biostatistics, pharmacology, biomedical informatics, ethics, behavioral science, engineering, law, health economics).

European Union Institutions

A major goal of this initiative is to develop a transnational Consortium of Clinical and Translational Centres that will cooperatively address impediments to clinical and translational science and will work toward 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.

There is already a Network bringing together 72 Clinical Research Centres in Ophthalmology from 16 European countries, the EVICR.net - European Vision Institute Clinical Research Network that could serve as an appropriate basis to promote and develop translational networking in Ophthalmology and Vision Sciences across the European Union.

4. 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 exists because they are unaware of the data or do not have access to the data. Standardizing 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 better able to 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 overall goal of this effort is to determine best practices in clinical research networks by conducting an inventory of existing national networks. This project is examining organizational and management structures of existing networks and will evaluate the types and volume of studies being conducted. Other parameters to be analyzed 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 conducting 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 optimizing training and career development programs 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-oriented environments that characterize today's emerging research efforts.

Ophthalmology residents should be exposed to training programmes in translational research and translational research projects.

Visits of resident ophthalmologists or fellows at basic research centers 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 sufficient large to catalyze the translation of research discoveries to patient care at the community level.

5. Coordinating Infrastructure

The EVICR.net - European Vision Institute Clinical Research Network is a network of European Ophthalmological Clinical Research Centres dedicated to perform multinational clinical research trials with the highest standards of quality, following the European and International Directives for Clinical Trial Research. At present, EVICR.net has 72 Centres members from 16 European countries.

This network should serve as the basis for promoting and consolidating clinical research networking in the European Union. Furthermore, most of the proposed Centres that were identified as having the necessary requirements to become a Clinical and Translational Research Centres Network 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 European Union.

A major initial step involves a complete inventory of the different participating Centres, their resources in personnel and equipment, their scientific productivity and their internationalization by partnerships with other similar institutions in the world. This inventory will help identify the available resources, how they could be synergized and the weaknesses that should be corrected.
EVICR.net offers an established basis for further development of improved organizational management structures. It has organizational Standard Operating Procedures (SOPs) and independent procedures for certification and quality control of the participating Centres.

EVICR.net has already established a Coordinating Infrastructure at AIBILI, in Coimbra, Portugal, to support Investigator-Driven Clinical Trials, functioning as a not-for-profit contract organization and creating the necessary conditions for efficient academic led trials. Appropriate recognition and funding is needed to consolidate this type of Coordinating Infrastructure.

A major final goal is to extend these networking activities to affiliated centres in each European Union region thus contributing progressively to spread harmonized information, governance, scientific language and training activities. This extension of networking in the different European regions will necessarily create a major organization 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 European Union Health Industry and Innovation.

6. Recommendations

Several areas were identified in which the practice of translational research can be strengthened, including the following:

Nurture team science

- Provide incentives for investigators engaged in team science associating laboratory science with clinical science. Changes in the culture of academic medical centers need to be stimulated to accomplish this.
- Provide project management functions, such as access to a "concierge" function, which serves as a "one stop shop" for research support by supporting a coordinating centralised infrastructure.
- Provide training to investigators in project management and leadership skills.
- The European Union Research Programme should develop and improve grant mechanisms that specifically support translational research teams associating laboratory science with clinical science.
- Enhance and continue to emphasize the mentoring function of active Clinical and Translational Centres.
- Find innovative ways to support research projects that are poised to move from the basic research stage to first tests in humans.

Improve understanding of and access to technology transfer functions

- Enhance investigators' understanding of the patent process, including disclosures and patent costs.
- Standardize technology transfer functions and methods across institutions.
- Promote training for early career investigators regarding collaborations with industry.

Regular funding of a Coordinating Centralised Infrastructure

- A coordinating infrastructure is essential for successful Investigator-driven clinical trials and is necessary to expand the ability to share resources across the active Clinical and Translational Centres, including shared core facilities.

Improve access to technologies and animal models.

- Increase the number and/or access to technologies and animal models specifically related to drug development.
- Develop a centralized database of animal models.
- Support development of instrument prototypes.

Annex 1: List of European Translational Research Centres

Austria

- Department of Ophthalmology, Medical University of Vienna, Vienna

Belgium

- Department of Ophthalmology, University Hospital Antwerp, Antwerp

France

- Centre d'Investigation Clinique, Centre National d'Ophtalmologie des Quinze-Vingts, Paris
- Service d'Ophtalmologie, Hôpital Purpan, Toulouse

Germany

- Department of Ophthalmology, University Medical Center, Johannes Gutenberg-University Mainz, Mainz
- Steinbeis-Transfer - Centre for Biomedical Optics and Function Testing (STZ), Centre for Ophthalmology, Tuebingen
- Department of Ophthalmology, University of Bonn, Bonn
- Department of Ophthalmology, University of Freiburg, Freiburg
- University Eye Hospital Leipzig, Leipzig
- Center for Vision Science, University Eye Clinic Bochum, Bochum
- Eye Centre Spreebogen, Berlin

Greece

- Institute of Vision and Optics (IVO), Crete
- Laboratory of Research and Clinical Applications in Ophthalmology, Department of Ophthalmology, Thessalonik

Italy

- G.B.Bietti Eye Foundation – IRCCS, Rome
- Institute of Ophthalmology, Catholic University, Rome
- Sezione di Oftalmologia, Dipartimento di Scienze Otorino-Odonto-Oftalmologiche e Cervico Facciali, Parma

Portugal

- AIBILI - Association for Innovation and Biomedical Research on Light and Image / Ophthalmology Department - University Hospital of Coimbra, Coimbra, Portugal

Spain

- IOBA - Instituto Universitario de Oftalmobiologia Aplicada, Valladolid
- VISSUM - Instituto Oftalmológico de Alicante, Alicante
- Institut Català de Retina (ICR), Barcelona

Switzerland

- Department of Ophthalmology, Inselspital, University of Bern, Bern
- Jules Gonin Eye Hospital, Department of Ophthalmology, Lausanne

The Netherlands

- Department of Ophthalmology, Academic Medical Center, Amsterdam
- Rotterdam Eye Hospital, Rotterdam

United Kingdom

- Clinical Trials Unit and Reading Centre, Moorfields Eye Hospital, NHS Foundation Trust, London
- Clinical Eye Research Centre, Royal Liverpool University Hospital, Liverpool

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