AIBILI 2016 REPORT
INTRODUCTION

AIBILI – Association for Innovation and Biomedical Research on Light and Image is a Research Technology Organisation in the health area dedicated to the development and clinical research of new products for medical therapy and diagnostic imaging.

It is a private non-profit organisation, founded in 1989, established to support translational research and technology transfer in the health area.

AIBILI is ISO 9001 certified for the following activities:
• performance of clinical research
• planning, coordination, monitoring of clinical research activities
• health technology assessment
• grading of eye exams
• research and development in new technologies for medicine in the areas of imaging, optics and photobiology
• preclinical studies of new molecules with potential medical use
• data centre activities

Clinical research is performed in accordance with ICH – Good Clinical Practice (GCP) Guidelines and national and European regulatory requirements.

AIBILI is the Coordinating Centre of EVICR.net – European Vision Institute Clinical Research Network, which is a platform for multinational clinical research in Ophthalmology in Europe and brings together 102 clinical research centres from 18 European countries.

AIBILI is organized in Research Centres and Organizational Units.

The Research Centres are:
• Coimbra Coordinating Centre for Clinical Research (4C)
• Clinical Trial Centre (CEC)
• Coimbra Ophthalmology Reading Centre (CORC)
• Centre for New Technologies in Medicine (CNTM)
• Centre for Health Technology Assessment and Drug Research (CHAD)

• EVICR.net – European Vision Institute Clinical Research Network, Coordinating Centre

Organizational Units are the Administrative Services (SA), the Quality Management Unit (UGQ), the Translational Research and Technology Transfer Unit (UTT) and the Information Technology Unit (IT) and Data Centre.

AIBILI is located at the Health Campus of Coimbra University since 1994 and has its own building with 1.454 m² and state-of-the-art equipment. Regarding human resources it has a permanent staff of 55 including medical doctors, researchers, engineers, pharmacologists, technicians, project managers, regulatory affairs, study coordinators and administrative personnel. Another 40 professionals collaborate regularly in research activities.

AIBILI has collaborations with national and international institutions:
• CF – Champalimaud Foundation
• CHUC – Coimbra University Hospital and its Centre of Responsibility in Ophthalmology
• FMUC – Faculty of Medicine of the University of Coimbra
• IBILI – Institute of Biomedical Research on Light and Image
• ICNAS – Institute of Nuclear Sciences Applied to Health
• Institute for Vision at the Federal University of S. Paulo, S. Paulo, Brazil
• L.V. Prasad Eye Institute, Hyderabad, India

In summary, the main goals of AIBILI are innovation and translational research that is to convert basic research knowledge into practical applications to enhance human health and wellbeing. It is important to realize that translational research has complementary domains:
• the “bench to bedside” – translating knowledge from the basic sciences into the development of new treatments (basic research to clinical research) and,
• translating the findings from clinical trials into everyday practice.

AIBILI is an infrastructure for clinical eye research and the Coordinating Centre of EVICR.net, the European Vision Institute Clinical Research Network.

AIBILI assumes a leading role in European Clinical Research in Vision and Imaging, bringing together academic institutions and industry, to improve diagnostic, prevention and treatment strategies in vision and enhance human health and wellbeing.
AIBILI ASSOCIATES

Founding Associates
• FLAD – Fundação Luso-Americana para o Desenvolvimento (Honorary Associate)
• IAPMEI – Instituto de Apoio às Pequenas e Médias Empresas e à Inovação
• José Cotta – EMS, S.A.
• José Cunha-Vaz
• Laboratório EDOL – Produtos Farmacêuticos, S.A
• Biofísica da Faculdade de Medicina da Universidade de Coimbra
• Farmacologia da Faculdade de Medicina da Universidade de Coimbra
• Serviço de Dermatologia do Centro Hospitalar Universitário de Coimbra
• SUCH – Serviço de Utilização Comum dos Hospitais

Other Associates
• Alcon Portugal – Prod. e Equip. Oftalmológicos, Lda.
• BIAL – Portela & Cª., SA
• Fundação Champalimaud (Honorary Associate)
• Laboratórios Pfizer, Lda.
• Novartis Farma, SA
• Centro de Oftalmologia da Universidade de Coimbra
• Universidade de Coimbra (Honorary Associate)

AIBILI BOARD OF DIRECTORS
(2014–2017)
• José Cunha-Vaz, President
• José Cotta – EMS, SA, Vice-President
• BIAL – Portela & Cª, SA
• Fundação Champalimaud
• Laboratórios Edol, Produtos Farmacêuticos, SA
• Serviço de Dermatologia do Centro Hospitalar Universitário de Coimbra
AIBILI

BOARD OF DIRECTORS

President
José Cunha-Vaz

CEO
Cecília Martinho

Administrative Services (SA)
Cecília Martinho

Quality Management (UGQ)
Rita Fernandes

Translational Research and Technology Transfer (UTT)
Daniel Fernandes

Information Technology (IT)
Data Centre (DC)
Carlos Domingues

Coimbra Coordinating Centre for Clinical Research 4C
Sandrina Nunes

Clinical Trial Centre CEC
Luísa Ribeiro

Coimbra Ophthalmology Reading Centre CORC
Conceição Lobo

Centre of New Technologies for Medicine CNTM
José Cunha-Vaz

Centre for Health Technology Assessment and Drug Research CHAD
Batel Marques
AIBILI AT A GLANCE 2016

DATA CENTRE (DC)
- Services 11

CENTRE OF NEW TECHNOLOGIES FOR MEDICINE (CNTM)
- Research Projects 10
  - Patents 3 (USA)
  - Pre Clinical Projects 5

EVICR.net COORDINATING CENTRE
- Industry Sponsored Clinical Trials 2
- Investigator Initiated Research 7

DATA CENTRE (DC)
- Services 11

COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH (4C)
- Coordination of Investigator Initiated Research
  - Multinational 12
  - National 11
- Coordination of Industry Sponsored Clinical Trials 2
- Other 2

COIMBRA OPHTHALMOLOGY READING CENTRE (CORC)
- Multinational Trials 7
- National Trials 9

CLINICAL TRIAL CENTRE (CEC)
- Industry Sponsored Clinical Trials 25
  - Multinational 3
  - National 4
  - Neurosciences 9
  - Ophthalmology 16
- Investigator Initiated Research (Ophthalmology)
  - Multinational 7
  - National 4

CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH (CHAD)
- Market Access 21
- Drug Safety 7

Pre Clinical Projects 5

- Translational Research Organization
- Experienced Staff and Modern Facility
- Independent Ethics Committee
- C-TRACER 2 – Champalimaud Foundation Translational Centre for Eye Research
- Compliance with ICH-GCP Guidelines
- ISO 9001 Certification
- CBC – Certified Clinical Site of Excellence – EVICR.net
AIBILI HIGHLIGHT NUMBERS 2016

Area 1,454 m²
Fulltime Staff 55
Nº of Consultants 40
Nº of PhD 20
Nº of ongoing studies, services, projects, contracts 138
Nº of patents 3 (USA) + 1 (PCT)
Nº of European Union funded projects (ongoing) 3
Nº of publications (2015–2016) 79
Nº of publications / PhD (2015–2016) 3,8
Income 2397,727 €

TYPE OF INCOME (2016)

INCOME (2012–2016)

External Scientific Council 2015
• Morton Goldberg, MD PhD – Johns Hopkins Hospital, Baltimore, USA
• Srinivas Sadda, MD PhD – Doheny Eye Institute, Los Angeles, USA
• Francesco Bandello, MD, PhD – Scientific Institute San Raffaele, Milan, Italy
Clinical Research Infrastructure

Translational research has proven to be a powerful process that drives the clinical research engine. A strong clinical research infrastructure is necessary to strengthen and accelerate this critical part of the clinical research process. The major need to perform high-quality investigator initiated research (IIR) is access to an infrastructure that functions as an academic CRO providing centralized services and logistical support in compliance with ICH-GCP Guidelines at affordable costs. This is particularly true when performing multinational clinical research bringing together clinical research centres from different countries where there are different national requirements making central coordination crucial.

Centralized support in trial design, biostatistics, ethics and regulatory affairs is necessary to coordinate and support interactions between the individual research centres. Topics involving such a centralized facility include, for example, limiting risk to participants, preventing bias, improving recruitment and patient 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, issues in diseases with limited treatment options and informed consent development. There is a crucial need for central coordination in order to implement and manage a multicentric clinical study involving different countries.

Another supporting service that is also essential in the performance a clinical trial is Pharmacovigilance. Specifically for ophthalmological clinical trials there is also need for central grading of the ophthalmological exams therefore requiring a central Reading Centre like CORC – Coimbra Ophthalmology Reading Centre.

Finally, to approach translational research it is crucial to consider its feasibility and have adequate planning of funding and resources needed. Therefore it is considered essential to have expertise on development of business models that take into account the potential market value of the drug, biomarker or medical device from the beginning of the translational process until it reaches the patient and is implemented into everyday clinical practice.
AIBILI is the headquarters and **Coordinating Centre** of the European Vision Institute Clinical Research Network – **EVICR.net**. EVICR.net is a network of European Ophthalmological Clinical Research Sites, dedicated to perform multinational clinical research in ophthalmology with the highest standards of quality, following the European, International regulations for Clinical Research and ICH-GCP Guidelines. EVICR.net aim is to strengthen the capacity of the European Union to explore the determinants of ophthalmic diseases and to develop and optimise the use of diagnostic, prevention and treatment strategies in ophthalmology contributing to bring better patient care to daily clinical practice. EVICR.net is a platform for ophthalmology multinational clinical trial research in Europe and a useful Industry resource in order to contribute to the development of new drugs, medical devices and biomarkers.

Any Clinical Research Site in Ophthalmology can apply for EVICR.net membership. In order to become a member, basic requirements such as dedicated space to perform clinical studies, qualified and experienced personnel, experience of multinational clinical studies and agree to implement organizational SOPs according to ICH-GCP Guidelines, provided by EVICR.net need to be fulfilled. Each Clinical Site will be submitted to an on-site evaluation visit by independent auditors, if applicable, and must agree to implement the recommended necessary actions in order to become a certified EVICR.net Clinical Site of Excellence. AIBILI is the EVICR.net Coordinating Centre and is organized to provide planning and management of multinational clinical studies. It has common and harmonized organizational and technical SOPs, quality control and staff training according to ICH-GCP Guidelines. EVICR.net serves as a fundamental resource for the development of multinational clinical research particularly supporting multinational Investigator Initiated Research (IIR) applying for EU funding or Industry IIR grants. Scientifically it is organized by ophthalmology subspecialty Expert Committees namely: Age-Related Macular Degeneration; Retinal Dystrophies; Diabetic Retinopathy and Vascular Diseases; Glaucoma; Anterior Segment; Ocular Surface, Inflammation, Dry-Eye & Allergies; and Reading Centres. It also has Transversal Sections in Rare Diseases and Medical Devices. At present, EVICR.net has 102 Clinical Ophthalmological Centres members from 18 European countries. The Network has 9 clinical trials ongoing of which 3 are European Union funded projects.

**AIMS AND OBJECTIVES**

The main aims and objectives of EVICR.net are:
- To guarantee a high level of quality and excellence in ophthalmology clinical research performed by its members according to ICH-GCP Guidelines
- To promote multinational investigator initiated research (IIR) within the European Union
- To coordinate training activities for its members
- To serve as a resource for Industry in performing multinational clinical research in ophthalmology
- To promote quality, transparency and optimal use of clinical research data
- To communicate with patients and citizens of the challenges and opportunities raised by clinical research in ophthalmology
The General Assembly consists of all EVICR.net members and is the supreme organ of the Network. The Steering Committee is responsible for the activities of the EVICR.net and acts as its decision-making body within the framework set by the General Assembly. The Steering Committee consists of: the Chairman, the Coordinator of each Expert Committee and the CEO of the Coordinating Centre. The Expert Committees have a fundamental role in the scientific organization of EVICR.net and cover the main ophthalmological research areas. The Industry Advisory Board advises the Steering Committee in all matters of strategic relevance, particularly pertaining collaborations with Industry. The Industry Advisory Board is composed of individuals or representatives of companies who have given support to the activities of EVICR.net. At the moment is composed by Alcon, Allergan, Bayer, Novartis, Pfizer, Santen and Théa.

The Coordinating Centre, AIBILI, is the single contact point for the members and industry when performing multinational ophthalmological clinical research in Europe. Annually the Coordinating Centre updates the EVICR.net Research Resources Directory where all members have their resources listed namely: staff, equipment and facilities as well as their scientific areas of clinical research and the five most relevant publications. All members have access to a restricted area in the website that is also kept update by the Coordinating Centre. The Coordinating Centre is responsible for the certification of EVICR.net Clinical Site Members.
SCIENTIFIC SECTIONS (2016–2019)

AGE-RELATED MACULAR DEGENERATION
Coordinator: Prof. Francesco Bandello (CS 67)
Members: Prof. Eric Souied (CS 3), Prof. Frank Holz (CS 15), Prof. Rufino Silva (CS 82), Prof. Sandrine Zweifel (CS 112), Prof. Angela Carneiro (CS 32), Dr. Emily Fletcher (CS 53)

RETINAL DYSTROPHIES
Coordinator: Dr. Hendrik Scholl (CS 110)
Members: Dr. Isabelle Audo (CS 6), Prof. Carel Hoyng (CS 17), Dr. Camiel J. J. Boon (CS 106), Dr. Ingeborgh van den Born (CS 40), Dr. João Pedro Marques (CS 01), Dr. David Keegan (CS 31)
Co-opted Member: Prof. Birgit Lorenz (CS 65)

DIABETIC RETINOPATHY & VASCULAR DISEASES
Coordinator: Prof. José Cunha-Vaz (CS 1)
Members: Prof. Michael Larsen (CS 30), Prof. Edoardo Midena (CS 39), Prof. Peter Scanlon (CS 53), Prof. Sobha Sivaprasad (CS 10), Prof. Noemi Lois (CS 35), Prof. João Figueira (CS 82)
Invited Member: Prof. Rafael Simó (CS 74)
Young Investigator: Dr. Maria Cristina Parravano (CS 20)

GLAUCOMA
Coordinator: Prof. Francesca Cordeiro (CS 84)
Members: Prof. Luísa Ribeiro (CS 1), Prof. Luca Rossetti (CS 16), Prof. Stefano Gandolfi (CS 37), Prof. Ingeborg Stalmans (CS 18), Dr. António Figueiredo (CS 101), Dr. Francesco Oddone (CS 20)

ANTERIOR SEGMENT
Coordinator: Prof. Marie-José Tassignon (CS 12)
Members: Prof. Gerd Auffarth (CS 1), Prof. David Varsano (CS 60), Prof. Joaquim Murta (CS 70), Prof. Jos Rozema (CS 12), Prof. Dominique Bremond-Gignac (CS 48), Prof. Gre P. M. Luyten (CS 106)
Co-opted Member: Prof. Jorge Alió (CS 7)

OCULAR SURFACE, INFLAMMATION, DRY-EYE & ALLERGIES
Coordinator: Prof. Marc D. de Smet (CS 108)
Members: Dr. Susan Lightman (CS 10), Dr. Elsabetta Miserochi (CS 67), Dr. Bahram Bodaghi (CS 113), Dr. Robert Finger (CS 15), Prof. Maria João Quadro (CS 114), Dr. Shiri Schulman (CS 60)

READING CENTRES
Coordinator: Prof. Tunde Peto (CS 35)
Members: Prof. Conceição Lobo (CS 1), Dr. Steffen Schmitz-Valckenberg (CS 15), Dr. Stela Vujosevic (CS 39), Dr. Alexander Schuster (CS 2), Prof. Steve Aldington (CS 53), Dr. Ramin Khoramnia (CS 56)

TRANSVERSAL SECTIONS
RARE DISEASES
Coordinator: Prof. Birgit Lorenz (CS 65)

MEDICAL DEVICES
Coordinator: Prof. Jorge Alió (CS 7)

CLINICAL STUDIES AND REGISTRIES
The EVICR.net Coordinating Centre assumes the leadership of coordination and management of Investigator Initiated Research (IIR) in ophthalmology across Europe through the Network. EVICR.net Members have the opportunity to participate in IIR within the Network as well as to submit abstracts for IIR to the Coordinating Centre in order to be evaluated by a specific Expert Committee. When approved, they will have access to support in coordinating and implementing the IIR within EVICR.net.

PROJECTS AND ACTIVITIES

<table>
<thead>
<tr>
<th>Area of Subspecialty</th>
<th>Amd and Retinal Dystrophies</th>
<th>Diabetic Retinopathy and Retinal Vascular Diseases</th>
<th>Glaucoma</th>
<th>Anterior Segment</th>
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<tbody>
<tr>
<td>Ongoing Clinical Research</td>
<td>Eur-USH (a) ATLANTIC (b) EUROCONDOR (a) PROTEUS (b) ARTES (b) STRONG (a) SPORT (b)</td>
<td>POLARIS IRISS</td>
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<tr>
<td>Clinical Trials (IIRs)</td>
<td>2</td>
<td>5</td>
<td>2</td>
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<td>Registries (Industry)</td>
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(a) EU funded
(b) Industry Grant
EVICR.net investigator initiated research (IIR) has been growing in the last years, giving the opportunity for investigators to perform multinational clinical research of high quality in compliance with ICH-GCP Guidelines assuming that the rights, safety and wellbeing of the trial subjects are protected and that the clinical data are credible. EVICR.net has contributed to the improvement of diagnostic, prevention and treatment strategies in ophthalmology. In 2016 there were nine ongoing multinational clinical research studies. Projects and Activities

**INVESTIGATOR INITIATED RESEARCH**

1. **EudraCT n° 2012-001200-38**
   - ClinicalTrials.gov nº NCT01726075
   - **EUROCONDOR** – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy
   - Project Coordinator: Rafael Simó, Barcelona, Spain
   - Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal (CSI)

2. **EudraCT n° 2014-000239-18**
   - **STRONG** – European Consortium for the Study of a Topical Treatment of Neovascular Glaucoma
   - Protocol nº GS-101-P1-NVR
   - Project Coordinator: Norbert Pfeiffer, Mainz, Germany (CS2)
   - Financial Support: European Union 7th Framework Programme – Call Health 2012 – Project nº 30532

3. **ClinicalTrials.gov nº NCT01954953**
   - **Eur-USH** – European young investigators network for Usher syndrome
   - Protocol nº P13-02
   - Project Coordinator: Kerstin Nagel-Wolfrum, Mainz, Germany (CS2)
   - Scientific Coordinator: J. Sahel, Paris, France (CS6)
   - Project Partners (6): Coimbra (2), Paris, Mainz, Montpellier, Nijmegen.
   - Financial Support: European Union 7th Framework Programme – Call E-RARE 2 – Project nº 12-058

4. **EudraCT n° 2013-003640-23**
   - ClinicalTrials.gov nº NCT01941329
   - **PROTEUS** – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy
   - Coordinating Investigator: João Figueira, Coimbra, Portugal (CSI)
   - IIR Grant: Novartis

5. **EudraCT n° 2013-003490-10**
   - ClinicalTrials.gov nº NCT01975714
   - **SPORT** – A randomized, 3 months, crossover, single-masked, investigator-led, multicenter trial on open-angle glaucoma or ocular hypertension patients
   - Coordinating Investigator: Ingeborg Stalmans, Leuven, Belgium (CS18)
   - IIR Grant: Allergan

6. **ClinicalTrials.gov nº NCT02121197**
   - **ARTESS** – A Collaborative Retrospective Trial on the Efficacy and Safety of intravitreal dexamethasone implant (Ozurdex) in patients with Diabetic Macular Edema (DME). The European DME Register Study
   - Protocol nº ECR-RET-2014-07
   - Coordinating Investigator: Anat Loewenstein, Tel Aviv, Israel (CS60)
   - IIR Grant: Allergan

7. **ClinicalTrials.gov nº NCT02495181**
   - **EudraCT n° 2015-001368-20**
   - **ATLANTIC** – A Randomized, Double-masked, Sham-controlled Phase 4 Study of the Efficacy, Safety, and
Tolerability of Intravitreal Aflibercept Monotherapy Compared to Aflibercept with Adjunctive Photodynamic Therapy in patients with Polypoidal Choroidal Vasculopathy

Coordinating Investigator: Rufino Silva, Coimbra, Portugal (CS82)


IIR Grant: Bayer

INDUSTRY SPONSORED CLINICAL TRIALS

1. ClinicalTrials.gov n° NCT01771081

POLARIS – A Prospective non-interventional study to assess the effectiveness of existing anti-vascular endothelial growth factor (Anti-VEGF) treatment regimens in patients with diabetic macular edema (DME) with central involvement


Sponsor: Bayer

2. ClinicalTrials.gov n° NCT01998412

IRISS – An open label, registry study of the safety of ILUVIEN® (fluocinolone acetonide 190 micrograms intravitreal implant in applicator)

Participating Centres (40): Portugal (4), Germany (8), United Kingdom (28).

Sponsor: Alimera

TECHNICIAN CERTIFICATION

Best-Corrected Visual Acuity Technician’s Certification for Allergan studies:

1. Protocol n.° 190942-038

64 technicians certified in France, Germany, Italy and UK.

2. Protocol n.° 150998-005 and 150998-006

70 technicians certified in Austria, France, Germany, Israel, Italy, Spain and UK.

ORGANIZATION OF EVICR.net ANNUAL MEETING

The 11th Annual Members Meeting took place on November 9-10, 2016, in Antwerp, Belgium, hosted by Prof. Marie-Jose Tassignon (CS12). The meeting was attended by 93 participants representing 42 Clinical Sites and Industry Advisory Board Members from Alcon+Novartis, Allergan, Bayer and Santen. Dr. Jee Lampol from the Diabetic Retinopathy Clinical Research Network – DRCR.net (USA) was the invited Speaker to our meeting in order to foster the collaboration of EVICR.net Diabetic Retinopathy Section and DRCR.net in clinical research.

The 12th EVICR.net annual meeting will take place in October 19–20, 2017, in GIESSEN, Germany, hosted by Prof. Birgit Lorenz (CS65).

ELECTIONS FOR THE EXPERT COMMITTEES

Following on the decision to have the AMD and Retinal Dystrophies Section divided in two, and a new Section on Ocular Surface EVICR.net has now seven Scientific Sections plus two Transversal Sections. During the 11th EVICR.net Members Meeting in Antwerp, Belgium, elections for the Expert Committees to initiate functions for a period of three years (2016–2019) took place at each Scientific Section.

CENTRE CERTIFICATION AND RE-CERTIFICATION

There are 58 certified Clinical Sites of Excellence and 44 in the certification process. Certified Clinical Sites of Excellence have the basic requirements such as dedicated space to perform clinical studies, qualified and experienced personnel, experience in clinical studies and implemented organizational SOPs ICH-GCP compliant.

STANDARD OPERATING PROCEDURES

EVICR.net has developed a Quality System for its members compliant with ICH-GCP Guidelines. It provides for free to its members 9 Organizational Standard Operating Procedures (SOPS). All our Clinical Sites Members agree to adopt these SOPs in their Centres which will be checked before they are certified as Sites of Excellence.

The implementation of these 9 Organizational SOPs will permit the Clinical Sites to have a standard way of working in compliance with ICH-GCP Guidelines when performing clinical research. EVICR.net has also developed 31 Technical SOPs for performing specific ophthalmic examinations or evaluations that can be used within the Network for clinical studies. These SOPs are also made available to the members.

In parallel, EVICR.net has developed 22 Organizational SOPs for the Reading Centres so they can work as a network of Reading Centres and be able to have the capacity to respond to the industry needs for grading ophthalmological images in a standardise way with the most novel equipments.

EVICR.net INVESTIGATOR INITIATED RESEARCH (IIR) INTERNAL PROCEDURES

Providing all the necessary support to the investigators to perform multinational investigator initiated clinical studies is one of the main aims of EVICR.net Information on how to submit Investigator Initiated Research (IIR) and the procedure to be follow whenever an idea for an investigation is presented within EVICR.net is available at the Network website www.evirc.net.

COLLABORATION WITH ECRIN – EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK

EVICR.net, as a disease oriented network in Ophthalmology, is an ECRIN-ERIC Affiliate Partner. ECRIN-ERIC is the European Clinical Research
Infrastructure Network that supports the conduct of independent, multinational clinical trials by managing and supporting clinical trials across borders, connecting networks, and advising and implementing policy, competitiveness and integration in European clinical research. EVICR.net provides scientific and medical expertise, access to patients and research infrastructure for multinational clinical research in vision and ophthalmology.

**ALLIANCES AND PARTNERSHIPS**

EVICR.net has established preferred alliances with two CROs, AppleTree (Switzerland) and Eurotrials (Portugal), for the EVICR.net Clinical Site certification process, to perform an independent evaluation visit of the Clinical Sites. Collaborations are also established with other CROs to move forward multinational clinical research in ophthalmology, namely with Covance, Parexel and Quintiles.

**EVICR.net MEMBERS (PER COUNTRY)**

**AUSTRIA (1)**

CS nº 19: Medical University of Vienna, Department of Ophthalmology, Vienna

**BELGIUM (3)**

CS nº 8: Ghent University Hospital, Department of Ophthalmology, Ghent
CS nº 12: Antwerp University Hospital, Department of Ophthalmology, Antwerp
CS nº 18: University Hospital Leuven, Department of Ophthalmology, Leuven

**DENMARK (2)**

CS nº 30: Glostrup Hospital, Department of Ophthalmology, Copenhagen University, Glostrup
CS nº 73: Odense University Hospital, Department of Ophthalmology, Odense

**FINLAND (1)**

CS nº 91: Department of Ophthalmology, Kuopio University Hospital, Kuopio

**FRANCE (13)**

CS nº 3: Centre Hospitalier Creteil, University Eye Clinic, Paris
CS nº 6: Centre National d’Ophthalmologie des Quinze-Vingts, Centre d’Investigation Clinique, Paris
CS nº 13: CHU Gabriel Montpied, Unité de Recherche Clinique, Service d’Ophthalmologie, Clermont-Ferrand
CS nº 14: Hôpital Lariboisière, Department of Ophthalmology, Paris
CS nº 42: University Hospital, CHU Dijon, Department of Ophthalmology, Dijon
CS nº 48: CLAIROP: Centre loco-régional d’Amiens pour l’Innovation et la Recherche en Ophtalmologie Pédiatrique, Amiens

CS nº 61: CHU Pellegrin, Service Ophtalmologie, Bordeaux
CS nº 86: Clinique Ophtalmologique, Centre Saint Victor, Centre Hospitalier Universitaire d’Amiens, Amiens
CS nº 92: Clinical Trial Unit, Department of Ophthalmology, CHU Nord, Aix Marseille University, Marseille
CS nº 93: Department of Ophthalmology, Centre Hospitalier Henri Duffaut, Avignon
CS nº 97: Coscas Eye Clinic, Paris
CS nº 99: Department of Ophthalmology, Croix Rousse University Hospital, Lyon
CS nº 113: Service d’Ophtalmologie, Hôpital Pitié-Salpêtrière, Paris

**GERMANY (16)**

CS nº 2: University Medical Center, Johannes Gutenberg University, Department of Ophthalmology, Mainz
CS nº 5: Faculty of Medicine Mannheim of the Ruprecht-Karls-University Heidelberg, Department of Ophthalmology, Mannheim
CS nº 9: University Hospital Tuebingen (UKT), STZ Biomed & STZ Eyetrial at the Center for Ophthalmology, Tuebingen
CS nº 11: University Eye Hospital Munich, Munich
CS nº 15: University of Bonn, Department of Ophthalmology, Bonn
CS nº 21: University Medical Center Hamburg-Eppendorf, Department of Ophthalmology, Hamburg
CS nº 24: University of Freiburg, Department of Ophthalmology, Freiburg
CS nº 27: University Eye Hospital, Leipzig
CS nº 43: RWTH Aachen University, Department of Ophthalmology, Aachen
CS nº 44: University Eye Clinic, Center for Vision Science, Bochum
CS nº 54: University of Düsseldorf, Department of Ophthalmology, Düsseldorf
CS nº 56: University of Heidelberg, International Vision Correction Research Centre (IVCRC), Heidelberg
CS nº 65: Justus-Liebig-University-Giessen, Department of Ophthalmology, Giessen
CS nº 77: Universität zu Köln, Zentrum für Augenheilkunde, Köln
CS nº 111: Department of Ophthalmology, University of Muenster Medical Center, Muenster

**GREECE (1)**

CS nº 71: Laboratory of Research and Clinical Applications in Ophthalmology, Aristotle Univ. of Thessaloniki, Department of Ophthalmology, AHEPA Univ. Hospital, Thessaloniki

**IRELAND (1)**

CS nº 31: Mater Vision Institute (MVI), Dublin
ISRAEL (3)
CS nº 60: Tel Aviv Sourasky Medical Center, Department of Ophthalmology, Tel Aviv
CS nº 88: Kaplan Medical Center, Ophthalmology Department, Rehovot
CS nº 100: Meir Medical Center, Kfar-Saba

ITALY (10)
CS nº 16: University of Milan, Centre for Clinical Trials at San Paolo Hospital, Milan
CS nº 20: G. B. Bietti Foundation – IRCCS, Rome
CS nº 34: Luigi Sacco Hospital, University of Milan, Department of Ophthalmology, Milan
CS nº 36: Catholic University, Institute of Ophthalmology, Rome
CS nº 37: Dipartimento di Scienze Biomediche, Biotecnologiche e Transazionali S.Bi.B.T., Parma
CS nº 39: University of Padova, Department of Ophthalmology, Center for Clinical Trials, Padova
CS nº 50: University of Udine, Department of Ophthalmology, Udine
CS nº 63: University G. d’Annunzio of Chieti-Pescara, Excellence Eye Research Centre, Chieti
CS nº 64: University of Bari, Department of Ophthalmology and Otolaryngology, Bari
CS nº 67: University Vita Salute – Scientific Institute of San Raffael, Department of Ophthalmology, Milan

NETHERLANDS (5)
CS nº 17: University Medical Centre St Radboud, Ophthalmic Trial Centre Nijmegen, Nijmegen
CS nº 25: Academic Medical Center, Department of Ophthalmology, Amsterdam
CS nº 40: Rotterdam Eye Hospital, Rotterdam
CS nº 76: University Eye Clinic, Maastricht
CS nº 106: Department of Ophthalmology, Leiden University Medical Center, Leiden

POLAND (1)
CS nº 33: Poznan University of Medical Sciences, Department of Ophthalmology, Poznan

PORTUGAL (14)
CS nº 1: AIBILI – Association for Innov. and Biom. Research on Light and Image, Coimbra
CS nº 28: Instituto de Oftalmologia Dr. Gama Pinto, Lisbon
CS nº 32: Oporto Medical School – Hospital S. João, Department of Ophthalmology, Oporto
CS nº 62: Centro Hospitalar de Lisboa Central, Centro de Investigação, Serviço de Oftalmologia, Lisbon
CS nº 70: University Hospital of Coimbra, Ophthalmology Department, Coimbra
CS nº 80: Instituto de Retina e Diabetes Ocular de Lisboa (IRL), Lisbon
CS nº 82: Espaço Médico de Coimbra, Coimbra
CS nº 90: Serviço de Oftalmologia, Hospital de Vila Franca de Xira, Vila Franca de Xira
CS nº 101: ALM-Oftalmolaser, Lisbon
CS nº 102: Instituto Português de Microcirurgia Ocular (IMO), Lisbon
CS nº 103: Serviço de Oftalmologia, Hospital de Braga, Braga
CS nº 104: Centro de Investigação, Serviço de Oftalmologia, Centro Hospitalar de Leiria E.P.E., Leiria
CS nº 107: Serviço Oftalmologia, Centro Hospitalar Porto-HSA, Oporto
CS nº 114: Unidade de Oftalmologia de Coimbra (UOC), Idealmed, Coimbra

SLOVAKIA (1)
CS nº 87: Department of Ophthalmology, Comenius University, Bratislava, Slovakia

SLOVENIA (1)
CS nº 23: University Medical Centre of Ljubljana, University Eye Hospital, Ljubljana

SPAIN (15)
CS nº 7: Vissum Corporación Oftalmológica Alicante, Alicante
CS nº 26: Centro de Oftalmología Barraquer, Barcelona
CS nº 38: Institut Català de Retina (ICR), Clinical Trial Unit, Barcelona
CS nº 41: Centro Médico Teknon, Institut de la Màcula i de la Retina, Barcelona
CS nº 51: Fundación Oftalmológica del Mediterráneo, Valencia
CS nº 52: University Hospital Josep Trueta of Girona, Department of Ophthalmology, Girona
CS nº 74: Hospital Vall d’Hebrón, Department of Ophthalmology, Barcelona
CS nº 75: Vallés Oftalmologia Research, Barcelona
CS nº 78: Instituto Oftalmológico Fernandez-Vega, Oviedo
CS nº 89: Ophthalmology Department, Dos de Maig Hospital, Barcelona
CS nº 95: Instituto de Microcirugia Ocular, Barcelona
CS nº 96: Ophthalmology Department, Hospital de LaPaz, Madrid
CS nº 98: Servicio Oftalmología, Hospital Universitario Y Politecnico de la Fe, Valencia
CS nº 105: Unidad Clinica de Retina – Servicio de Oftalmologia, Complejo Hospitalario Universitario de Albacete
CS nº 109: Department of OphthalmologyFundación Jiménez Díaz University Hospital, Madrid
SWITZERLAND (6)
CS n° 22: Inselspital, University of Bern, Department of Ophthalmology, Bern
CS n° 49: Jules Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne
CS n° 85: Clinical Research Centre Mémorial A. de Rothschild, Geneva
CS n° 108: MiOS – Retina and Inflammation, SA, Lausanne
CS n° 110: University Hospital Basel, University Eye Clinic, Basel
CS n° 112: Department of Ophthalmology, University Hospital Zurich, Zurich

UNITED KINGDOM (9)
CS n° 10: Moorfields Eye Hospital NHS Foundation Trust, Clinical Trial Unit, London
CS n° 35: The Queen’s University and Royal Group of Hospitals Trust, Ophthalmology and Vision Science, Belfast
CS n° 53: Gloucestershire Hospitals NHS Foundation Trust, Clinical Trials Unit, Department of Ophthalmology, Gloucestershire
CS n° 58: Royal Liverpool University Hospital, Clinical Eye Research Centre, St. Paul’s Eye Unit, Liverpool
CS n° 66: Frimley Park Hospital Foundation Trust, Ophthalmology Clinical Trials Unit, Surrey
CS n° 68: Heart of England NHS Trust, Ophthalmic Research Unit, Birmingham
CS n° 69: King’s Health Partners, Laser and Retinal Research Unit, London
CS n° 81: Royal Surrey County Hospital, NHS Foundation Trust, Ophthalmic Research Unit, Guildford
CS n° 84: ICORG – Imperial College Ophthalmologic Research Group, London
4C – COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH
– AN ACADEMIC CRO

Director: Sandrina Nunes, PhD

Staff: Ana Pedroso, Ângela Ferrão, Catarina Gomes, Cecilia Martinho, Conceição Lobo, Dalila Alves, Daniel Fernandes, Hugo Mendes, Liliana Carvalho, Joaquim Murta, José Cunha-Vaz, Maria Viegas Nascimento, Miguel Costa, Rita Fernandes, Rufino Silva, Sónia Simões, Tiago Ferreira, Vanessa Santos

The Coimbra Coordinating Centre for Clinical Research (4C) is a structure to support the development and coordination of Investigator Initiated and Industry Sponsored Clinical Research by providing the following services:

- Study Design
- Study Protocol Development
- Inform Consent Form Development
- Case Report Form Design
- Database Design, Validation and Implementation (with AIBILI Data Centre)
- Clinical Sites Feasibility
- Standard Operational Procedures Development
- Regulatory Affairs (Submission and Reports)
- Contracts Negotiation
- Study Management
- Monitoring
- Data Management
- Pharmacovigilance (with AIBILI CHAD)
- Biostatistics
- Final Study Report
- Medical Writing
- Quality Assurance

4C is staffed with one Director, four medical consultants, ten project and study managers (CRA), two data managers and two statistician and two administrative assistants.

PROJECTS

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<thead>
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<th>Studies</th>
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<td>Investigator Initiated Research</td>
<td>EUROCONDOR</td>
<td>LIFE STYLE AND FOOD HABITS IN POPULATION AGED &gt;55</td>
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<td>Other</td>
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**MULTINATIONAL STUDIES**

1. EudraCT n° 2012-001200-38  
ClinicalTrials.gov n° NCT01726075  
**EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy**  
Protocol n° 4C-2011-02  
Project Coordinator: Rafael Simó, Barcelona, Spain  
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal  
N° of Patients (included): 450  
Sponsor: BCN Peptides  
4C Services: Protocol design, coordination, data management, statistical analysis/final report and publication.

2. EudraCT n° 2014-000239-18  
**STRONG – European Consortium for the Study of a Topical Treatment of Neovascular Glaucoma**  
Protocol n° GS-101-P1-NVR  
Project Coordinator: Norbert Pfeiffer, Mainz, Germany  
Coordinating Investigator: Norbert Pfeiffer, Mainz, Germany  
Participating Centres (35): Albacete, Alicante, Barcelona (3), Bonn, Chieti, Coimbra, Dusseldorf, Freiburg, Gienben, Gottingen, Hannover, Koln, Lisbon, Liverpool (2), Mainz, Milan, Parma, Porto, Surrey, Tubingen, Valencia. Other Centres to be selected.  
N° of Patients (expected): 333  
Duration expected: Sep.2011 – ongoing  
Sponsor: Gene Signal SAS  
Financial Support: European Union 7th Framework Programme – Call Health 2012 – Project n° 305521  
4C Services: Clinical Sites feasibility and coordination.

3. EudraCT n° 2013-003640-23  
ClinicalTrials.gov n° NCT01941329  
**PROTEUS – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy**  
Protocol n° ECR-RET-2013-05  
Coordinating Investigator: João Figueira, Coimbra, Portugal  
N° of Patients (included): 87  
Sponsor: AIBILI (EVICR.net)  
IIR Grant: Novartis  
4C Services: Protocol design, coordination, monitoring, data management, statistical analysis/final report and publication.

4. ClinicalTrials.gov n° NCT01607190  
**C-TRACER Project nº 1 – Biomarkers of Diabetic Retinopathy Progression**  
Protocol n° 4C-2012-02  
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal  
Participating Centres (2): Coimbra (Portugal), Hyderabad (India).  
N° of Patients (included): 205  
Sponsor: AIBILI  
IIR Grant: Champalimaud Foundation  
4C Services: Protocol design, coordination, monitoring, data management, statistical analysis/final report and publication.

5. ClinicalTrials.gov n° NCT01745263  
**EudraCT n° 2012-00124941**  
**DO-HEALTH VitaminD3 – Omega3 – Home Exercise HeALTHy Ageing and Longevity Trial**  
Coordinating Investigator: Heike A. Bischchoff-Ferrari, Zurich, Switzerland  
Participating Centres (8): Basel (2), Berlin, Coimbra, Geneve, Innsbruck, Toulouse, Zurich  
Principal Investigator: José A. Pereira da Silva  
N° of Patients (included): 301  
Duration expected: Mar.2012 – Aug.2017  
Sponsor: University of Zurich  
4C Services: IMP management for the Site – University of Coimbra.

6. EudraCT n° 2013-003490-10  
ClinicalTrials.gov n° NCT01975714  
**SPORT – A randomized, 3 months, crossover, single-masked, investigator-led, multicenter trial on open-angle glaucoma or ocular hypertension patients**  
Protocol n° ECR-GLC-2013-06  
Coordinating Investigator: Ingeborg Stalmans, Leuven, Belgium  
N° of Patients (included): 67  
Sponsor: AIBILI (EVICR.net)  
IIR Grant: Allergan  
4C Services: Protocol design, coordination, data management, final report and publication.
7. ClinicalTrials.gov n° NCT01771081
POLARIS – A Prospective non-interventional study to assess the effectiveness of existing anti-vascular endothelial growth factor (Anti-VEGF) treatment regimens in patients with diabetic macular edema (DME) with central involvement
Protocol n° 16459
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal
Nº of Patients (included): 182
Sponsor: Bayer
4C Services: Clinical Sites feasibility and coordination.

8. ClinicalTrials.gov n° NCT01954953
EuR-USH – European young investigators network for Usher syndrome
Protocol n° P13-02
Project Coordinator: Kerstin Nagel-Wolfrum, Mainz, Germany
Coordinating Investigator: Jose Sahel, Paris, France
Project Partners (6): Coimbra (2), Paris, Mainz, Montpellier, Nijmegen.
Duration of data collection: 2 years (Sep.2013 – Jan.2016)
Sponsor: Centre Hospitalier National d’Ophthalmologie des Quinze-Vingts
4C Services: Revision of clinical protocol, procedures, CRF, CRF and Clinical Sites feasibility assessment.

9. ClinicalTrials.gov n° NCT02211979
ARTES – A Collaborative Retrospective Trial on the Efficacy and Safety of Intravitreal dexamethasone implant (Ozurdex) in patients with Diabetic Macular Edema (DME). The European DME Register Study
Protocol n° ECR-RET-2014-07
Coordinating Investigator: Anat Loewenstein, Tel Aviv, Israel
Nº of Patients (included): 302
Sponsor: AIBILI (EVICR.net)
IIR Grant: Allergan
4C Services: Protocol design, coordination, data management, statistical analysis/final report and publication.

10. ClinicalTrials.gov n° NCT01998412
IRISS – An open label, registry study of the safety of Iluvien® (fluocinolone acetonide 190 µg intravitreal implant in applicator)
Protocol n° M-01-12-001
Coordinating Investigators: Usha Chakravarthy, Belfast, UK; Gisbert Richard, Hamburg, Germany; Eric Souied, Paris, Paris
Participating Centres (40): Portugal (4), Germany (8), United Kingdom (28).
Nº of Patients (included): 548
Duration of clinical phase: between 3 and 5 years (Apr.2014 – Apr.2019)
Sponsor: Alimera
4C Services: Coordination, data management.

11. EudraCT n° 2013-000337-13
ClinicalTrials.gov n° NCT01864265
Protocol n° PreCePra
Coordinating Investigator: Georg Schett, Erlanger, Germany
Principal Investigator: José A. Pereira da Silva
Participating Centres: Coimbra.
Sponsor: University Hospital Erlangen
4C Services: Submission and monitoring.

12. ClinicalTrials.gov n° NCT02495181
EudraCT n° 2015-001368-20
ATLANTIC – A Randomized, Double-masked, Sham-controlled Phase 4 Study of the Efficacy, Safety, and Tolerability of Intravitreal Afibercept Monotherapy Compared to Afibercept with Adjunctive Photodynamic Therapy in patients with Polypoidal Choroidal Vasculopathy
Coordinating Investigator: Rufino Silva, Coimbra, Portugal
Participating Centres (18): Albacete, Barcelona (4), Braga, Coimbra (2), Las Palmas, Leiria, Lisbon (4), Oviedo, Porto (2), Vila Franca de Xira.
Nº of Patients (expected): 50
Duration of Clinical Phase: 3 years (Dec.2015 – Dec.2018)
Sponsor: AIBILI (EVICR.net)
IIR Grant: Bayer
4C Services: Protocol design, coordination, monitoring, data management, statistical analysis/ final report and publication.

13. LOBS – The longitudinal observational early markers study
Protocol n° LOBS
Coordinating Investigator: Usha Chakravarthy, Belfast, North Ireland; Rufino Silva, Coimbra, Portugal
Participating Centres (3): Portugal, Italy,
1. ClinicalTrials.gov nº NCT01715870
Life style and food habits questionnaire in the Portuguese population aged 55 or more
Protocol nº 4C-2012-04
Coordinating Investigator: Rufino Silva, Coimbra, Portugal
Participating ARSC Centres (2): Mira and Loussã
Nº of Patients (included): 1618
Duration of data collection: 16 months
(Dec 2012 – Mar. 2017)
Sponsor: AIBILI
IIR Grant: Novartis
4C Services: Protocol design, coordination, data management/statistical analysis/final report and publication.

2. ClinicalTrials.gov nº NCT01440660
Phenotypes of Nonproliferative Diabetic Retinopathy in Diabetes type 2 patients identified by Optical Coherence Tomography, Colour Fundus Photography, Fluorescein Leakage and Multifocal Electrophysiology (DIAMARKER)
Protocol nº 4C-2011-01
Principal Investigator: Luísa Ribeiro, Coimbra, Portugal
Participating Centres (1): Coimbra
Nº of Patients (included): 20
Sponsor: AIBILI
Financial Support: QREN – Quadro de Referência Estratégico Nacional – Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico – Project nº 13853

3. ClinicalTrials.gov nº NCT01947881
CHARTRES – Characterization of Eyes with Diabetic Macular Edema That Show Different Treatment Response to Intravitreal Anti-VEGF
Protocol nº 4C-2013-05
Principal Investigator: João Figueira, Coimbra, Portugal
Participating Centres (1): Coimbra
Nº of Patients (included): 101
Duration of clinical phase: 6 months
Sponsor: AIBILI
IIR Grant: NOVARTIS
4C Services: Protocol design, study submission, coordination, monitoring, data management, statistical analysis/final report and publication.

4. ClinicalTrials.gov nº NCT02748824
AMD Incidence – Five-year incidence of Age-related Macular Degeneration in the central region of Portugal
Protocol nº 4C-2016-09
Coordinating Investigator: Rufino Silva, Coimbra, Portugal
Participating ARSC Centres (2): Mira and Lousã
Nº of Patients (included): 485
Sponsor: AIBILI
IIR Grant: Novartis
4C Services: Protocol design, coordination, data management/statistical analysis/final report and publication.

8. Retmarker – Validation and data analysis for the Retmarker DR software
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal
4C Services: study submission, statistical analysis and publication.

9. ClinicalTrials.gov n° NCT02391558
OCTA – Clinical evaluation of noninvasive OCT Angiography using a Zeiss OCT Prototype to replace fluorescein angiography.
Protocol n° 4C-2015-07
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal
Participating Centres (1): Coimbra
Duration of clinical phase: 7 months (Sep.2015 – Apr.2016)
Sponsor: AIBILI
4C Services: study submission, statistical analysis and publication.

10. ClinicalTrials.gov n° NCT02500862
EyeMarker – Characterization of Potential Biomarkers of Eye Disease and Vision Loss
Protocol n° 4C-2015-08
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal
Participating Centres (1): Coimbra
Sponsor: AIBILI
4C Services: study submission, statistical analysis and publication.

11. ClinicalTrials.gov n° NCT03010397
PROGRESS – Progression of Diabetic Retinopathy. Identification of signs and surrogate outcomes
Principal Investigator: Inês Marques, Coimbra, Portugal
Duration expected: Out.2016 – Out.2019
Sponsor: AIBILI
4C Services: Submission, eCRF, Data Analysis and Publication

OTHER
1. ECRIN-IA – European Clinical Research Infrastructures Network – Integrating Activity
Project Coordinator: Jacques Demotes, Paris, France
Financial Support: European Union 7th Framework Programme – Call Infrastructures 2011 – Project nº 284395
4C Services: Participation in developing a questionnaire to identify Clinical Research Centres and Development Centres dedicated to Medical Devices and developing Medical Devices Monitoring SOP/Guidelines.

2. E3 – European Eye Epidemiology Network
Project Coordinator: Cecile del Court, Bordeaux, France
4C Services: data handling and publication review

COORDINATION OF INVESTIGATOR INITIATED VS INDUSTRY SPONSORED TRIALS AT 4C (2012–2016)

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<th>Year</th>
<th>Investigator Initiated</th>
<th>Industry Sponsored</th>
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<td>2016</td>
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CORC – COIMBRA OPHTHALMOLOGY READING CENTRE

The Coimbra Ophthalmology Reading Centre (CORC) focus its activities in grading fundus images and OCT images of the retina, as well as functional evaluations of the retina using mfERG. It serves as central Reading Centre for a series of clinical studies, mainly in Diabetic Retinopathy (DR) and Age-related Macular Degeneration (AMD), some of them performed within the EVICR.net.

CORC is also the central Reading Centre for the Diabetic Retinopathy Screening Programme of the Central Region of Portugal since 2011. CORC has a secure custom-designed web based tool to transmit images between Clinical Sites and CORC. This system is hosted in the AIBILI’s Data Centre.

For grading purposes CORC uses licensed software from the equipment suppliers, such as Cirrus HD-OCT (Carl Zeiss Meditec), Heidelberg Eye Explorer (Heidelberg Engineering), RETI-system (Roland Consult), Topcon OCT (Topcon Corporation), etc. For research purposes CORC also has novel software programmes, developed in-house, to reliably quantify neovascularization of the retina and leakage, assess microaneurysm turnover in diabetic patients (RetmarkerDR®), classify and quantify AMD lesions and disease activity in patients with AMD (RetmarkerAMD® Research) and perform segmentation of the retinal layers and quantify cystoid-like spaces on OCT.

CORC has dedicated staff composed by CORC Director, a Management Team involving Project Managers, Grading Supervisors and an Administrative Coordinator, a Grading Team of 20 graders (10 ophthalmologist graders and 10 technical graders, being 4 orthoptists) and a Secretariat Team involving general secretariat and study coordinators.

### MAIN ACTIVITIES

- Grading of ophthalmic exams for characterization and quantification of ophthalmic disease
  - Grading of fundus images
  - Grading OCT
  - Grading mfERG

- Project management
- Acquisition and grading protocol development
- Technicians training and certification
- Equipment certification

### AREA

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<thead>
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<th>Area</th>
<th>Ongoing Projects</th>
<th>Type of Exam</th>
<th>Type of Grading</th>
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<td><strong>Diabetic Retinopathy (DR)</strong></td>
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<td>CFP</td>
<td>ETDRS / DR Grading; Automated microaneurysm assessment (RetmarkerDR®); Screening DR</td>
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<tr>
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<td>CFP/FA</td>
<td>Classification/quantification of DR characteristics, including proliferative DR and diabetic macular edema; High-risk proliferative DR assessment; Quantification of neovascularization, capillary closure and leakage</td>
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<td>OCT</td>
<td>Retinal Thickness; Retinal Nerve Fiber Layer Thickness; Ganglion Cell Layer Thickness; Presence and location of key features for DR; Segmentation analysis of the retinal layers; Quantification of cysts</td>
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<td>mfERG</td>
<td>Amplitude/Implicit time of P1 &amp; Z-score analysis</td>
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<td><strong>Age-related Macular Degeneration (AMD)</strong></td>
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<td>CFP/FA/ICG</td>
<td>Classification/quantification of ARM/AMD lesions (RetmarkerAMD Research); Classification/quantification of Polypoidal Choroidal Vasculopathy / AMD characteristics</td>
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<td>OCT</td>
<td>Retinal Thickness; Presence and location of key features for AMD</td>
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</tbody>
</table>

**CFP** – Color Fundus Photography; **FA** – Fluorescein Angiography; **ICG** – Indocyanine Green Angiography; **mfERG** – multifocal Electroretinography; **OCT** – Optical Coherence Tomography.
DIABETIC RETINOPATHY

1. Diabetic Retinopathy Screening – Central Region of Portugal

Coordination: Helder Ferreira (ARS Centro), Coimbra, Portugal

Nº of Patients: > 90,000 screened/graded diabetic patients since July 2011. 18,845 in 2016

Sponsor: Health Administration of Central Region of Portugal (ARS Centro)

CORC Services: Grading of color fundus photography for Diabetic Retinopathy Screening purposes using an automated first-step analysis by Retmarker.

2. EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, randomised controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy

EudraCT nº 2012-001200-38
ClinicalTrials.gov nº NCT01726075
Protocol nº 4C-2011-02
Project Coordinator: Rafael Simó, Barcelona, Spain
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal


Nº of Patients (included): 449

Sponsor: BCN Peptides


CORC Services: Technicians and equipment certification for color fundus photography, OCT and multifocal electroretinography; ETDRS grading of color fundus photography and microaneurism turnover assessment of color fundus photography using RetmarkerDR®, Grading of OCT (RNFL thickness, ganglion cell layer thickness and overall retinal thickness analysis); Grading of multifocal electroretinography (amplitude and implicit time of P1 and Z-score analysis).

3. PROTEUS – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy

EudraCT nº 2013-009640-23
ClinicalTrials.gov nº NCT01941329
Protocol nº ECR-RET-2013-05
Coordinating Investigator: João Figueira, Coimbra, Portugal


Nº of Patients (included): 87
Duration of clinical phase p/patient: 1 year (Apr.2014 – May 2016)

Sponsor: AIBILI (EVICR.net)

IIR Grant: Novartis

CORC Services: Technicians and equipment certification for color fundus photography and fluorescein angiography; Grading for High-Risk Proliferative Diabetic Retinopathy criteria on color fundus photography and fluorescein angiography and quantification of neovascularization.

4. CHARTRES – Characterization of Eyes with Diabetic Macular Edema that show different Treatment Response to Intravitreal anti-VEGF

ClinicalTrials.gov nº NCT01947881
Protocol nº 4C-2013-05

Principal Investigator: João Figueira, Coimbra, Portugal

Participating Centres (1): AIBILI-CEC, Coimbra, Portugal

Nº of Patients (included): 71

Sponsor: AIBILI

IIR Grant: Novartis

CORC Services: ETDRS grading of color fundus photography; Grading OCT (overall retinal thickness analysis; presence and location of cysts, neurosensorial detachment, diffuse ME; integrity of photoreceptors; presence and extension of leakage); Grading fluorescein angiography for quantification of capillary closure and leakage.

5. AQUA – Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment

EudraCT nº 2014-005119-17
ClinicalTrials.gov nº NCT02581995

Protocol nº BAY 86-5321 / 17850

Participating Centres (75): Austria (2), Canada (7), Czech Republic (5), France (2), Germany (11), Hungary (5), Italy (10), Lithuania (2), Poland (9), Portugal (5), Slovakia (5), Spain (6), Switzerland (2), United Kingdom (6)

Nº of Patients (included): 555


Sponsor: Bayer AG

CORC Services: Technicians and equipment certification for color fundus photography; ETDRS grading of color fundus photography.
6. VIOLET – An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg Eylea administered by intravitreal injections to subjects with diabetic macular edema (DME)

EudraCT n° 2014-004938-25
ClinicalTrials.gov n° NCT02818998
Protocol n° BAY 86-5321 / 17613
Participating Centres (88): Austria (3), Canada (10), Czech Republic (3), France (8), Germany (12), Hungary (5), Italy (12), Lithuania (2), Poland (9), Portugal (5), Slovakia (5), Spain (6), Switzerland (2), United Kingdom (6)
Sponsor: Bayer AG
CORC Services: Technicians and equipment certification for color fundus photography, fluorescein angiography and OCT; ETDRS grading of color fundus photography; Grading of DR on fluorescein angiography and OCT.

7. THR-317-001 – A Phase 2, single-masked, multicentre study to evaluate the safety and efficacy of 2 dose levels of THR-317 for the treatment of diabetic macular oedema (DME)

EudraCT n° 2016-002100-25
Protocol n° THR-317-001
Participating Centres (15): Czech Republic (5), Hungary (6), Slovakia (4)
Sponsor: Thrombogenics NV
CORC Services: Technicians and equipment certification for color fundus photography, fluorescein angiography and OCT; Grading of DR on color fundus photography, fluorescein angiography and OCT.

8. PROGRESS – Progression of Diabetic Retinopathy. Identification of Signs and Surrogate outcomes

Protocol n° CEC/007/16
Principal Investigator: Inês Marques
Participating Centres (1): AIBILI-CEC, Coimbra, Portugal
Sponsor: AIBILI
CORC Services: ETDRS grading of color fundus photography; Grading OCT (overall and layer-by-layer retinal thickness analysis; edema and ellipsoid zone analysis); Grading of OCTA (vessel density analysis).

9. Diabetic Retinopathy Screening – Pilot Studies with Retmarker

Project Coordinator: José Cunha-Vaz, Coimbra, Portugal
CORC Services: Collaboration with Retmarker to support the expansion of Retmarker® technology for Diabetic Retinopathy Screening Programs; Grading of color fundus photography of pilot studies for Diabetic Retinopathy Screening.

10. OCT-A (Optical Coherence Tomography Angiography): Evaluation and Comparison with FA

Project Coordinator: José Cunha-Vaz, Coimbra, Portugal
CORC Services: Exploratory and collaborative work together with CNTM and CEC for the analysis / classification of OCT-A with special focus on healthy and diabetics and comparison with FA. Grading OCT-A and FA images.

11. Exploratory analysis on the correlation of Fluorescein Angiography images and OCT-Leakage

Project Coordinator: José Cunha-Vaz, Coimbra, Portugal
CORC Services: Exploratory and collaborative work together with CNTM and CEC for the analysis and comparison of OCT-Leakage vs FA. Grading leakage on FA images.

AGE-RELATED MACULAR DEGENERATION

12. Epidemiological study of the prevalence of age-related macular degeneration in Portugal

ClinicalTrials.gov n° NCT01298674
Protocol n° CC-01-2009
Coordinating Investigator: Rufino Silva, Coimbra, Portugal
Participating ARSC Centres (2): Mira and Lousã, Portugal
Nº of Patients (included): Mira: 2.976; Lousã: 3.023
Sponsor: AIBILI
IIR Grant: Novartis
CORC Services: Color fundus photography grading to determine presence of pathologies and grading of Age-related Macular Degeneration cases using RetmarkerAMD.

13. RETRIAL – Reticular pseudodrusen and the five-year risk of progression for late AMD: a multimodal imaging approach

Project Coordinator: Rufino Silva, Coimbra, Portugal
Nº of Patients (included): 63
CORC Services: Grading key features of ARM/AMD computing their number, size and location using the Retmarker AMD Research; Determine the presence, area and number of reticular pseudodrusen using Retmarker AMD.
14. ATLANTIC – A Randomized, Double-masked, Sham-controlled Phase 4 Study of the Efficacy, Safety, and Tolerability of Intravitreal Afibercept Monotherapy Compared to Afibercept With Adjunctive Photodynamic Therapy in patients with Polypoidal Choroidal Vasculopathy

EudraCT nº 2015-001368-20
ClinicalTrials.gov nº NCT02495181
Protocol nº ECR-AMD-2015-09
Coordinating Investigator: Rufino Silva, Coimbra, Portugal
Participating Centres (19): Portugal (10) and Spain (9)
Nº of Patients (expected): 50. Started recruitment
Sponsor: AIBILI (EVICR.net)
IIR Grant: Bayer
CORC Services: Technicians and equipment certification for color fundus photography, fluorescein angiography, indocianine-green angiography and OCT; Grading of Polypoidal Choroidal Vasculopathy characteristics on color fundus photography, fluorescein angiography, indocianine-green angiography and OCT.

15. AZURE – An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg afibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)

EudraCT nº 2013-000120-33
ClinicalTrials.gov nº NCT02540954
Protocol nº BAY 86-5321 / 16598
Participating Centres (99): Austria (1), Canada (4), Czech Republic (6), France (10), Germany (16), Hungary (3), Italy (19), Lithuania (2), Poland (6), Portugal (4), Slovakia (4), Spain (5), Switzerland (2), United Kingdom (17)
Nº of Patients (expected): 330. Started recruitment
Sponsor: Bayer AG
CORC Services: Technicians and equipment certification for color fundus photography, fluorescein angiography and OCT; Grading of AMD on color fundus photography, fluorescein angiography, indocianine-green angiography and OCT.

16. AMD Incidence Central Portugal – Coimbra Eye Study: The five-year incidence of Age-Related Macular Degeneration. A clinical study with color fundus photography, optical coherence tomography and blood sample collection in Mira

ClinicalTrials.gov nº NCT02748824
Protocol nº 4C-2016-09
Principal Investigator: Rufino Silva, Coimbra, Portugal
Participating Centres (1): Primary Healthcare Centre of Mira, Portugal

Nº of Patients (expected): 3,000. Started recruitment
Sponsor: AIBILI
IIR Grant: Novartis
CORC Services: General grading of color fundus photography, fundus autofluorescence, infrared photography and OCT to determine pathologies present; grading of AMD in color fundus photography (RetmarkerAMD), fundus autofluorescence, infrared photography and OCT for the AMD identified cases.
RELEVANT PUBLICATIONS


The Centre for Health Technology Assessment and Drug Research (CHAD) focus is on evaluation of medicines and other medicinal products for market access purposes, aiming at financing and reimbursement and pharmacovigilance. CHAD provides scientific information to support the decision making in healthcare policy and practice. Health Technology Assessment studies are necessary to ensure equity in the access to medicines and the most favourable benefit/risk and cost/effectiveness ratios in the drug use process. It is, therefore, of capital importance in both drug reimbursement decisions at both ambulatory and hospital settings. CHAD is also a qualified resource to work closely with Pharmaceutical Industry in all the different phases of drug development. CHAD provides pharmacovigilance services necessary in clinical studies. It has a pharmacovigilance software fully compliant with the regulations, directives, and the general guidance related to electronic reporting of adverse events (US FDA 21 CFR part 11 and EMA’s Good Pharmacovigilance Practice (GVP) Guidelines) for this purpose, as well as SOPs ICH-GCP compliant to perform pharmacovigilance clinical research. It has a license to use MedDRA, a standardised international medical terminology designed for use in safety monitoring of medicinal products through all phases of the development cycle (i.e., from clinical trials to post-marketing surveillance) that supports ICH electronic communication within the E2B Individual Case Safety Report. Since 2008 CHAD has been responsible for a Pharmacovigilance Unit of the National Pharmacovigilance System which is contracted with the National Authority of Medicines and Health Products (INFARMED, IP).

MAIN ACTIVITIES
1. Health Technology Assessment, pricing and reimbursement (medicines and medical devices)
2. Primary research
3. Secondary research
4. Pharmacovigilance and Risk Management services

PROJECTS / SERVICES
1. Pharmacovigilance Unit of the Centre Region of the National Pharmacovigilance System
   Support: INFARMED
   Coordinators: Batel Marques and Carlos Fontes Ribeiro
2. Pharmacovigilance of PROTEUS Study
   Sponsor: AIBILI (EVICR.net)
   Principal Investigator: Batel Marques
3. Pharmacovigilance of PreCePra Study
   Sponsor: University Hospital Erlangen
   Principal Investigator: Batel Marques
4. Systematic review of canagliflozin
   Sponsor: Janssen-Cilag
   Principal Investigator: Batel Marques
5. Pharmacovigilance of RESPOND Study
   Sponsor: AIBILI
   Principal Investigator: Batel Marques
6. Pharmacovigilance of ATLANTIC Study
   Sponsor: AIBILI (EVICR.net)
   Principal Investigator: Batel Marques
7. Evaluation of the therapeutic value, economic value and budget impact model for Cerdeliga®
   Sponsor: Sanofi
   Principal Investigator: Batel Marques and Óscar Lourenço
8. Evaluation of the Added Therapeutic Value Report of evolocumab
   Sponsor: Amgen
   Principal Investigator: Batel Marques
9. Evaluation of the therapeutic value of Kyprolis®
   Sponsor: Amgen
   Principal Investigator: Batel Marques
10. Evaluation of the therapeutic value of Cotellic®
    Sponsor: Roche
    Principal Investigator: Batel Marques
11. Evaluation of the therapeutic value of Vimizim®
Sponsor: PharSolution
Principal Investigator: Batel Marques

12. Evaluation of the therapeutic value of Prolia®
Sponsor: Amgen
Principal Investigator: Batel Marques

13. Evaluation of the economic value and budget impact model for Perjeta®
Sponsor: Roche
Principal Investigator: Batel Marques

14. Evaluation of the therapeutic value of Edarclor®
Sponsor: Tecnimede
Principal Investigator: Batel Marques

15. Evaluation of the therapeutic value of Triveram®
Sponsor: Servier
Principal Investigator: Batel Marques

16. Evaluation of the therapeutic value of Zinbryta®
Sponsor: Biogen Idec
Principal Investigator: Batel Marques

17. Evaluation of the therapeutic value of Orkambi®
Sponsor: Vertex
Principal Investigator: Batel Marques

18. Pharmacovigilance of BETA3 Study
Sponsor: University of Leipzig
Principal Investigator: Batel Marques

19. Evaluation of the therapeutic value of ibrutinib
Sponsor: Janssen-Cilag
Principal Investigator: Batel Marques

20. Pharmacovigilance of SAVE-IT Study
Sponsor: Portuguese Society of Cardiology
Principal Investigator: Batel Marques

21. Therapeutical and Pharmacological evaluation of Dafion®
Sponsor: AIBILI
Principal Investigator: Batel Marques

22. Guidelines for the market access of biological drugs
Sponsor: AIBILI
Principal Investigator: Batel Marques

23. Evaluation of the therapeutic value of Gazyvaro®
Sponsor: Roche
Principal Investigator: Batel Marques

24. Evaluation of the therapeutic value of Kyprolis®
Sponsor: Amgen
Principal Investigator: Batel Marques

25. Evaluation of the therapeutic value of Parsabiv®
Sponsor: Amgen
Principal Investigator: Batel Marques

26. Reassessment of the therapeutic value of Vipidia®, Vipdomet® and Incresync®
Sponsor: Tecnimede
Principal Investigator: Batel Marques

27. Evaluation of the therapeutic value of alectinib
Sponsor: Roche
Principal Investigator: Batel Marques

28. Evaluation of the budget impact of Kalydeco®
Sponsor: Vertex
Principal Investigator: Batel Marques

No of Projects at CHAD (2012–2016)

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<td>25</td>
</tr>
<tr>
<td>2016</td>
<td>21</td>
<td>7</td>
<td>–</td>
<td>28</td>
</tr>
</tbody>
</table>
**INCOME (2012–2016)**

- 2012: €403,572
- 2013: €336,508
- 2014: €377,995
- 2015: €265,630
- 2016: €234,780

**RELEVANT PUBLICATIONS**


DC – DATA CENTRE

Director: Carlos Domingues, BSc
Staff: Carlos Domingues, Hugo Morgado, Patrícia Silva, Telmo Miranda, Torcato Santos, José Monteiro

AIBILI Data Centre was built specifically to support AIBILI's information systems but the existing space and environment conditions allow to grow up to store clients/partners data and information. Inside the Data Centre, the server racks are connected to two separate power circuits, protected by two redundant Uninterruptable Power Supplies (UPS). These redundant power supply units ensure that a failure of one power supply unit does not cause any problems. If one power sector fails, then the second one will ensure that power is still supplied to servers. The UPS also ensures that the quality remains constant. It compensates for voltage and frequency fluctuations and thereby effectively protects sensitive computer electronic components and systems. Block batteries ensure that all operating applications can run for almost three hours. For Data Centre cooling AIBILI has implemented a cold air container solution with redundant air conditioning units. The air is directed to the container through the floor and flows through the racks, dissipating the heat produced by servers and providing adequate temperature and humidity for electronic equipment’s. Water detection sensors on the floor and automatic fire extinguisher (based on gas-based suppression system FM200) complements the Datacentre asset-protection.

Presently Information Technology Unit maintains and supports more than 30 servers (either virtual or physical) in both ORACLE and HyperV cluster technology. There are specific Standard Operating Procedures (SOPs) in place, developed according IT best practices such as Information Technology Infrastructure Library (ITIL), and project management standards such as recommended by the Project Management Institute (PMI). All changes in the production environment are preceded by testing and validation processes, according to GAMPs V-model and methodology. This Unit is responsible to guarantee the safety and integrity of the data and images collected all in compliance with GCP Guidelines and applicable national legislation. AIBILI specific SOPs for Information Technology and datacentre also comply with US FDA 21 CFR part 11 (Guidance for Electronic Records) and ISO 27001 (Information Security Management). Regular internal audits and penetration tests are performed to ensure the safety and integrity of data.

All this information is categorized and specific backup policies are defined according information value. Long term storage procedures are in place to assure all the information lifecycle. Information Technology Unit manages over than 30 TB of useful storage (clinical images and databases, administrative information, project information and long term storage)

AIBILI Data Centre was certified by ECRIN – European Clinical Research Infrastructure Network (www.ecrin.org) in April 2016. Compliance with ECRIN v3 standards confirms AIBILI capacity to provide appropriate and effective data management services for multinational, randomised controlled trials.

MAIN ACTIVITIES
• CDMS (Clinical Data Management System) validation, implementation and support
• eCRF (Electronic Case Report Form) development and support
• Key users helpdesk
• CORC – IT platform support
• Data export and biostatistics support
• Long term storage

PROJECTS / SERVICES
1. PROTEUS – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy

Data Centre Services: Reading centre platform support, long term storage.

2. Diabetic Retinopathy Screening – Central Region of Portugal
Data Centre Services: Reading centre data transmission support, long term storage.

3. DIAMARKER – Phenotypes of Nonproliferative Diabetic Retinopathy in Diabetes type 2 patients identified by Optical Coherence Tomography, Colour Fundus Photography, Fluorescein Leakage and Multifocal Electrophysiology
Data Centre Services: eCRF development, data export and biostatistics support, long term storage.
4. **AMD Incidence Central Portugal** – Coimbra Eye Study: The five-year incidence of Age-Related Macular Degeneration. A clinical study with color fundus photography, optical coherence tomography and blood sample collection in Mira
Data Centre Services: eCRF development, data export and biostatistics support, reading centre platform support, long term storage.

5. **EUROCONDOR** – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy
Data Centre Services: eCRF development, data export and biostatistics support, reading centre platform support, long term storage.

6. **C-TRACER Project** – Biomarkers of Diabetic Retinopathy Progression
Data Centre Services: eCRF development, data export and biostatistics support, long term storage.

7. **ATLANTIC** – A Randomized, Double-masked, Sham-controlled Phase 4 Study of the Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Monotherapy Compared to Aflibercept with Adjunctive Photodynamic Therapy in patients with Polypoidal Choroidal Vasculopathy
Data Centre Services: eCRF development, data export and biostatistics support, reading centre platform support, long term storage.

8. **VIOLET** – An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg Eylea administered by intravitreal injections to subjects with diabetic macular edema (DME)
Data Centre Services: Reading centre platform support, long term storage.

9. **AZURE** – An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)
Data Centre Services: Reading centre platform support, long term storage.

10. **AQUA** – Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment
Data Centre Services: Reading centre platform support, long term storage.

11. **THR-317-001** – A Phase 2, single-masked, multicentre study to evaluate the safety and efficacy of 2 dose levels of THR-317 for the treatment of diabetic macular oedema (DME)
Data Centre Services: Reading centre platform support, long term storage.

### Nº OF PROJECTS/SERVICES AT DC (2016)

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<th>Year</th>
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</tr>
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### INCOME (2016)

<table>
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<tr>
<th>Income (€)</th>
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<tbody>
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Clinical patient-oriented research involves characterizing disease progression and testing new discoveries by carrying out carefully controlled investigations in patients, i.e., clinical trials. This includes testing not only new drugs, but also new methods, devices, imaging and surgical procedures as well as well-designed prospective, observational, longitudinal studies. It is a fundamental step in the translation process of bringing innovation to the clinical practice.

Our research is focused in age-related eye diseases with special emphasis on diabetic retinopathy and age-related macular degeneration. The results of our research have had impact worldwide with frequent international publications and our translational research programme has contributed to improving management of these diseases.

Age-related eye diseases affect more than 10% of the western world population. The most common eye diseases are macular degeneration, diabetic retinopathy and glaucoma. Diabetic retinopathy is the most frequent cause of new cases of blindness in individuals aged 20–74 (working age years) resulting in most disability and person-years of vision lost than other diseases.

Through EVICK.net AIBILI is also involved in research with other eye diseases. Our research interest has been particularly focused on development of biomarkers of disease activity and progression as well as early detection using novel imaging methodologies. Early detection and validation of biomarkers of disease progression allow timely intervention and open much needed opportunities for new models of prospective health care and ultimately better patient care. The challenge of developing strategies based on a personalized medicine approach are addressed by our research group.

Finally, our research programme is looking at stem cells to repair advanced stages of anterior segment and retinal disease. Our research group is involved in a large number of multinational industry-sponsored clinical trials as well as in investigator initiated clinical trials, three of them funded by the 7th European Union Research Framework Programme as described in section A.1.
B1

BIOMARKERS OF PROGRESSION OF DIABETIC RETINOPIA

José Cunha-Vaz, MD, PhD

Other Research Personnel: Ana Rita Santos, Conceição Lobo, Inês Marques, Isabel Pires, Luisa Ribeiro, Sandrina Nunes, Sílvia Simão

Diabetic Retinopathy remains the most frequent complication of diabetes and the main cause of vision loss in the professionally active age-group 24–70 years of age. Today, despite the goal of tight blood glucose control and the use of retinal photo-coagulation and new drugs, blindness still occurs. Therapies targeted at the earliest stages of retinal disease, involving necessarily the demonstration of efficacy of a new drug are needed and remain a priority for eye research. To achieve this goal it is urgent to identify biomarkers of disease progression that can be accepted as surrogates for generally accepted endpoints.

Our research group identified a biomarker of diabetic retinopathy progression: microaneurysm turnover. Microaneurysm turnover on fundus photographs using the Retmarker® has the potential to become an extremely valuable biomarker of the overall progression of diabetic retinal vascular disease. Microaneurysm turnover appears to be a direct indicator of the progression of retinal vascular damage and activity of disease.

Reduction in macular thickening by measuring the changes in retinal thickness with dedicated instrumentation is another promising biomarker. The measurements are reliable, and changes in retinal thickness are a direct indication of macular edema and breakdown of the blood-retinal barrier. Recent work by our group shows that it is possible to quantify the alteration of the blood-retinal barrier, non-invasively, by measuring the optical reflectivity of the different retinal layers. OCT Leakage was introduced in 2016 by our group as a non-invasive imaging method of automated identification and quantification of changes in retinal extracellular due to alteration of the Blood-Retinal Barrier.

Our research group also found that there is great individual variation in the course of diabetic retinopathy. We were able to identify three major phenotypes of diabetic retinopathy progression with different risks for vision loss which offers the opportunity to develop new management strategies and making treatment more effective (personalized medicine).

INVESTIGATOR INITIATED RESEARCH
EUROCONDOR – Neurodegeneration as an early event in the pathogenesis of Diabetic Retinopathy: A multicentric, prospective, phase II-III, double-blind randomized controlled trial to assess the efficacy of neuroprotective drugs administered topically to prevent or arrest Diabetic Retinopathy
EudraCT nº 2012-001200-38
ClinicalTrials.gov nº NCT01726075

C-TRACER Project nº 1 – Biomarkers of Diabetic Retinopathy Progression
ClinicalTrials.gov nº NCT01607190
Protocol nº 4C-2012-02
Participating Centres (2): Coimbra (Portugal), Hyderabad (India).
IIR Grant: Champalimaud Foundation

SELECTED PUBLICATIONS


Contacts
José Cunha-Vaz, MD, PhD
Phone: +351 239 480 136
E-mail: cunhavaz@aibili.pt
It is well known that the duration of diabetes, blood pressure and glucose levels are relevant factors in the development of Diabetic Retinopathy (DR); however, these factors alone do not explain the occurrence and progression of DR. It is clear that in some patients DR progresses very slowly, without the development of vision loss in the short term, whereas in others, even under a similar duration of diabetes and metabolic control, there is a rapid advance to macular edema or neovascularization leading to vision loss. This strongly suggests the possibility of a genetic predisposition to retinopathy. Our research group performed a genotyping study to investigate the association of 11 candidate genes and to identify genetic biomarkers that can help predict DR progression in type 2 diabetic patients. A population of 307 patients, stratified in the 3 phenotypes of DR progression previously identified based on microaneurysm turnover and central macular thickness was genotyped for 174 single nucleotide polymorphisms (SNPs) from the genes ACE, AGER, AKR1B1, ICAM1, MTHFR, NOS1, NOS3, PPARGC1A, TGFBI, TNF and VEGFA. The results obtained indicate that specific gene variants in ICAM1, PPARGC1A and MTHFR are associated with different NPDR phenotypes, being likely candidates to explain different disease mechanisms underlying the different phenotypes of progression, thus opening new perspectives for improved understanding of diabetic retinal disease and its evolution to vision-threatening complications. Further studies are in progress involving larger groups of patients from multicentric studies.

SELECTED PUBLICATIONS


Macular edema is a nonspecific sign of ocular disease and not a specific entity. It should be viewed as a special and clinically relevant type of macular response to an altered retinal environment. In most cases, it is associated with an alteration of the blood-retinal barrier (BRB). Starling’s law, which governs the movements of fluids, applies in this type of edema.

Multimodal macula mapping uses a variety of diagnostic tools and techniques to obtain additional information. These imaging techniques are essential to guide the indications for current treatment and to assess the response to treatment. The introduction of OCT Leakage by AIBILI and its association with OCT Angiography is expected to revolutionise the management of diabetic macular edema.

Our research group is using novel imaging technologies to test different approaches to treatment of diabetic macular edema, such as intravitreal injections of anti-VEGF agents and/or thrombolytic agents.

INVESTIGATOR INITIATED RESEARCH

PROTEUS – Prospective, randomized, multicenter, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy

EudraCT nº 2013-003640-23
ClinicalTrials.gov nº NCT01941529
Protocol nº ECR-RET-2013-05
Coordinating Investigator: João Figueira, Coimbra, Portugal
IIR Grant: Novartis

ARTES – A Collaborative Retrospective Trial on the Efficacy and Safety of intravitreal dexamethasone implant (Ozurdex) in patients with Diabetic Macular Edema (DME).

The European DME Register Study
ClinicalTrials.gov nº NCT02121197
Protocol nº ECR-RET-2014-07
Coordinating Investigator: Anat Loewenstein, Telaviv, Israel
IIR Grant: Allergan

RESPOND – A non-randomised, open-label, multicenter phase 4 pilot study of the effect and safety of Iluvien® in chronic diabetic macular edema patients considered insufficiently responsive to available therapy with or without intravitreal corticosteroid therapy

EudraCT nº 2014-003490-23
Protocol nº 4C-2014-06
Coordinating Investigator: João Figueira, Coimbra, Portugal
Participating Centres: Coimbra (2), Porto, Vila Franca de Xira
IIR Grant: Alimera

SELECTED PUBLICATIONS


DEVELOPMENT OF NOVEL BIOMARKERS AND TESTING TREATMENTS FOR SIGHT THREATENING AGE-RELATED MACULAR DEGENERATION

Rufino Silva, MD, PhD

Other Research Personnel: Ana Rita Santos, João Figueira, Maria Luz Cachulo

Age-related macular degeneration (AMD) causes loss of visual acuity by progressive destruction of macular photoreceptor cells and retinal pigment epithelial cell function. These features are commonly referred to as dry AMD or age related maculopathy (ARM). Dry AMD affects near 6% of Caucasian individuals aged 65–74 and rises to 20% of those aged >75.

In some individuals neovascularization is stimulated from the choriocapillaris, perhaps by vascular endothelial growth factor (VEGF) and/or other local inflammatory cytokines, to grow through a fragmented Bruch’s membrane under the RPE and/or under the retina. When neovascularisation is present the condition is termed wet, exudative or neovascular AMD. Neovascular AMD occurs in ~10–20% of people with dry AMD and causes accelerated and severe visual loss by leakage of serum and blood and then scarring under the macula. Increased longevity in developed countries has already made AMD the dominant cause of visual disability, and the numbers projected to be visually disabled by this condition may substantially increase in the future.

It is crucial to understand the natural history of the conversion from dry to neovascular AMD, to characterize the different phenotypes of AMD and to identify markers of this conversion. Identification of such markers would enhance our ability to identify the earliest signs of neovascular AMD, which is currently limited by the inadequacies of existing diagnostic imaging modalities. Also, the identification of predictive markers for choroidal neovascularization (CNV) will allow efficient targeting and testing of new therapies with a higher probability of success.

Our research is looking to identify the sequence of changes in the chorioretinal interface during the development of CNV and the progression from dry to neovascular AMD, to identify the morphological features that define the earliest identifiable CNV lesion that may be appropriate for treatment with an anti-VEGF therapy and to evaluate the sensitivity of quantitative image analysis relative to clinical observations and evaluation of the images.

Main areas of research are: Early markers of progression in AMD; AMD Portuguese Epidemiological Study; Characterization of food habits in the Portuguese population and correlation with AMD prevalence; Phenotypic and genotypic characterization of AMD Portuguese Population; Polypoidal choroidal neovascularization; Genotypic and phenotypic characterization of retinal angiomaticous proliferation.

INVESTIGATOR INITIATED RESEARCH

Life style and food habits questionnaire in the Portuguese population aged 55 or more
ClinicalTrials.gov nº NCT00715870
Protocol nº 4C-2012-04
Participating ARSC Centres (2): Mira and Loussã, Portugal
IIR Grant: Novartis

Metabolomics, Genetics and Environment – a novel integrative approach to Age-Related Macular Degeneration (DN0654)
Partners (3): Aveiro, Coimbra, Harvard

LOBS – Longitudinal Observational early Biomarkers Study
Participating Centres (4): Coimbra, Belfast, Milan, Los Angeles.
Financial Support: Roche

ATLANTIC – A Randomized, Double-masked, Sham-controlled Phase 4 Study of the Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Monotherapy Compared to Aflibercept With Adjunctive Photodynamic Therapy in patients with Polypoidal Choroidal Vasculopathy
EudraCT nº 2015-001368-20
ClinicalTrials.gov nº NCT02495181
Participating Centres (19): Portugal (10) and Spain (9)
IIR Grant: Bayer

Genotypic and Phenotypic characterization of retinal angiomaticous proliferation (RAP) lesions
Protocol nº CEC/006/2015
Participating Centres (1): Coimbra
Sponsor: AIBILI
AMD Incidence Central Portugal – Coimbra Eye Study: The five-year incidence of Age-Related Macular Degeneration. A clinical study with color fundus photography, optical coherence tomography and blood sample collection in Mira ClinicalTrials.gov nº NCT02748824 Protocol nº 4C-2016-09 Participating Centres (1): Mira Sponsor: AIBILI IIR Grant: Novartis

SELECTED PUBLICATIONS


Holz, F; Dugel, P; Weissgerber, G; Hamilton, R; Silva, R; Bandello, F; Larsen, M; Weichselberger, A; Wenzel, A; Schmidt, A; Escher, D; Sararols, L; Souied, E: Single-Chain Antibody Fragment VEGF Inhibitor RTH258 for Neovascular Age-Related Macular Degeneration: A Randomized Controlled Study. Ophthalmology 2016 May;123(5):1080–9.

Age-related macular degeneration (AMD) is considered to be the third major cause of blindness in the world and it is first in rank in the developed countries when it comes to the population of 55 years of age or older. Furthermore, the overall aging of the world population puts it in a position of primary importance as a public health problem.

Clinical funduscopic early disease signs are the presence of drusen with or without retinal pigment alterations, which are important markers of progression for late forms of the disease. Late AMD is responsible for severe and irreversible vision loss and it includes two morphologically distinct types: neovascular age-related macular degeneration (NV-AMD) and geographic atrophy (GA).

The early diagnosis of individuals at risk of developing late AMD is of paramount importance. Multiple risk factors for AMD, which go beyond the ocular signs, have been taken into consideration. Thus, risk factors that have to do with genetics, demography, nutrition, the environment as well as personal habits and lifestyles have become important study areas. However, the evidence and the estimated association between disease and risk factors are sometimes inconsistent.

Considering the clinical relevance of this age-related disease, several epidemiologic studies have been performed all over the world. In view of the paucity of population-based epidemiological data on AMD in southern Europe (e.g. Thessaloniki Eye Study, PAMDI Study) and its environmental specificities our group has performed the Coimbra Eye Study. Our group has been able to provide precise estimates of the prevalence of early and late AMD in Portugal and to identify its risk factors. Additionally the role of nutritional and lifestyle risk factors associated with the development of AMD was taken into account in an extension of the present study held in a subgroup of the main population. An incidence epidemiological study of AMD in Portugal is currently in progress.

PROJECTS

Life style and food habits questionnaire in the Portuguese population aged 55 or more
ClinicalTrials.gov nº NCT01715870
Protocol nº 4C-2012-04
Participating ARSC Centres (2): Mira and Lousã, Portugal
IIR Grant: Novartis

AMD Incidence Central Portugal – Coimbra Eye Study: The five-year incidence of Age-Related Macular Degeneration. A clinical study with color fundus photography, optical coherence tomography and blood sample collection in Mira
ClinicalTrials.gov nº NCT02748824
Protocol nº 4C-2016-09
Participating Centres (1): Primary Healthcare Centre of Mira, Portugal
Sponsor: AIBILI
IIR Grant: Novartis

SELECTED PUBLICATIONS


STEM CELLS IN THE TREATMENT OF EYE DISEASES

Joaquim Murta, MD, PhD

Other Research Personnel: Andreia Rosa, Esmeralda Costa, Maria João Quadrado

This research programme is directly related to a joint effort performed between the LV Prasad Eye Institute, India (C-TRACER 1), AIBILI (C-TRACER 2) together with the Department of Ophthalmology of the University Hospital of Coimbra and the Institute for Vision at the Federal University of S. Paulo, Brazil (C-TRACER 3).

C-TRACER 1, in Hyderabad, has been able to set up an outstanding and innovative stem cell research programme. It has offered limbal stem cell therapy to a large number of patients in India, whose corneal surface had been damaged by burns. C-TRACER 1 long-term results on this procedure (designated as cultivated limbal epithelial transplantation or CLET) has been internationally recognized. More recently, C-TRACER 1 has also moved to study the applications of stem cell biology to retinal disorders, this is being done by using human embryonic stem cells (HESCs) and differentiating them to certain retinal cells (e.g. retinal pigment epithelium (RPE)) and also to generate induced pluripotent cells (IPSCs) from skin fibroblasts and differentiating them to RPE cells.

C-TRACER 3, in S. Paulo, has set a cell biology lab where it has been possible to cultivate human limbal epithelial, conjunctival epithelial, endothelial and keratocytes stem cells.

C-TRACER 2, in Coimbra, together with the Dep. of Ophthalmology of the Univ. of Coimbra, is in the process of initiating stem cell research, cultivating human limbal epithelial cells and establishing primary cultures of human corneal endothelium (hCE), understanding its physiology and therapeutic potentialities. The three C-TRACERS are starting autologous ex vivo transplantation of conjunctival and oral mucosal epithelial stem cells for ocular surface reconstruction in bilateral total limbal stem cell deficiency. They are also developing a multicentric protocol using dental pulp stem cell transplantation for this group of patients. Finally, the three C-TRACERS are working together to share and develop new cell biology technology for retinal diseases.

PROJECTS

C-TRACER Project – Use of stem-cells in the repair of corneal and retinal diseases
Participating Centres (2): Coimbra (Portugal), Hyderabad (India).
Champalimaud Foundation

SELECTED PUBLICATIONS


B7

INDUSTRY SPONSORED CLINICAL TRIALS

**DIABETIC MACULAR EDEMA**

1. An Open Label, Registry Study of the Safety of ILUVIEN® 190 Micrograms Intravitreal Implant in Applicator (IRIS)
   - ClinicalTrials.gov n° NCT01998412
   - Patients enrolled: 3
   - Recruitment rate: ongoing
   - Sponsor: Alimera

2. Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment (AQUA)
   - EudraCT nº 2014-005119-17
   - Patients enrolled: 18
   - Recruitment rate: 360%
   - Sponsor: Bayer

3. A randomized, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety and tolerability of orally administered BI 1026706 for 12 weeks in patients with mild visual impairment due to center-involved diabetic macular edema (DME) (BI 1322.20)
   - EudraCT nº 2015-005293-33
   - ClinicalTrials.gov n° NCT02732951
   - Patients enrolled: 3
   - Recruitment rate: ongoing
   - Sponsor: Unifarma – Boehringer

4. An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with diabetic macular edema (DME) (VIOLET – BAY 86-5321/76513)
   - EudraCT nº 2014-004938-25
   - Patients enrolled: 1
   - Recruitment rate: ongoing
   - Sponsor: Bayer

**AGE-RELATED MACULAR DEGENERATION**

5. Study to observe the effectiveness and safety of ranibizumab through individualized patient treatment and associated outcomes (Luminous)
   - ClinicalTrials.gov n° NCT01318941
   - Patients enrolled: 427
   - Recruitment rate: 107%
   - Sponsor: Novartis

6. A 12-month, phase IV, randomized, open label, multicenter study to compare efficacy of 0.5 mg ranibizumab PRN versus 2 mg aflibercept bimonthly intravitreal injections on retinal thickness stability till month 6 of treatment and explore functional outcomes up to month 12 in patients with neovascular (wet) age-related macular degeneration (AMD) (SALT)
   - EudraCT nº 2013-002431-15
   - Patients enrolled: 50
   - Recruitment rate: 1000%
   - Sponsor: Novartis

7. A phase 3 randomized, double-masked, controlled trial to establish the safety and efficacy of intravitreous administration of FOVISTA TM (Anti PDGF-B Pegylated Aptamer) administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® Monotherapy in subjects with subfoveal neovascular Age-Related Macular Degeneration (FOVISTA)
   - EudraCT nº 2013-003018-42
   - Patients enrolled: 6
   - Recruitment rate: 75%
   - Sponsor: OphthTech

8. A phase III, multicenter, randomized, double-masked, sham-controlled study to assess the efficacy and safety of lampalizumab administered intravitreally to patients with geographic atrophy secondary to age-related macular degeneration (SPECTRI)
   - EudraCT nº 2014-000106-35
   - Patients enrolled: 3
   - Recruitment rate: 60%
   - Sponsor: Roche

9. An Interventional, multicentre, randomized study of nutritional supplements in unilateral wet AMD. (RETILUT)
   - Patients enrolled: 20
   - Recruitment rate: 100%
   - Sponsor: Thea

10. A Two-Year, Randomized, Double-Masked, Multicenter, Two-Arm Study Comparing the Efficacy and Safety of RTH258 6 mg Versus Aflibercept in Subjects with Neovascular Age-Related Macular Degeneration (HARRIER)
    - EudraCT nº 2014-004886-26
    - Patients enrolled: 4
    - Recruitment rate: ongoing
    - Sponsor: Alcon

11. Neovascular Age-Related Macular Degeneration (AZURE)
    - EudraCT nº 2012-003763-22
    - Patients enrolled: 12
    - Recruitment rate: ongoing
    - Sponsor: Bayer

**GLAUCOMA**

12. Long-Term Surveillance Study of Latanoprost to Monitor Hyperpigmentation changes in the eye in Pediatric Populations (A611144)
    - Patients enrolled: 3
    - Recruitment rate: 100%
    - Sponsor: Pfizer

**DRY EYE**

13. A Phase II, Multicenter, Randomized, Double-Blinded, 4 Parallel Arms, Controlled 6-Month Trial Designed to Evaluate the Safety and Efficacy of PAD Ciclosporin (CsA 0.06% and 0.03%) Ophthalmic Dispersions Administered Once Daily in Combination with Lubricant Therapy and a 3-Month Post-Treatment Safety Follow-Up in Moderate to Severe Dry Eye Patients (MC2-03-C1 – PADCicle)
    - EudraCT nº 2015-000937-54
    - Patients enrolled: 3
    - Recruitment rate: ongoing
    - Sponsor: MC2 Biotek
**OPHTHALMIC SAFETY**

14. Randomized, open label multi-center study comparing cabazitaxel at 25 mg/m2 in combination with prednisone every 3 weeks to Docetaxel in combination with prednisone in patients with metastatic castration resistant prostate cancer not pre-treated with chemotherapy (Firstana) EudraCT n° 2010-022064-12

Patients enrolled: 5
Recruitment rate: 83%
Sponsor: Sanoﬁ

15. A single arm, open-label, multicenter study evaluating the long-term safety and tolerability of 0.5mg fingolimod (FTY720) administered orally once daily in patients with relapsing forms of multiple sclerosis (FTY 720 2399)

EudraCT n° 2010-020515-37

Patients enrolled: 28
Recruitment rate: 100%
Sponsor: Novartis

**NEUROLOGICAL DISORDERS**

17. Efficacy and safety of Eslicarbazepine acetate (BIA 2-093) as monotherapy for patients with newly diagnosed partial-onset seizures: a double-blind, double-dummy, randomized, active-controlled, parallel-group, multicenter clinical study (BIA-2093-311)

EudraCT n° 2009-011135-13

Patients enrolled: 6
Recruitment rate: 40%
Sponsor: Bial

18. A multicenter, double-blind, double-dummy, follow-up study evaluating the long-term safety of lacosamide (200 to 600mg/d) in comparison with carbamazepine (400 to 1200mg/d), used as monotherapy in subjects with partial-onset or generalized tonic-clonic seizures ﬁll6 years of age coming from the SP0993 study (SP0994)

EudraCT n° 2010-021238-74

Patients enrolled: 2
Recruitment rate: 34%
Sponsor: UCB

19. A multicenter, randomized, double-blind, placebo-controlled variable treatment duration study evaluating the efficacy and safety of siponimod (BAF312) in patients with secondary progressive multiple sclerosis (EXPAND)

EudraCT n° 2012-003056-36

Patients enrolled: 13
Recruitment rate: 130%
Sponsor: Novartis

20. A Randomized, Placebo Controlled, Parallel-Group, Double Blind Efficacy and Safety Trial of MK-8931 in Subjects with Mild to Moderate Alzheimer’s Disease (EPOCH)

EudraCT n° 2011-003151-20

Patients enrolled: 18
Recruitment rate: 90%
Sponsor: MSD

21. A phase III, multicenter, randomized, double-blind, double-dummy, active controlled, parallel group study to evaluate the efficacy and safety of RPC1063 administered orally (SUNBEAM)

EudraCT n° 2014-002320-27

Patients enrolled: 12
Recruitment rate: 120%
Sponsor: Receptos


EudraCT n° 2015-001243-36

Patients enrolled: 2
Recruitment rate: 100%
Sponsor: Bial

23. A multi-site, open-label extension Trial of Oral RPC1063 in relapsing Multiple Sclerosis (RPC01-3001 – DAYBREAK)

EudraCT n° 2015-002500-91

Patients enrolled: 11
Recruitment rate: 100%
Sponsor: Celgene

24. Multicenter, randomised, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis (AC-058301 – OPTIMUM)

ClinicalTrials.gov n° NCT02425644

EudraCT n° 2012-000540-10

Sponsor: Actelion

25. A randomized, double-blind, placebo-controlled and delayed-start study of LY3314814 in Mild Alzheimer’s Disease Dementia (DAYBREAK – 1BD-MC-AZET)

EudraCT n° 2015-005625-39

Sponsor: Eli Lilly
### Nº OF INVESTIGATOR INITIATED VS INDUSTRY SPONSORED TRIALS PERFORMED AT CEC (2012–2016)

<table>
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<th>Industry Sponsored</th>
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### CENTRE FOR CLINICAL TRIALS – INCOME (2012–2016)

![Bar chart showing income from 2012 to 2016]
The eye offers unique opportunities to obtain in a non-invasive manner information on the body, in general and of the brain in particular. It is, in fact, a window to the body. The retinal circulation and the retina can be examined using a variety of methods. Our research group has focused on development of new imaging techniques of the eye fundus without disturbing in any way the ocular and body environment. We are particularly interested in methodologies that allow repeated observations and measurements in order to identify early alterations and the degree of activity of these alterations when present over time. Fundus Digital Photography and Optical Coherence Tomography are non-invasive examinations that offer extremely promising perspectives as the information collected can be analysed automatically. The analysis of the data can also be tailored to specific purposes, allowing validating imaging biomarkers of disease. These imaging biomarkers may give information on retinal and eye disease but also may serve as indicators of systemic disease, such as brain degenerative diseases and circulatory disorders. Our group has been able to identify biomarkers of disease progression, such as microaneurysm turnover in diabetic retinopathy identified automatically by software developed in-house, the Retmarker®, and identify non-invasively changes in the Blood-Retinal Barrier in the retina.
PATENTS AND PRODUCTS

1. Retmarker®
Partner: Retmarker, Portugal
Retmarker® is a software that provides information to monitor the progression of retinal diseases, which are the leading causes of blindness in the Western world. Monitoring of progression of retinal diseases is much needed to gather information to support diagnosis, definition of treatment strategies and to evaluate the treatment’s effectiveness. There are a number of Retmarker products, namely:
   - The RetmarkerC® is an innovative software solution that uses image processing technology and the latest medical research to deliver a product that detects retinal changes automatically, effectively and effortlessly.
   - The RetmarkerDR® is a software solution for predicting Diabetic Retinopathy (DR) progression from its Nonproliferative stage to Clinically Significant Macular Edema (CSME), a sight-threatening stage.
   - The RetmarkerAMD® Research is a software solution for the assisted grading of retinographies from patients with Age-Related Macular Degeneration (AMD).
Product available / More information: www.retmarker.com

2. Ocular Fluorometer
Partner: OverPharma, Portugal
Measurement of fluorescence in the cornea, aqueous, lens and anterior vitreous. It is used to measure natural autofluorescence (intravenous or oral) of these sites of the eye and to measure the penetration of fluorescein into the eye after local or systemic administration giving information on the alteration of the blood-ocular barriers.

3. OCT Leakage
Optical Coherence Tomography (OCT) is an imaging modality undergoing a fast growth of application in the field of ophthalmology because of its unique ability for non-invasive structural imaging of the ocular fundus, allowing to assess the structure of the human retina in vivo. Our group is developing applications that resort to advanced imaging algorithms to enable analysis of OCT data, focusing on the segmentation of the different layers of the retina and the permeability of the Blood-Retinal Barrier. A novel analysis “Method and device for the non-invasive indirect identification of sites of alterations of the Blood–Retinal Barrier” was published under the Patent Cooperation Treaty number WO2016/174637A1.

The industry’s recognition of AIBILI’s innovative research on Diabetic Retinopathy is demonstrated by the clinical and scientific consultation agreement with Carl Zeiss Meditec on the development of OCT AngioPlex system. This group also develops and provides regulatory compliant software applications needed for grading activities at Coimbra Ophthalmology Research Centre (CORC).

**RESEARCH CONTRACTS**

**Quantification of Retinal Microvasculature in Retinal Disease**
Sponsor: Carl Zeiss Meditec

**PROJECTS**

**Development and validation of a semi-automatic segmentation application for OCT data**
Support: AIBILI

**OCT – Leakage; Quantification of BRB alterations in diabetic patients through identification of zones of low optical reflectivity in Optical Coherence Tomography**
Support: AIBILI

**FILTER – Framework to develop and validate automated image analysis systems for early diagnosis and treatment of eyes at risk in blinding age related disease**
Support: AIBILI

**SELECTED PUBLICATIONS**


MULTIMODAL IMAGING OF DIABETIC RETINAL DISEASE

Conceição Lobo, PhD

Other Research Personnel: Isabel Pires, José Cunha-Vaz, Ana Rita Santos, Torcato Santos, Mário Soares

It is widely accepted that the early detection of the alterations of the retina in diabetes is important in order to preserve vision and halt the disease progression to a later stage where alterations cannot be reverted and vision is at risk. Based in this concept our research group has been focused in the last decade on the development of in vivo human imaging techniques for the assessment of Diabetic Retinopathy (DR) development and progression, with special attention to the early stages of the disease.

Using Optical Coherence Tomography (OCT), a non-invasive method, it is possible to measure the retinal thickness and follow the progression of retinal edema. The development of a segmentation algorithm to identify the different layers of the retina opened the possibility to better characterize the exact location of these initial alteration associated with decrease in optical reflectivity. The changes in extracellular space as a result of alteration of the Blood-Retinal Barrier (BRB) can be correlated with detection of initial changes occurring in deep retinal capillary net by the novel OCT microangiography. Multimodal imaging of the retina using standardized methodology including OCT microangiography that may contribute to the better characterization of these alterations.

PROJECTS

- Evaluation of blood-retinal barrier functional alterations by optical coherence tomography

- Optical Modelling of the Human Retina in Health and Disease: from structure to function

- Quantification of Retinal Microvasculature in Retinal Disease
  Sponsor: Carl Zeiss Meditec

SELECTED PUBLICATIONS


Diabetic Macular Edema (DME) is the most frequent cause of vision loss in patients with Diabetic Retinopathy (DR). It is the result of the disruption of Blood-Retinal Barrier (BRB) and consequent leakage to the retina, leading to increase of macular thickness (MT) and loss of visual acuity (VA).

The vascular endothelial grown factor (VEGF) is one of the major contributors of changes in the BRB. Recently, intravitreal injections of anti-VEGF have demonstrated good efficacy in reducing the MT, however, not always followed by functional improvement. Recent studies have revealed that the existence of photoreceptors damage, presence/location of cystoid spaces and volume of intraretinal fluid can condition the treatment response, but very few methods exist to quantify and differentiate the intraretinal fluid. Moreover, studies that correlate the response to anti-VEGF treatment use only VA measurements which appear to be difficult to correlate with the treatment effect. We are looking at the changes occurring in DME, before and after treatment using Optical Coherence Tomography (OCT) and also with the most recent technology OCT Angiography, correlating these changes with a variety of differentiated functional evaluations. The main goal is to identify potential predictive factors of a good or poor visual response to anti-VEGF treatment which may be used as a metric for visual prognosis, opening new perspectives in the management of DME with expected impact in clinical practice.

**PROJECTS**

CHARTRES – Characterization of Eyes With Diabetic Macular Edema That Show Different Treatment Response to Intravitreal Anti-VEGF

ClinicalTrials.gov nº NCT01947881

Protocol nº 4C-2013-05

Participating Centres (1): Coimbra, Portugal

IIR Grant: Novartis

**SELECTED PUBLICATIONS**


Testing and validation of automated analysis of digital fundus images using the retmarker. contribution to oct structural analysis of the retina for screening

Luísa Ribeiro, MD, PhD
Other research personnel: Ana Rita Santos, Catarina Neves, João Figueira, José Cunha-Vaz, Marta Lopes, Rufino Silva, Conceição Lobo, Sandrina Nunes, Torcato Santos, Patricia Barreto, Pedro Melo, Silvia Simão

Diabetic retinopathy (DR) and age-related macular degeneration (AMD) are chronic retinal diseases that may eventually progress to develop sight-threatening complications and even blindness. Our group has shown that the evolution and progression of these diseases vary between different individuals. It is, therefore, of fundamental importance to monitor the progression of the disease in an individual patient and identify the patients that are “progressors”, i.e., showing signs of rapid disease progression. We have introduced the concept of velocity of progression in retinal disease management. Using fundus digital photography, a simple, non-invasive examination, our group has developed the RetmarkerDR®, a new methodology of automated analysis capable of identifying changes occurring in the eye fundus, by comparing successive visits to the reference image based on co-registration and exact co-localization of the changes.

The methodologies developed by our group opened also new perspectives for improved screening of diabetic retinopathy working together with the Coimbra Ophthalmology Reading Centre that is responsible for the Diabetic Retinopathy Screening Program in the Central Region of Portugal.

Contacts
Luísa Ribeiro, MD, PhD
Phone: +351 239 480 148/124
E-mail: lr@aiibili.pt

Selected Publications


Retinal degenerative diseases affect millions of patients worldwide. In the last decade, basic and clinical scientific research gathered a massive amount of data that allowed a better insight into the pathogenesis of these diseases, at both molecular and cellular level. Despite these advances, and the identification of potential therapeutic targets and a few biomarkers, the translation of this knowledge into effective treatments for patients suffering from retinal degenerative diseases is still limited. Therefore, efforts aimed at identifying new therapeutic targets and new therapeutic modalities are needed.

We have been interested in understanding the pathogenesis of two retinal degenerative diseases: diabetic retinopathy and glaucoma. Regarding diabetic retinopathy, we have been interested in understanding both blood-retinal barrier dysfunction and neural dysfunction and degeneration. In glaucoma, our main goal is the neuroprotection of retinal ganglion cells. In fact, neuroprotection can be also viewed as an additional therapy in diabetic retinopathy. Moreover, it has been proved that neuroinflammation has a key role in the pathogenesis of both diseases, and the development of therapies targeting neuroinflammatory processes can be also considered.

To achieve our goals we have been using several in vitro models, such as primary bovine retinal endothelial cell cultures, primary mixed retinal neural cell cultures, purified primary retinal ganglion cell cultures, purified primary retinal microglial cell cultures, organotypic retinal cultures (from mouse, rat and human), and endothelial and microglial cell lines, as well as several animal models: type 1 diabetes animal model (streptozotocin model), elevated intraocular pressure model (episcleral vein cauterization model), ischemia-reperfusion model and excitotoxic models (intravitreal injection of excitotoxic drugs). In our studies, we use biochemistry and cell and molecular biology techniques, bioimaging (fluorescence and confocal microscopy), as well as structural and functional observations including ocular coherence tomography, electroretinography (full field and pattern) and visual evoked potentials.
Diabetic retinopathy is a major complication of diabetes and, despite recent advances in prevention and treatment, it is still a leading cause of vision loss and blindness worldwide in working age adults. Diabetic retinopathy is a neurovascular disease and it has been claimed that inflammation, which may affect both blood-retinal barrier and neural components, plays a critical role in the pathogenesis and progression of the disease. In recent years, several options for the treatment of diabetic retinopathy, targeted to the more advanced stages of the disease (macular edema or proliferative diabetic retinopathy), have been developed. However, these treatments are not very effective in some patients. Moreover, despite retinal neural dysfunction and degeneration, less attention has been given to neuroprotective strategies in diabetic retinopathy. Therefore, the development of new treatments for diabetic retinopathy is needed. We have been investigating the molecular and cellular mechanisms underlying the pathogenesis of diabetic retinopathy, namely the mechanisms underlying endothelial, glial and neuronal cell dysfunction and death. Our ultimate goal is to identify potential therapies targeted for the early stages of the disease, aiming preventing or delaying the blood-retinal barrier breakdown and neurodegenerative processes. We are also evaluating the role of choroid in retinal dysfunction triggered by diabetes.

Glucoma is a progressive and non-curable retinal degenerative disease and is the second cause of blindness worldwide, affecting approximately 70 million people. The disease is characterized by loss of retinal ganglion cells and damage to the optic nerve. Chronic neuroinflammation has been recognized to play an important role in the pathogenesis of glaucoma. Indeed, increasing evidence has demonstrated that microglial cells become reactive in the glaucomatous optic nerve head and retina. Elevated intraocular pressure (IOP) has been recognized as a major risk factor for the development of glaucoma, and lowering the IOP remains the only current therapeutic approach for glaucoma patients. However, despite good IOP control, the disease still progresses in several patients. Therefore, neuroprotection has been regarded as an additional therapeutic strategy. Our working hypothesis is that the control of microglia-mediated neuroinflammation confers protection to the retina, particularly to retinal ganglion cells, by inhibiting the release of pro-inflammatory and neurotoxic factors that contribute to neuronal dysfunction and pathology. Using in vitro and animal models we have been testing the potential protective effects exerted by the modulation of neuropeptide Y and adenosine. The ultimate goal is to identify new molecular targets with the potential to be translated into new therapies to treat glaucoma.
Exosomes as amplifiers of inflammation: microglia-Müller cell communication in glaucoma

Financial Support: Faculty of Medicine, University of Coimbra – GAI-Santander Totta 2016_224

SELECTED PUBLICATIONS


AIBILI was recognized in 2010 as a Champalimaud Translational Centre for Eye Research (C-TRACER) by the Champalimaud Foundation for its activities in translational eye research. The work of AIBILI and particularly of the Coimbra Coordinating Centre for Clinical Research (4C) in the coordination of the European Vision Institute Clinical Research Network (EVICR.net) were very relevant for this recognition.

The Champalimaud Foundation has been progressively establishing a Network of C-TRACERs involving major eye research centres looking for collaborations in a global perspective to improve patient eye care worldwide.

This Network is of great relevance to AIBILI because it brings together under the Champalimaud Foundation three major eye research institutions in the world and creates links between three major continents, Asia, Europe and South America.

AIBILI is C-TRACER 2 in the C-TRACERs Network. The C-TRACERs Network brings together the LV Prasad Eye Institute in Hyderabad, India, C-TRACER 1 and the Institute for Vision at the Federal University of S. Paulo at S. Paulo, Brazil, C-TRACER 3 with AIBILI, C-TRACER 2.

The research of the C-TRACERs Network is at present, focused on identification of biomarkers of disease progression with particular impact on the prevention and personalized management of diabetic retinopathy, one of the major causes of vision loss and on the use of stem-cells in the repair of corneal and retinal diseases. New methodologies of stem-cell preparation and conditioning developed at C-TRACER 1, LV Prasad Eye Institute, are expected to contribute to more efficient corneal repair in situations of previously irreversible vision loss. These techniques and methodologies are being used at the Department of Ophthalmology of the Coimbra University Hospital (CHUC) with the direct support of AIBILI, C-TRACER 2.

Another area of major relevance is the development of teleophthalmology using automated image analysis and centralized reading centres creating the conditions for more efficient ophthalmological care and making it possible to reach isolated/inaccessible populations/communities. Improved access to expert eye care and strategies of mass screening are goals of the C-TRACERs Network to translate their research activities into clinical practice always taking into account patient needs and contributing to improved health care at reduced costs.
C-TRACER PROJECT Nº 1
The first multinational project funded by the Champalimaud Foundation within the C-TRACERs Network is focused on the characterization of different phenotypes of progression of diabetic retinopathy using the RetmarkerDR® developed at C-TRACER 2, AIBILI. It is expected to predict the individual cases that are at risk to develop clinically significant macular edema. This approach will contribute to establish personalized management of diabetic retinopathy and will also reduce the costs involved in the treatment of diabetes. This observational study is expected to add important data that will help diabetic retinopathy management at initial stages of the disease in India and in European Union, two ethnical populations with different characteristics in the world.

This study was initiated in June 2012. The current status of the clinical sites is as follows:

**C-TRACER 1 – LV Prasad Eye Institute:**
Coordinator: Prof. Balasubramanian
Principal Investigator: Dr. Rajeev Pappuru
Recruitment Period: 05/2013 – 03/2014
Nº of Subjects included: 104
Last Visit from the last patient: 27-05-2016

**C-TRACER 2 – AIBILI:**
Coordinator: Prof. Cunha-Vaz
Principal Investigator: Dr. Luísa Ribeiro
Recruitment Period: 11/2012 – 10/2013
Nº of Subjects included: 101
Last Visit from the last patient: 19-11-2015

# PROJECTS

**C-TRACER Project nº 1 – Biomarkers of Diabetic Retinopathy Progression**
ClinicalTrials.gov nº NCT01607190
Protocol nº 4C-2012-02
Coordinating Investigator: José Cunha-Vaz, Coimbra, Portugal
Participating Centres (2): Coimbra (Portugal), Hyderabad (India).
Nº of Patients (included): 205
Clinical Phase: 2 years
IIR Grant: Champalimaud Foundation

**C-TRACER Project – Use of stem-cells in the repair of corneal and retinal diseases**
Participating Centres (2): Coimbra (Portugal), Hyderabad (India).
Champalimaud Foundation
4.1. ADMINISTRATIVE SERVICES

Staff: Cecília Martinho, Paulo Barros, Joana Ecsodi, Rita Almeida, Cátia Marques, Carlos Franco, Tânia Melro

The Administrative Services is responsible for the management of AIBILI and to perform all the administrative tasks, including finances and accountability, human resources management, as well as maintenance of infrastructure according to the institution’s needs. The Administrative Services establishes a direct liaison between the Board of Directors of AIBILI and its Centres and supporting Units.

4.2. QUALITY MANAGEMENT

Staff: Cecília Martinho, Rita Fernandes

AIBILI is ISO 9001 certified for the activities of: Performance of Clinical Research; Planning, Coordination, Monitoring of Clinical Research Activities, Health Technology Assessment, Grading of Eye Exams, Research and development in new technologies for medicine in the areas of Imaging, Optics and Photobiology, Preclinical studies of new molecules with potential medical use and Data Centre activities.

AIBILI Quality Manual states that it has a Quality Management System (QMS) and the necessary resources to provide the services and meet the needs and expectations of its Clients and interested parties.

It has a Standard Operating Procedure (SOP) Manual which contains general organizational SOPs and specific SOPs for each process, in compliance with ISO 9001, ICH-GCP Guidelines, requirements for Certification of ECRIN Data Centres as well as regulatory requirements, statutory and legal, applicable to AIBILI activities.

The Quality Management Unit assures that the QMS is maintained effective and efficient permitting improvement and that data obtained in AIBILI is valid and reliable.

Currently the QMS is being adapted to the new version of the ISO 9001.

Internal auditing is a guarantee that procedures are followed at AIBILI and the QMS is in improvement aiming to satisfy the needs of our Clients and interested parties.

AIBILI’s Quality Management Unit is also recognized by others and provides consultancy services when required, helping other healthcare institutions to implement quality systems ISO 9001 and ICH-GCP compliant.

4.3. TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER

Staff: Cecília Martinho, Daniel Fernandes, Paulo Barros

The Translational Research and Technology Transfer Unit is responsible to provide all the administrative support to facilitate and promote the transfer of R&D activities and pre-clinical studies to the development of clinical trials and to enhance the adoptions of best practices in the community. It is responsible for perspectives and analysis of technology transfer, creating the conditions for contracting with industry, namely intellectual property implications.

This Unit is responsible to identify and apply for external funding, namely R&D programs for the health market. Currently this Unit is managing the participation of AIBILI in Horizon 2020 projects and supporting the other partners on administrative and legal issues.

The Translational Research and Technology Transfer Unit is also responsible for promoting AIBILI and the activities of its Centres, being the main contact point for partnership and collaborations with AIBILI.
4.4. INFORMATION TECHNOLOGY

**Staff:** Carlos Domingues, Hugo Morgado, Patrícia Silva, Telmo Miranda, Torcato Santos, José Monteiro

The Information Technology Unit is responsible for the management and maintenance of AIBILI Data Centre, networks and information systems. The Data Centre, built in 2014 for storing AIBILI’s critical information, houses all AIBILI servers/systems: the Electronic Medical Record that is daily used to collect patient clinical information at CEC; the custom-designed web based platform used to exchange grading data and images by CORC; the Clinical Data Management System that is used in the development of eCRFs for each clinical trial; the PhVC Manager – Extedo that is used for pharmacovigilance in clinical trials by CHAD as well as the Clinical Trial Management System (CTMS) used for the management of multiple multinational clinical studies by 4C. There are also other administrative information systems supported in AIBILI’s Data Centre.

AIBILI is member of the Health Cluster Portugal (HCP) which main objective is the promotion and implementation of initiatives and activities leading to the consolidation of a national cluster for competitiveness, innovation and technology in the health area.

More information: [www.healthportugal.com](http://www.healthportugal.com)

AIBILI, through VICT – Vision and Imaging Consortium for Translational Research, is integrated in the Translational and Clinical Research Infrastructures Specialization Platform – Health Cluster Portugal – (TRIS-HCP) initiative. TRIS-HCP is integrated in the National Roadmap of Research Infrastructures of Strategic Relevance, established by FCT – the Portuguese Foundation for Science and Technology.

More information: [www.healthportugal.com/tris-hcp](http://www.healthportugal.com/tris-hcp)

AIBILI started a sub-cluster in Ophthalmology within HCP with the aim to increase Portuguese participation in international partnerships, attract national and foreign investment in health and make Portugal an important partner in ophthalmology healthcare and research. This Ophthalmology sub-cluster brings together public and private hospitals, clinics and industry, aiming to implement outcomes of ICHOM - The International Consortium for Health Outcomes Measurement, as a measure of value in the provision of healthcare, as well as support the development of a clinical research network in Portugal.

More information: [www.healthportugal.com/tris-hcp](http://www.healthportugal.com/tris-hcp)

**Contacts**

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Participation of AIBILI, as an Academic CRO, in the Clinical Trials Day organized by PtCRIN at INFARMED in Lisbon.

Participation of AIBILI, as an Academic CRO, in the Coimbra International Ophthalmology Meeting organized by the Department of Ophthalmology of the Coimbra University Hospital.
Prof. Cunha-Vaz received the EURETINA Award 2016 during the open ceremony of the EURETINA 2016 Congress that took place in Copenhagen, Denmark.

Dr. Luisa Ribeiro Director of the Clinical Trial Centre completed her PhD degree with the thesis on “Characterization of the initial stages of diabetic retinopathy, early diagnosis and biomarkers of the activity of diabetic retinopathy” which was approved with distinction and unanimous praise.
The CHAD – Centre for Health Technology Assessment and Drug Research, as the Pharmacovigilance Unit of the Centre Region (UFC) of the National Pharmacovigilance System, organized a Regional Pharmacovigilance Meeting in Coimbra.

AIBILI, as Coordinating Centre of the EVICR.net, organized the 11th Members Meeting which took place in Antwerp, Belgium, hosted by the Antwerp University Hospital (CS12), with attendance of around 93 participants from 42 Centres and with active participation of Industry Advisory Board Members.
AIBILI has an Independent Ethics Committee (IEC/IRB) that is responsible for protecting the rights, safety and wellbeing of human subjects involved in clinical studies (not involving Investigational Medicinal Products (IMP’s) or medical devices) performed at AIBILI according to the Portuguese Law nº 21/2014. In 2016, AIBILI Ethics Committee has reviewed and approved three ophthalmological clinical studies fulfilling the conditions previously indicated and was kept informed of the approval of proposals submitted to the National Ethics Committee for Clinical Research (CEIC). AIBILI Ethics Committee is available to be called upon CEIC’s request, in case it is needed for the review of ophthalmology clinical trials or studies since it has expertise in this scientific area.

**ETHICS COMMITTEE**

**Contacts**
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E-mail: ces@aibili.pt

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**MEMBERS**

**President**
Francisco Manuel Corte-Real Gonçalves, MD, PhD
(Sub-Director and Professor at the Faculty of Medicine, University of Coimbra)

**Vice-President**
André Dias Pereira, PhD
(Director of the Centre for Biomedical Law of the University of Coimbra and Professor at the Faculty of Law, University of Coimbra)

**Secretary**
Margarida Caramona, PhD
(Director of the Pharmacology Laboratory and Professor at the Faculty of Pharmacy, University of Coimbra)

**Members**
José Moura Pereira, MD
(Ophthalmologist at the University Hospital of Coimbra)

Maria Elizabete Batista Geraldes, MD
(Endocrinologist at the University Hospital of Coimbra)

Paulo Simões
(Father, Director of University Institute of Justice and Peace, Coimbra)

Filomena Maria Ferreira Ramos Mena
(Nurse at the National Institute of Forensic Medicine, Coimbra)
PARTNERSHIPS

ECRIN-ERIC – EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK – EUROPEAN RESEARCH INFRASTRUCTURE CONSORTIUM

ECRIN-ERIC ([www.ecrin.org](http://www.ecrin.org)) is a network dedicated to improving the health of patients and citizens across the world through clinical research. ECRIN-ERIC supports multinational collaboration in clinical research, acting through correspondents hosted in national clinical research hubs and networks. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.

AIBILI, as Coordinating Centre of EVICR.net, a disease oriented network in ophthalmology for clinical research, is an Affiliate Partner of ECRIN-ERIC. Thus, EVICR.net serves as a resource to ECRIN-ERIC in the area of vision and ophthalmology clinical research, particularly providing scientific and medical expertise, access to patients and investigation capacity.

PTCRIN – PORTUGUESE ACADEMIC CLINICAL RESEARCH INFRASTRUCTURES NETWORK

PtCRIN ([www.ptcrin.pt](http://www.ptcrin.pt)) is the national clinical research network aiming to facilitate and improve quality in clinical research and to increase national and international research collaboration for the benefit of patients, citizens and the healthcare system. AIBILI is a founding member of the PtCRIN.

EATRIS – EUROPEAN INFRASTRUCTURE FOR TRANSLATIONAL MEDICINE

EATRIS ([www.eatris.eu](http://www.eatris.eu)) is a client driven, non-profit organization comprising European academic centers of excellence in translational research. EATRIS partner institutes support in bringing innovative ideas for novel preventive, diagnostic or therapeutic products towards first in human application and on to clinical proof of concept. EATRIS partner institutes provide services and expertise in the following areas: Advanced therapy medicinal products and biologics; Biomarkers; Imaging and tracing; Small molecules; and Vaccines.

HCP – Health Cluster Portugal is leading an initiative called TRIS-HCP which is a virtual organizational system that brings together Portuguese R&D institutions, hospitals and academic medical centres. AIBILI is one of the institutions with expertise in translational research in ophthalmology with emphasis in the area of Biomarkers and Imaging.
AIBILI BUILDING

3rd floor
- SA – Administrative Services
- 4C – Coimbra Coordinating Centre for Clinical Research
- CHAD – Centre for Health Technology Assessment and Drug Research
- EVICR.net Coordinating Centre

2nd floor
- CEC – Clinical Trial Centre

1st floor
- CNTM – Centre of New Technologies for Medicine
- CORC – Coimbra Ophthalmology Reading Centre
- IT – Information Technology / Data Center
- SA – Administrative Services