

2018 REPORT





2018 REPORT



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INTRODUCTION

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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 not-for-profit organisation, founded in 1989, established to support technology transfer and translational research in the health area.

AIBILI is ISO 9001:2015 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 area of imaging**
- **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 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**)

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

AIBILI is located in the area of the Health Campus of Coimbra University since 1994 and has its own building with 1.454 m² and state-of-the-art equipment funded by European Union funds through PEDIP. Regarding human resources it has a permanent staff of 52 including medical doctors, researchers, engineers, pharmacologists, technicians, project managers, statisticians data managers, study coordinators and administrative personnel. Another 38 professionals collaborate regularly in research activities.

AIBILI has collaborations with national and international institutions, namely but not limited to:

- ARSC – Health Administration of the Centre Region of Portugal
- CF – Champalimaud Foundation
- CHUC – Coimbra University Hospital and its Centre of Responsibility in Ophthalmology
- FMUC – Faculty of Medicine of the University of Coimbra
- i3S – Institute for Research and Innovation in Health of the University of Porto
- iCBR – Coimbra Institute for Clinical and Biomedical Research
- INFARMED – National Authority of Medicines and Health Products, I.P.
- Institute for Vision at the Federal University of S. Paulo, S. Paulo, Brazil
- L.V. Prasad Eye Institute, Hyderabad, India
- P-BIO – Portugal's Biotechnology Industry Organization

In summary, the main goals of AIBILI are translational research and innovation contributing to the conversion of basic research knowledge into practical applications in order to improve human health and wellbeing.



Centro Interface

INTERFACE CENTRE FOR HEALTH AND LIFE SCIENCES

AIBILI is an Interface Centre in the Health Sector of the National Technology Network. This recognition identifies AIBILI as the technology transfer centre acting as the facilitating partner between scientific institutions, enterprises and industry in order to bring novel products to the market.

AIBILI strategy for the period 2019-2021 focuses on its role as the Centre for Technological Interface of Portugal in the Health Sector. The innovation and technological objectives focus on:

- Maintaining its position as a Reference Centre for coordination and logistical support of clinical research activities at the European level by supporting new clinical studies
- Development of imaging biomarkers of progression and response to treatment
- Assessment of economic viability in the development of new products

In the coordination and logistical support activities of clinical research it is crucial to maintain and guarantee the international recognition already achieved. The internationalization already achieved with EVICR.net and C-TRACERS Networks create unique opportunities for Portuguese SMEs and research centres to participate in new studies. AIBILI will continue to expand its partnerships with Portuguese companies and universities in order to foster the development of new products.

Innovation is focused in the development of imaging biomarkers of progression and response to treatment of retinal and brain diseases. AIBILI will continue contributing to the development of screening programmes using tele-ophthalmology particularly in primary healthcare centres, promoting clinical research and reaching out to different population of patients. AIBILI also intends to pursue its research activities in the area of artificial intelligence applications to image analysis of eye images with potential application in new methodologies of prevention and establishment of imaging biomarkers creating opportunities for companies of the health sector to develop and market new products.

In the area of assessment of economic viability of the translational process in the development of new products it is intended to evaluate the economic viability of medicines, design of the value strategy, regulation and translation of technology that will allow greater knowledge of the chain value and transfer of knowledge to SMEs, market access, as well as follow-up and effectiveness after commercialization.



BIOTECHNOLOGY AND LIFE SCIENCES FOCUS: HUMAN HEALTH

FINANCIADO POR



Fundo de Inovação,
Transferência de Tecnologia
e Economia Circular



PROGRAMA
INTERFACE



Programa
Nacional
de Reformas



REPÚBLICA
PORTUGUESA

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 & C^a, SA
- Centro de Oftalmologia da Universidade de Coimbra
- Conceição Lobo
- Francisco Batel Marques
- Fundação Champalimaud (Honorary Associate)
- Hospital Cuf Coimbra / José de Mello Saúde
- Laboratórios Pfizer, Lda.
- Novartis Farma, SA
- Universidade de Coimbra (Honorary Associate)

AIBILI BOARD OF DIRECTORS

(2017–2020)

- José Cunha-Vaz, President
- José Cotta – EMS, SA, Vice-President (Conceição Lobo)
- BIAL – Portela & C^a, SA (Tice Macedo)
- Fundação Champalimaud (António Parreira)
- Laboratórios Edol, Produtos Farmacêuticos, SA (Gonçalo Pimpão)
- Serviço de Dermatologia do Centro Hospitalar Universitário de Coimbra (Américo Figueiredo)
- Francisco Batel Marques

BOARD OF DIRECTORS

President
José Cunha-Vaz

CEO
Cecília Martinho

 **EVICR.net**
Coordinating Centre
Cecília Martinho

Administrative Services (SA)
Cecília Martinho

Quality Management (QMU)
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 for New
Technologies
in Medicine
CNTM**
José Cunha-Vaz

**Centre for
Health Technology
Assessment and
Drug Research
CHAD**
Batel Marques

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AIBILI AT A GLANCE 2018

COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH (4C)

21

Coordination of Investigator Initiated Research

16

Coordination of Industry Sponsored Clinical Trials

2

Multinational 9 National 7

Other

3

DATA CENTRE (DC)

16

Data Centre Services

16

CLINICAL TRIAL CENTRE (CEC)

21

Investigator Initiated Research (Ophthalmology)

6

Industry Sponsored Clinical Trials

15

Multinational 2 National 4

Ophthalmology 9
Neurosciences 5
Cancer 1

COIMBRA OPHTHALMOLOGY READING CENTRE (CORC)

18

Contracts for Centralized Reading

18

Multinational Trials 9 National Trials 9

CENTRE OF NEW TECHNOLOGIES FOR MEDICINE (CNTM)

10

Research Projects

10

Patents 3 (USA) + 1 (PTC)

CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH (CHAD)

28

Contracts

28

Market Access 21 Drug Safety 7

AREA	1.454 m²
FULLTIME STAFF	52
Nº OF PHD	19
Nº OF CONSULTANTS	38
Nº OF ONGOING STUDIES, SERVICES, PROJECTS, CONTRACTS	114
Nº OF PATENTS	3 (USA) + 1 (PCT)
Nº OF EUROPEAN UNION FUNDED PROJECTS (ONGOING)	2
Nº OF PUBLICATIONS (2017-2018)	86
Nº OF PUBLICATIONS / PHD (2017-2018)	4,5

3

RESEARCH AND INNOVATION

3.1 IMAGING BIOMARKERS

The eye offers unique opportunities to obtain in a non-invasive manner information on the body, in general and of the retina and 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, using a novel patented algorithm, the OCT-Leakage.

PATENTS AND PRODUCTS

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 a 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

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.

OCT Leakage

Method and device for the non-invasive indirect identification of sites of alterations of the Blood-Retinal Barrier, in particular to the automated analysis of retinal extracellular space using Optical Coherence Tomography.

PCT number WO2016/174637 A1.

OCT-LEAKAGE. LAYER BY LAYER FLUID ANALYSIS OF THE RETINA

Torcato Santos, BSc

Other Research Personnel: Ana Rita Santos, Catarina Neves, José Cunha-Vaz, Luis Mendes, Telmo Miranda

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 the assessment of 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.



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PROJECTS

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

SELECTED PUBLICATIONS

Cunha-Vaz J, Santos T, Ribeiro L, Alves D, Marques I, Goldberg M, OCT-Leakage - A New Method to Identify and Locate Abnormal Fluid Accumulation in Diabetic Retinal Edema, *Invest. Ophthalmol. Vis. Sci.*, 2016, vol. 57, N. 15, pp. 6776-6783.

Cunha-Vaz J, Santos T, Alves D, Marques I, Neves C, Soares M, Lobo C, Agreement between OCT-Leakage and Fluorescein Angiography to identify sites of alterations of the Blood-Retinal Barrier, *Ophthalmology*, 2017, vol. 124, N 10, pp 1432-1436.

Santos A; Alves D; Santos T; Figueira J; Silva R; Cunha-Vaz J, Measurements of Retinal Fluid by OCT-Leakage in Diabetic Macular Edema. A Biomarker of Visual Acuity Response to Treatment, *Retina*. 2017 Oct 26. doi: 10.1097/IAE.0000000000001905.

ARTIFICIAL INTELLIGENCE FOR CHARACTERIZATION OF RETINAL BIOMARKERS



Luis Mendes, PhD

Other Research Personnel: Ana Rita Santos, Cláudia Farinha, Conceição Lobo, Inês Marques, José Cunha-Vaz, Luisa Ribeiro, Rufino Silva, Sérgio Carvalho, Telmo Miranda, Thiago Martins, Torcato Santos

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Diabetic retinopathy (DR) and Age-related macular degeneration (AMD) are leading causes of vision loss worldwide. Currently the availability of automatic tools that allow the automatic detection and characterization of lesions is very limited. However, this situation is expected to change. In recent years, the availability of huge amount of data and the development of disruptive deep learning techniques are pushing artificial intelligence to another level. Related to DR and AMD, deep learning methods have been stated to be developed for automatic grading color fundus images (CFP) and optical coherence tomography imaging (OCT). The main goals of this group are the development, testing, and validation of cognitive computing methods applied to state-of-art imaging data

to be used in the screening and management of eye disease. The main advantages of these tools are the reduction of the time spent by an expert in the analysis of the raw data, especially for the OCT, as well as improve the reproducibility and the accuracy of the results. The availability of new drugs capable of vision restoration in these diseases offers important opportunities for teleophthalmology programs. Another related goal is the creation of a multimodal imaging dataset suitable for the training and validation of automatic methods. The main research line related to the development of novel methods is the development of novel hybrid algorithms that combine classical image processing methods with advanced machine learning methods such as deep learning.

RESEARCH CONTRACTS

Quantification of Retinal Microvasculature in Retinal Disease

Sponsor: Carl Zeiss Meditec

PROJECTS

ARTEYE - Artificial Intelligence-based Analysis using deep learning to identify and quantify eye disease

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

Financial support: Portugal 2020 - 02/SAICT/2017 - Project n° 032412

Biomarkers of Diabetic Retinopathy Progression

Artificial Intelligence Collaboration Project with Roche

SELECTED PUBLICATIONS

Ribeiro L, Oliveira CM, Neves C, Ramos JD, Ferreira H, Cunha-Vaz J, Screening for Diabetic Retinopathy in the Central Region of Portugal. Added Value of Automated Disease/No Disease? Grading. *Ophthalmologica*, 2014, vol. 233, pp. 96-103.

MULTIMODAL IMAGING OF DIABETIC RETINAL DISEASE

José Cunha-Vaz, MD, PhD

Other Research Personnel: Isabel Pires, Conceição Lobo, 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. Quantitative measurements based on optical coherence tomographic angiography (OCTA) may

have value in managing diabetic retinopathy (DR). Vessel density measured by OCTA provides a quantitative metric of capillary closure that correlates with severity of DR and may allow staging, diagnosis, and monitoring that do not require subjective evaluation of fundus images. Additionally, using SD-OCT, OCT leakage in eyes with diabetic retinopathy is possible to identify the location of the sites of lower reflectivity corresponding to abnormal retinal fluid. Multimodal imaging of the retina allows combined identification of the three main disease-pathways occurring in the diabetic retina: neurodegeneration, edema and capillary closure.

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 retinal vascular metrics using the OCT AngioPlex medical device.

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RESEARCH CONTRACTS

Quantification of Retinal Microvasculature in Retinal Disease

Sponsor: Carl Zeiss Meditec

SELECTED PUBLICATIONS

Durbin MK, An L, Shemonski DS, Soares M, Santos T, Lopes M, Neves C, Cunha-Vaz J, Quantification of Retinal Microvascular Density in Optical Coherence Tomography Angiography Images in Diabetic Retinopathy, JAMA Ophthalmol. 2017, vol. 135, N 4, pp 370-376.

Pappuru RKR, Ribeiro L, Lobo C, Alves D, Cunha-Vaz J.: Microaneurysm turnover is a predictor of diabetic retinopathy progression. Br J Ophthalmol. 2018 Apr 26. pii: [bjophthalmol-2018-311887](https://doi.org/10.1136/bjophthalmol-2018-311887). doi: [10.1136/bjophthalmol-2018-311887](https://doi.org/10.1136/bjophthalmol-2018-311887).

Soares M, Neves C, Pereira Marques I, Pires I, Schwartz

C, Ângelo Costa M, Santos T, Durbin M, Cunha-Vaz J: Comparison of Diabetic Retinopathy Classification using Fluorescein Angiography and Optical Coherence Tomography Angiography. Br J Ophthalmol 2017;101:62-68.

Cunha-Vaz J, Santos T, Alves D, Marques I, Neves C, Soares M, Lobo C: Agreement between OCT-Leakage and Fluorescein Angiography to identify sites of alteration of the Blood-Retinal Barrier in Diabetes. Ophthalmolgy Retina 2017;1:395-403.

Marques I, Mendes L, Santos T, Alves D, Lobo C, Cunha-Vaz J: Non-invasive multimodal imaging of DR. In Imaging Techniques edited by José Cunha-Vaz (Coimbra) and Adrian Koh (Singapore). ESASO Course Series 2017.

Marques I, Alves D, Santos T, Mendes L, Santos AR, Lobo C, Durbin M, Cunha-Vaz J: Multimodal imaging of the initial stages of diabetic retinopathy. Different disease pathways in different patients. Diabetes. 2018 Dec 6. pii: [db181077](https://doi.org/10.2337/db181077). doi: [10.2337/db18-1077](https://doi.org/10.2337/db18-1077).

MORPHOLOGICAL CHARACTERIZATION OF RESPONSE TO ANTI-VEGF TREATMENT IN DIABETIC MACULAR EDEMA

Ana Rita Santos, MSc

Other Research Personnel: João Figueira, Rufino Silva, Sílvia Simão, Torcato Santos



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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 growth 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. However very few methods exist to quantify and differentiate the intraretinal fluid, specially in an automatic and non-invasive way. Moreover,

studies that correlate the response to anti-VEGF treatment use only VA measurements, which appear to be not enough 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 as VA, multifocal ERG and microperimetry. 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. Our group has identified the potential of OCT-Leakage to identify poor responders to therapy by quantifying remaining fluid in the outer layers of the retina.

PROJECTS

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

ClinicalTrials.gov n° NCT01947881

SELECTED PUBLICATIONS

Santos AR, Gomes SC, Figueira J, Nunes S, Lobo CL, Cunha-Vaz JG. Degree of decrease in central retinal thickness predicts visual acuity response to intravitreal ranibizumab in diabetic macular edema. *Ophthalmologica*. 2014;231(1):16-22.

Santos AR, Ribeiro L, Bandello F, Lattanzio R, Egan C, Frydkjaer-Olsen U, Garcia-Arumi J, Gibson J, Grauslund J, Harding SP, Lang GE, Massin P, Midea E, Scanlon P, Aldington SJ, Simão S, Schwartz C, Ponsati B, Porta M, Costa MÁ, Hernández C, Cunha-Vaz J, Simó R; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR): Functional and Structural Findings of Neurodegeneration in Early Stages of Diabetic Retinopathy: Cross-sectional Analyses of Baseline Data of the EUROCONDOR Project. *Diabetes*. 2017 Sep;66(9):2503-2510. doi: 10.2337/db16-1453.

Santos AR, Schwartz C, Simão S, Costa M., Alves D, Ribeiro ML, Figueira J, Cunha-Vaz J: OCT Predictors for BCVA Response to Intravitreal anti-VEGF Treatment in Eyes with Diabetic Macular Edema. *Invest Ophthalmol Vis Sci*. 2016.

Santos AR, Costa MÁ, Schwartz C, Alves D, Figueira J, Silva R, Cunha-Vaz JG: Optical Coherence Tomography Baseline Predictors For Initial Best-Corrected Visual Acuity Response To Intravitreal Anti-Vascular Endothelial Growth Factor Treatment In Eyes With Diabetic Macular Edema: The Chartres Study. *Retina*. 2018 Jun;38(6):1110-1119.

Santos AR, Alves D, Santos T, Figueira J, Silva R, Cunha-Vaz J: Measurements of Retinal Fluid by OCT Leakage in Diabetic Macular Edema. A Biomarker of Visual Acuity Response to Treatment. *Retina*. 2019 Jan;39(1):52-60. doi: 10.1097/IAE.0000000000001905.

3.2 CLINICAL RESEARCH

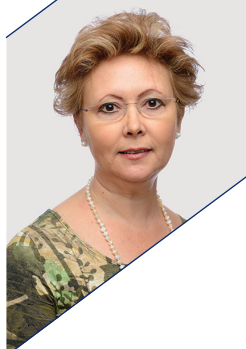
Clinical patient-oriented research involves characterizing disease progression and testing new discoveries by carrying out carefully controlled research studies in patients, i. e., clinical trials. This includes testing not only new drugs, but also new methods, devices, imaging and surgical procedures as well as well-designed prospective, observational, longitudinal studies. Clinical research is a fundamental stage 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 world-wide with frequent international publications and our translational research programme focused on the development of new imaging technologies is expected to contribute to improved management of these diseases.

Through EVICR.net – European Vision Institute Clinical Research Network, AIBILI is also involved in multinational clinical research in other eye diseases.

Our research interest has been particularly focused on precision medicine, through the 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 will 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 the focus of our research group.

BIOMARKERS OF PROGRESSION OF DIABETIC RETINOPATHY



Luisa Ribeiro, MD, PhD

Other Research Personnel: Ana Rita Santos, Conceição Lobo, Inês Marques, Isabel Pires, José Cunha-Vaz, Sandrina Nunes, Sílvia Simão

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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. 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).

Furthermore, we found that these phenotypes are determined by three different disease pathways: neurodegeneration, edema and capillary closure. We have found that only capillary closure and microvascular alterations associated with Phenotype C correlate with disease severity.

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 n° 2012-001200-38

ClinicalTrials.gov n° NCT01726075

Financial Support: European Union 7th Framework Programme – Call Health 2011 - Project n° 278040-2

C-TRACER Project n° 1 – Biomarkers of Diabetic Retinopathy Progression

ClinicalTrials.gov n° NCT01607190

CORDIS - Characterization of retinal vascular disease in eyes with mild to moderate Nonproliferative diabetic retinopathy in Diabetes type 2, using novel non-invasive imaging methods, in a longitudinal and prospective clinical study with 2 years of duration

Financial support: Portugal 2020 - 02/SAICT/2017 – Project n° 030375

SELECTED PUBLICATIONS

Santos AR, Ribeiro L, Bandello F, Lattanzio R, Egan C, Frydkjaer-Olsen U, García-Arumí J, Gibson J, Grauslund J, Harding S P, Lang GE, Massin P, Midena E, Scanlon P, Aldington SJ, Simão S, Schwartz C, Ponsati B, Porta M, Costa MA, Hernández C, Cunha-Vaz J and Simó R: Functional and Structural Findings of Neurodegeneration in Early Stages of Diabetic Retinopathy: Cross-sectional Analyses of Baseline Data of the EUROCONDOR Project. *Diabetes* 2017 Sep;66 (9):2503-2510.

Ribeiro L, Pappuru R, Lobo C, Alves D, Cunha-Vaz J: Phenotypes of mild nonproliferative diabetic retinopathy with different risks for development of macular edema (C-TRACER study). *Ophthalmic Res.* DOI: 10.1159/000484666.

Lobo C, Pires I, Alves D, Pappuru R, Ribeiro L, Cunha-Vaz J.: Subclinical Macular Edema as a Predictor of Progression to Central-Involved Macular Edema in Type 2 Diabetes. *Ophthalmic Res.* 2018; 60(1):18-22.

DIABETIC RETINOPATHY PROGRESSION TO VISION THREATENING COMPLICATIONS

Inês Marques, MD

Other Research Personnel: Ana Rita Santos, Catarina Neves, Conceição Lobo, Dalila Alves, João Figueira, José Cunha-Vaz, Luís Mendes, Luísa Ribeiro, Marta Lopes, Sílvia Simão, Torcato Santos



Progression of Diabetic Retinopathy (DR) has been classified according to the ETDRS grading. This classification, although appropriate for late stages of DR, does not help in grading initial DR stages. Progression of DR does not occur at the same rate in all patients, some of them never develop vision loss even after many years of disease, whether other patients suffer from vision threatening complications early during the course of the disease. Our group was the first to identify different phenotypes with different risk of progression to sight threatening complications. A prospective interventional longitudinal clinical study is in progress to characterize both functionally and morphologically initial DR stages.

Epidemiologic characterization of a pool of 200 patients is being performed in this longitudinal study, with a mean of 7 years of follow up. Structural OCT and OCT-Angiography imaging technology, 7 field colour fundus photography (CFP) are used for DR characterization analysing different variables, namely capillary perfusion, FAZ metrics, presence of edema and retinal neurodegeneration. This study will contribute to test the concept of different phenotypes of diabetic retinopathy progression and move forward in the quest to develop strategies for personalized management of diabetic retinopathy.

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INVESTIGATOR INITIATED RESEARCH

PROGRESS – Progression of Diabetic Retinopathy.

Identification of signs and surrogate outcomes

ClinicalTrials.gov n° NCT03010397

SELECTED PUBLICATIONS

Marques I, Mendes L, Santos T, Alves D, Lobo C, Cunha-Vaz J: Non-invasive multimodal imaging of DR. In *Imaging Techniques* edited by José Cunha-Vaz (Coimbra) and Adrian Koh (Singapore). ESASO Course Series 2017.

Marques I, Alves D, Santos T, Mendes L, Santos AR, Lobo C, Durbin M, Cunha-Vaz J: Multimodal imaging of the initial stages of diabetic retinopathy. Different disease pathways in different patients. *Diabetes*. 2018 Dec 6. pii: db181077. doi: 10.2337/db18-1077.



EPIDEMIOLOGICAL CHARACTERIZATION OF AMD. CHARACTERIZATION OF PROGRESSION OF AMD FROM INTERMEDIATE TO LATE FORMS OF AMD

Maria da Luz Cachulo, MD, PhD

Other Research Personnel: António Vieira, Conceição Lobo, Dalila Alves, Inês Lains, João Figueira, José Cunha-Vaz, Luisa Ribeiro, Rufino Silva, Sandrina Nunes, Sílvia Simão, Victor Rodrigues

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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 funduscopy 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 n° NCT01715870

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 n° NCT02748824

SELECTED PUBLICATIONS

Cachulo ML, Lobo C, Figueira J, Ribeiro ML, Lains I, Vieira A, Nunes S, Costa M, Simão S, Rodrigues V, Vilhena N, Cunha-Vaz J, Silva R: Prevalence of Age-Related Macular Degeneration in Portugal: The Coimbra Eye Study - Report 1. *Ophthalmologica* 2015;233(3-4):119-127.

Cachulo ML, Lobo C, Figueira J, Ribeiro L, Lains I, Nunes S, Costa MA, Simão S, Rodrigues V, Cunha-Vaz J, Silva R: Age-related Macular Degeneration in Portugal: prevalence and risk factors in a coastal and an inland town. The Coimbra Eye Study – Report 2. *Acta Ophthalmol.* 2016 Sep;94(6):e442-53.

Kaszubski PA, Ben Ami T, Saade C, Nabati C, Kumar V, Santos AR, Silva R, Cachulo ML, Cunha-Vaz JG, Smith RT: Changes in Reticular Pseudodrusen Area in eyes that Progressed from early to late Age-related Macular Degeneration. *Int Ophthalmol.* DOI 10.1007/s10792-017-0485-7.

Tsikata E, Lains I, Gil J, Marques M, Brown K, Mesquita T, Melo P, Cachulo ML, Kim I, Demetrios V, Murta J, Miller J, Silva R, Miller Chen, Husain D: Automated Brightness and Contrast Adjustment of Color Fundus Photographs for the Grading of Age- Related Macular Degeneration. *Translational vision science & technology.* 2017 Mar 13;6(2):3.

EVALUATION OF NOVEL TREATMENT OPTIONS FOR COMPLICATIONS OF DIABETIC RETINOPATHY

João Figueira, MD, PhD

Other Research Personnel: Ana Rita Santos, Conceição Lobo, Dalila Alves, Isabel Pires, José Cunha-Vaz, Luísa Ribeiro, Rufino Silva, Sandrina Nunes



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). 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 and develop biomarkers of response to treatment.

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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 n° 2013-003640-23

ClinicalTrials.gov n° NCT01941329

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 therapies with or without intravitreal corticosteroid therapy

EudraCT n° 2014-003491-23

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

ClinicalTrials.gov n° NCT01947881

SELECTED PUBLICATIONS

Wang JC, Lains I, Providência J, Armstrong GW, Santos AR, Gil P, Talcott KE, Marques JH, Figueira J, Vavvas DG, Kim IK, Miller JW, Husain D, Silva R, Miller JB: Diabetic Choroidopathy: Choroidal Vascular Density and Volume in Diabetic Retinopathy with Swept-Source Optical Coherence Tomography. *Am J Ophthalmol.* 2017 Oct 5. pii: S0002-9394(17)30422-1.

Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, Varano M, Sivaprasad S, Eleftheriadis H, Menon G, Amaro M, Ayello Scheer S, Creuzot-Garcher C, Nascimento J, Alves D, Nunes S, Lobo C, Cunha-Vaz J; For the EVICR.net Study Group: Ranibizumab Plus Panretinal Photocoagulation versus Panretinal Photocoagulation Alone for High-Risk Proliferative Diabetic Retinopathy (PROTEUS Study). *Ophthalmology.* 2018 May; 125(5):691-700. doi: 10.1016/j.ophtha.2017.12.008.

VALIDATION OF OUTCOMES AND TESTING TREATMENTS FOR SIGHT THREATENING AGE-RELATED MACULAR DEGENERATION



Rufino Silva, MD, PhD

Other Research Personnel: Ana Rita Santos, Conceição Lobo, Dalila Alves, Inês Lains, João Figueira, José Cunha-Vaz, Maria Luz Cachulo, Sandrina Nunes, Sílvia Simão

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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.

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 group participates in MACUSTAR, an IMI2 project, with main objective to develop novel clinical endpoints for clinical trials with a regulatory and patient access intention in patients with intermediate Age-Related Macular Degeneration (iAMD). Additional objectives are to characterize visual impairment in iAMD and its progression, as well as, identify risk factors for progression to late stage AMD.

INVESTIGATOR INITIATED RESEARCH

Metabolomics, Genetics and Environment – a novel integrative approach to Age-Related Macular Degeneration (INO654)

Financial Support: FCT – Foundation for Science and Technology, Portugal – HMSP-ICJ/0006/2013

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 n° 2015-001368-20
ClinicalTrials.gov n° NCT02495181

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 n° NCT02748824

MACUSTAR – Intermediate AMD: Development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention

ClinicalTrials.gov n° NCT03349801
Financial Support: European Union and EFPIA - Innovative Medicines Initiative 2 Joint Undertaking - Grant Agreement n° 116076

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.

Cachulo ML, Lobo C, Figueira J, Ribeiro L, Lains I, Nunes S, Costa MA, Simão S, Rodrigues V, Cunha-Vaz J, Silva R: Age-related Macular Degeneration in Portugal: prevalence and risk factors in a coastal and an inland town. The Coimbra Eye Study – Report 2. *Acta Ophthalmol.* 2016 Sep;94(6):e442-53.

Silva, R; Berta, A; Larsen, M; Macfadden, W; Feller, C; Monés, J; Group, TREND S. 2018. "Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration: Results with Ranibizumab from the TREND Study. *Ophthalmology* 125, 1: 57 - 65. doi: 10.1016/j.ophtha.2017.07.014.

Lains, I; Kelly, RS; Miller, JB; Silva, R; Vavvas, DG; Kim, IK; Murta, JN; Lasky-Su, J; Miller, JW; Husain, D: Human Plasma Metabolomics Study across All Stages of Age-Related Macular Degeneration Identifies Potential Lipid Biomarkers. *Ophthalmology*. doi: 10.1016/j.ophtha.2017.08.008.

3.3 HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH

The demands on health services and the challenges of drug development, in the light of increased aging of population, changing patterns of disease and increased costs of medicines, creates the need for research on the effectiveness, the

safety and the economics of drugs R&D and reimbursement. Research in CHAD is, through several interconnected ongoing projects, aimed at real world outcomes, safety, economics and market access of drugs.

DRUSER.net – DRUG SAFETY AND EFFECTIVENESS RESEARCH NETWORK

Diogo Mendes, PhD, **Francisco Batel Marques**, PhD

Other Research Personnel: Ana Penedones, Carlos Alves, Alcina Ponte, Alexandra Escada, Ana Filipa Fernandes, Ana Isabel Fonte, Teresa Catré, Ângela Neves, Angelina Martins, António Rodrigues, Emília Faria, Graça Rigueiro, Joana Matos da Silva, Márcia Loureiro, Maria Francisca Almeida, Maria Viegas do Nascimento, Michele Martins, Natália António, Rui Sousa Silva, Susana Cavadas

The DruSER.Net is a research network of Hospitals and Primary Healthcare Centers, which is coordinated by the Pharmacovigilance Unit of Coimbra.

The main objective of the DruSER.Net is to investigate and monitor safety and effectiveness

of medicines used in routine clinical practice and therefore contributing for patient safety through the conduction of research projects using real-world data.

SELECTED PUBLICATIONS

Mendes D, Alves C, Loureiro M, Fonte A, Batel-Marques F. Drug-induced hypersensitivity: A 5-year retrospective study in a hospital electronic health records database. *J Clin Pharm Ther.* 2019 Feb;44(1):54-61. doi: 10.1111/jcpt.12752.



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SYSTEMATIC REVIEW: ROLE IN DRUG SAFETY AND CLINICAL EFFECTIVENESS ASSESSMENT

Ana Penedones, MSc

Other Research Personnel: Carlos Alves, Francisco Batel Marques

The aim of this research is to understand the actual role of systematic reviews in drugs' safety assessment and to compare the methodologies of the two major orientations to plan and conduct

systematic reviews. It will be analysed the combination of several types of studies (from experimental data to case reports) when performing a systematic review of drug safety.

SELECTED PUBLICATIONS

Penedones A, Batel Marques F. Methodologic Assessment of the Systematic Reviews of Ophthalmic Adverse Drug Reactions Published in Ophthalmology Journals: A Systematic Review. *Ophthalmic Res.* 2018;60(2):55-68.



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NETWORK META-ANALYSIS

Carlos Alves, PhD

Other Research Personnel: Diogo Mendes, Francisco Batel Marques

The aim of this research is to assess whether it is possible to produce reliable risk estimates from a network meta-analysis including simultaneously clinical trials and observational studies in order

to establish comparisons between treatments which would not be possible to compare based exclusively on data from experimental studies.

SELECTED PUBLICATIONS

Alves, C., Mendes, D., Batel Marques, F. (2018) "Statins and risk of cataracts: a systematic review and meta-analysis of observational studies." *Cardiovasc Ther.* e12480. 10.1111/1755-5922.12480. Epub Ahead of Print.

Alves, C., Ribeiro, I., Penedones, A., Mendes, D., Batel Marques, F. (2017) "Risk of Ophthalmic Adverse Effects in Patients Treated with MEK Inhibitors: A Systematic Review and Meta-Analysis." *Ophthalmic Res.* 57(1):60-69.



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ECONOMIC EVALUATION OF OPHTHALMIC MEDICINES: DOES THE RESULTS ESTIMATED BASED ON PRE-MARKETING EVIDENCE CORRELATES WITH CLINICAL PRACTICE?

Inês Ribeiro, MSc

Other Research Personnel: Carlos Alves, Dalila Alves, Francisco Batel Marques

The main objective of this project is to clarify the role of pharmacoeconomic studies as a tool to inform policy decision making of ophthalmic drugs. The research will also identify, characterize and assess the methodological quality of phar-

macoeconomic studies of ophthalmic drugs, and it will evaluate if the results of economic studies reflect the findings from real-world clinical practice evidence.



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SELECTED PUBLICATIONS

Ribeiro I, Batel Marques F, Alves D, Alves C. A systematic review of the methodological quality of economic studies evaluating ophthalmic drugs. *Expert Rev Pharmacoecon Outcomes Res.* 2019 Feb 5. doi:10.1080/14737167.2019.1579646.

COIMBRA PHARMACOVIGILANCE REGIONAL CENTRE

Francisco Batel Marques, PhD

Other Research Personnel: Carlos Fontes Ribeiro, Diogo Mendes, Ana Penedones, Ricardo Correia de Matos, Alexandra Escada, Natália António, Margarida Caramona, Tice Macedo

The main aim is to validate the post-marketing adverse drug reactions reported to the Coimbra Regional Unit of the Portuguese Pharmacovigi-

lance System, by assessing causality, seriousness and previous knowledge. Different techniques for safety signals generation are being tested and applied.



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SELECTED PUBLICATIONS

Batel Marques F, Penedones A, Mendes D, Alves C. Outcomes from the first 6 years of operation of the Central Portugal Pharmacovigilance Unit. *J Patient Saf.* 2016. doi:10.1097/PTS.0000000000000273.

Batel Marques F, Mendes D, Alves C, Penedones A, Dias P, Martins A, Santiago LM, Fontes-Ribeiro C, Caramona M, Macedo T. Pharmacovigilance in Portugal: Activity of the Central Pharmacovigilance Unit. *Acta Med Port* 2015 Mar-Apr; 28(2):222-232.

Mendes D, Alves C, Batel Marques F. Nurses' spontaneous reporting of adverse drug reactions: expert review of routine reports. *Journal of Nursing Management* 2012 DOI: 10.1111/jonm.12003.

3.4 INTERNATIONAL NETWORKING

EVICR.net – EUROPEAN VISION INSTITUTE CLINICAL RESEARCH NETWORK



EVICR.net has a Coordinating Centre, AIBILI, who is responsible for the management of the Network, coordination of multinational clinical research studies as well as developing training activities. The EVICR.net is a network of European Ophthalmological Clinical Research Centres, dedicated to perform multinational clinical research in ophthalmology with the highest standards of quality, following the European and International Directives for Clinical Research according to harmonized SOPs.

EVICR.net strengthens 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, by performing multinational clinical research.

It is a platform for ophthalmology multinational clinical research in Europe and a structure to support multinational Investigator-Initiated Research (IIR).

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.

EVICR.net is also a resource for Industry in the development of new drugs and medical devices in ophthalmology.

In order to become a member of EVICR.net, each Clinical Research Centre must apply to the Network and fulfil basic requirements such as dedicated space to perform clinical studies, qualified and experienced personnel, experience of multinational clinical research and to agree to implement organizational Standard Operating Procedures (SOPs) according to ICH GCP Guidelines.

Once a member, the Clinical Site adopts/harmonises EVICR.net SOPs with the help of the Coordinating Centre in order to become a certified Clinical Site of Excellence of EVICR.net.

Scientifically it is organized by ophthalmology subspecialty Expert Committees namely: Age-Related Macular Degeneration; Retinal Dystrophies; Diabetic Retinopathy and Vascular Diseases; Glaucoma; Anterior Segment; and Ocular Surface, Inflammation, Dry-Eye & Allergies. It also has Transversal Sections in Rare Diseases, Medical Devices and Reading Centres.

At present, EVICR.net has 101 Clinical Ophthalmological Centres members from 15 European countries.

MULTINATIONAL CLINICAL RESEARCH STUDIES (2010-2018)

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 2018 there were six ongoing multinational clinical research studies of which 2 are European Union funded projects.

MULTINATIONAL CLINICAL RESEARCH STUDIES UNDER EVICR.net

Number of Multinational Clinical Research Studies



ONGOING PROJECTS AND ACTIVITIES

- Age-Related Macular Degeneration
 - ATLANTIC (IIR, Industry grant)
 - MACUSTAR (IIR, EU funded)
 - MADEOS (External-sponsored)
- Diabetic Retinopathy
 - EUROCONDOR (IIR, EU funded)
 - IRIS (Industry-sponsored)
- Anterior Segment
 - REDCAKE (IIR, Flemish grant)

EDUCATIONAL PROGRAMME

The EVICR.net has developed a continual training and educational programme with webinars on ophthalmology clinical research. The Educational Programme is organized in modules each with three webinars of one hour. Currently the following modules are available:

Module	Multinational Clinical Research Organization	Diabetic Macular Edema Understanding and Management	Diabetic Macular Edema, Imaging, Biomarkers and Anti-VEGF Management	Glaucoma Risk Factors and Management	Dry Eye Diagnosis and Treatment
WEBINARS	WEBINAR #1	WEBINAR #4		WEBINAR #8	WEBINAR #11
	How to setup a clinical research study	DME definition, classification and imaging		Landmark clinical trials in glaucoma	Dry eye syndrome: signs and symptoms
	<i>S. Nunes</i>	<i>J. Cunha-Vaz</i>		<i>E. Normando</i>	<i>J. Gil</i>
	WEBINAR #2	WEBINAR #5		WEBINAR #9	WEBINAR #12
	Clinical research organization	Predicting progression and treatment response		Risk factors in glaucoma	Diagnosis in dry eye syndrome
	<i>L. Ribeiro</i>	<i>J. Cunha-Vaz</i>		<i>F. Cordeiro</i>	<i>J. Gil</i>
	WEBINAR #3	WEBINAR #6	WEBINAR #7	WEBINAR #10	WEBINAR #13
	SOPs – quality and certification	Treatment of DME	Anti-VEGF treatment of DME	Glaucoma – Who to treat and when	Treatment of dry eye syndrome
	<i>C. Martinho / R. Fernandes</i>	<i>J. Cunha-Vaz</i>	<i>J. Cunha-Vaz</i>	<i>S. Gandolfi</i>	<i>E. Costa</i>

More information: www.evicr.net

C-TRACER – CHAMPALIMAUD TRANSLATIONAL CENTRE FOR EYE RESEARCH



Champalimaud Foundation

AIBILI is recognized as a C-TRACER – Champalimaud Translational Centre for Eye Research by the Champalimaud Foundation for its activities in translational eye research.

More information:

<http://first.fchampalimaud.org/en/champalimaud-research/c-tracer/>

This Network is of great relevance 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.

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

ECRIN – EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK



ECRIN-ERIC 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

More information:

<https://www.ecrin.org/>

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 multinational clinical research, particularly by providing scientific and medical expertise, access to patients and research capacity.

EATRIS – EUROPEAN INFRASTRUCTURE FOR TRANSLATIONAL MEDICINE

eatris

European infrastructure
for translational medicine

EATRIS 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

More information:
<https://eatris.eu/>

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.

AIBILI, with capacities for the Biomarkers and Imaging platforms, has been accepted as a member of the EATRIS Portuguese-Hub, led by INFARMED, and is in the process of integrating this European Network.

ERN-EYE – EUROPEAN REFERENCE NETWORK ON RARE EYE DISEASES



European
Reference
Networks

Eye Diseases (ERN-EYE)

The European Reference Network (ERN) on Rare Eye Diseases (ERN-EYE) is led by Prof. Hélène Dollfus (Strasbourg, France) and is composed of 29 healthcare providers from 13 European countries. ERN-EYE is organized in thematic groups:

More information:
<https://www.ern-eye.eu/>

Retinal; Neuro-ophthalmology; Paediatric Ophthalmology and Anterior Segment.

EVICR.net is a Member of the Scientific, Medical and Ethical Advisory Board (SMEAB). EVICR.net collaborates with ERN-EYE through the Rare Diseases Transversal Section and with experience in Quality Systems and certification of Clinical Sites as well as by providing overall management and logistical support needed in multinational investigator initiated studies in rare eye diseases.

4

RESEARCH CENTRES

4C – COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH



Director: **Sandrina Nunes**, PhD

Staff: Ana Rita Oliveira, Beatriz Melício, Cecília Martinho, Conceição Lobo, Dalila Alves, Daniel Fernandes, Daniel Silva, Isidoro Videira, Joana Tavares, Liliana Carvalho, Joaquim Murta, José Cunha-Vaz, Maria Viegas Nascimento, Mariana Martinho, Pier Basile, Rita Fernandes, Rufino Silva, Sónia Simões, 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 (by AIBILI Data Centre)
- Clinical Sites Feasibility Assessment
- Standard Operational Procedures Development
- Regulatory Affairs (Submission and Reports)
- Contracts Negotiation
- Study Management
- Monitoring
- Data Management
- Pharmacovigilance (by AIBILI CHAD)
- Biostatistics
- Final Study Report
- Medical Writing
- Quality Assurance

Nº OF PROJECT AT 4C (2016-2018)

Year	Coordination of Clinical Trials (nº)		Other	Total
	Investigator Initiated	Industry Sponsored		
2016	23	2	2	27
2017	22	2	4	28
2018	16	2	3	21

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RELEVANT PUBLICATIONS

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- Finger RP, Schmitz-Valckenberg S, Schmid M, Rubin GS, Dunbar H, Tufail A, Crabb DP, Binns A, Sánchez CI, Margaron P, Normand G, Durbin MK, Luhmann UFO, Zamiri P, Cunha-Vaz J, Asmus F, Holz FG; on behalf of the MACUSTAR consortium: MACUSTAR: Development and clinical validation of functional, structural and patient-reported endpoints in intermediate age-related macular degeneration. *Ophthalmologica* 2018. Aug 28:1-12.
- Nunes S, Alves D, Barreto P, Raimundo M, da Luz Cachulo M, Farinha C, Lains I, Rodrigues J, Almeida C, Ribeiro L, Figueira J, Santos L, Silva R: Adherence to a Mediterranean diet and its association with age-related macular degeneration. *The Coimbra Eye Study-Report 4. Nutrition*. 2018 Jul - Aug;51-52:6-12.
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CEC – CLINICAL TRIAL CENTRE



Director: **Luisa Ribeiro**, MD, PhD

Staff: Aida Vitorino, Ana Maria Nunes, Ana Rita Santos, Andreia Rosa, Catarina Eloy, Céu Simões, Conceição Lobo, Eugénia Cardoso, Filipe Martins, Inês Marques, Isabel Pires, João Figueira, José Cunha-Vaz, Maria da Luz Cachulo, Marta Lopes, Patrícia Barreto, Patrícia Martins Oliveira, Paulo Marques, Pedro Faria, Renata Castanheira, Ricardo Araújo, Rufino Silva, Sandra Pardal, Sílvia Simão

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The Clinical Trial Centre (CEC) performs randomized clinical trials with special emphasis on ophthalmology. CEC has dedicated facilities and updated ophthalmological equipment.

Clinical patient-oriented research involves characterizing disease progression and testing new discoveries by carrying out carefully controlled research studies 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.

Our research is focused in age-related eye diseases with special emphasis on diabetic retinopathy and age-related macular degeneration.

CEC is certified as Clinical Site of Excellence by the EVICR.net - European Vision Institute Clinical Research Network (Clinical Site nº 1), that is a clinical trial centre in ophthalmology that complies with ICH GCP Guidelines with written SOPs, has the necessary equipment and personnel to perform clinical trials and has proven expertise and scientific publications in this area.

Nº OF INVESTIGATOR INITIATED AND INDUSTRY SPONSORED STUDIES PERFORMED AT CEC (2016-2018)

Year	Nº OF CLINICAL STUDIES		
	Investigator Initiated	Industry Sponsored	Total
2016	7	25	32
2017	6	23	29
2018	6	15	21

RESEARCH FOCUS (SEE PAGES 18 – 22)

- Biomarkers of progression of Diabetic Retinopathy
- Vision Threatening Complications in Diabetic Retinopathy Progression
- Epidemiological characterization of AMD. Characterization of progression of AMD from intermediate to late forms of AMD
- Evaluation of novel treatment options for complications of Diabetic Retinopathy
- Validation Outcomes and testing treatments for sight threatening Age-Related Macular Degeneration

INDUSTRY SPONSORED CLINICAL TRIALS

DIABETIC MACULAR EDEMA

1. An Open Label, Registry Study of the Safety of ILUVIEN® 190 Micrograms Intravitreal Implant in Applicator (IRISS) ClinicalTrials.gov n° NCT01998412

2. 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 86-5321/17613)

EudraCT n° 2014-004938-25

3. A phase III, multicentre, randomized, double-masked, active comparator-controlled study to evaluate the efficacy and safety of RO6867461 in patients with diabetic macular edema (Rhine)

EudraCT n° 2017-005105-12

4. A two-year, three-arm, randomized, double-masked, multicentre, phase III study assessing the efficacy and safety of brolocizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL)

EudraCT n° 2017-004742-23

AGE-RELATED MACULAR DEGENERATION

5. 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 n° 2014-004886-26

6. 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) (AZURE)

EudraCT n° 2012-003763-22

GLAUCOMA

7. Long-Term Surveillance Study of Latanoprost to Monitor Hyperpigmentation changes in the eye in Pediatric Populations (A6111144)

DRY EYE

8. A Phase II, Multicenter, Randomized, Double-Masked, 4 Parallel Arms, Controlled 6-Month Trial Designed to Evaluate the Safety and Efficacy of PAD Ciclosporin (CsA 0.06% and 0.03%) Ophthalmic Dispersion 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 - PADCiclo)

EudraCT n° 2015-000937-54

UVEITIS

9. A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis (M11-327)

EudraCT n° 2009-016196-29

NEUROLOGICAL DISORDERS

10. A multicenter, randomized, double-blind, parallel-group, 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

11. 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 - Open-Label ESL Extension - (BIA-2093-311)

EudraCT n° 2015-001243-36

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

EudraCT n° 2015-002500-91

13. 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

14. A randomized, double-blind, placebo-controlled and delayed-start study of LY3314814 in Mild Alzheimer's Disease Dementia (DAYBREAK - I8D-MC-AZET)

EudraCT n° 2015-005625-39

CANCER

15. A randomized, open label, multicenter Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.

EudraCT n° 2016-004340-11

CORC – COIMBRA OPHTHALMOLOGY READING CENTRE



Director: **Conceição Lobo**, MD, PhD

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The Coimbra Ophthalmology Reading Centre (CORC) focus its activities in grading retinal diseases on fundus images and OCT images of the retina, as well as functional evaluations of the retina using mfERG and visual fields.

It serves as central Reading Centre for a series of multinational/multicentric clinical studies, mainly in Diabetic Retinopathy (DR) and Age-related Macular Degeneration (AMD). 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 (<https://studies.corc.pt/>). 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), RETIsystem (Roland Consult), Topcon OCT (Topcon Corporation), etc.

For research, CORC has novel in-house developed software to assess microaneurysm turnover in DR (RetmarkerDR®), classify and quantify AMD lesions (RetmarkerAMD) and perform segmentation of the retinal layers on OCT.

MAIN SERVICES

- Development of study-specific Acquisition Protocols
- Technicians training and certification
- Equipment certification
- Web-based platform for exams' submission
- Development of study-specific Grading Protocols
- Grading of ophthalmic exams (retinal fundus images, OCT, mfERG and visual fields) by trained graders for characterization and quantification of ophthalmic disease
- Eligibility review services
- Provides data backup procedures and a disaster recovery plan
- Provides secure long-term archiving of study materials, both digital and hardcopy

Nº OF PROJECTS AT CORC (2016-2018)

Year	Nº of Projects			
	Diabetic Retinopathy	AMD	Retinitis Pigmentosa	Total
2016	11	5	-	16
2017	11	3	1	15
2018	10	7	1	18

RELEVANT PUBLICATIONS

Soares M, Neves C, Marques IP, Pires I, Schwartz C, Costa MÃ, Santos T, Durbin M, Cunha-Vaz J. Comparison of diabetic retinopathy classification using fluorescein angiography and optical coherence tomography angiography. *Br J Ophthalmol*. 2017 Jan;101(1):62-68. doi: 10.1136/bjophthalmol-2016-309424.

Simão S, Costa MÃ, Sun JK, Cunha-Vaz J, Simó R; European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR). Development of a Normative Database for Multifocal Electroretinography in the Context of a Multicenter Clinical Trial. *Ophthalmic Res*. 2017;57(2):107-117. doi: 10.1159/000450958.

Figueira J, Fletcher E, Massin P, Silva R, Bandello F, Midena E, Varano M, Sivaprasad S, Eleftheriadis H, Menon G, Amaro M, Ayello Scheer S, Creuzot-Garcher C, Nascimento J, Alves D, Nunes S, Lobo C, Cunha-Vaz J; EVICR.net Study Group. Ranibizumab Plus Panretinal Photocoagulation versus Panretinal Photocoagulation Alone for High-Risk Proliferative Diabetic Retinopathy (PROTEUS Study). *Ophthalmology*. 2018 May;125(5):691-700. doi: 10.1016/j.ophtha.2017.12.008.

Martins A, Farinha C, Raimundo M, Lopes M, Santos AR, Melo P, Marques M, Marques JP, Barreto P, Cachulo ML, Neves C, Cunha-Vaz J, Silva R. Multimodal Evaluation of the Fellow Eye of Patients with Retinal Angiomatous Proliferation. *Ophthalmic Res*. 2018;59(2):88-97. doi: 10.1159/000481262.

Farinha C, Cachulo ML, Alves D, Pires I, Marques JP, Barreto P, Nunes S, Costa J, Martins A, Sobral I, Láins I, Figueira J, Ribeiro L, Cunha-Vaz J, Silva R. Incidence of Age-Related Macular Degeneration in the Central Region of Portugal: The Coimbra Eye Study – Report 5. *Ophthalmic Res*. [Accepted for publication Dec/2018].

CNTM – CENTRE FOR NEW TECHNOLOGIES IN MEDICINE

Director: **José Cunha-Vaz**, MD, PhD

Staff: Luis Mendes, Rufino Silva, Telmo Miranda, Torcato Santos



Contacts

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The Centre for New Technologies in Medicine (CNTM) develops new medical diagnostic techniques with special emphasis on the area of eye fundus imaging.

The eye offers unique opportunities to obtain in a non-invasive manner information on the body, in general and of the retina and brain in particular. It is, in fact, a window to the body. We are particularly interested in methodologies that allow repeated observations and measurements

in order to identify early alterations that may allow timely therapeutical interventions, e.g., precision medicine.

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, using a novel patented algorithm, the OCT-Leakage.

RESEARCH FOCUS (SEE PAGES 13 – 16)

- OCT-Leakage. Layer by layer fluid analysis of the retina
- Artificial intelligence for characterization of retinal biomarkers
- Multimodal imaging of diabetic retinal disease
- Morphological characterization of response to anti-VEGF treatment in Diabetic Macular Edema

Nº OF PROJECTS AT CNTM (2016-2018)

Year	Nº of Projects
2016	10
2017	11
2018	10

CHAD – CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH

Director: [Francisco Batel Marques](#), PhD

Staff: Ana Penedones, Carlos Alves, Carlos Fontes Ribeiro, Daniel Fernandes, Diogo Mendes, Inês Ribeiro, Óscar Lourenço, Maria Viegas Nascimento, Tice Macedo



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).

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MAIN ACTIVITIES

1. Health Technology Assessment, pricing and reimbursement (medicines and medical devices)
2. Primary research (Patient-based outcomes and real world effectiveness studies)
3. Secondary research (Literature searching and evaluation, Systematic reviews and meta-analysis, Indirect/mixed treatment comparisons according to methodological guidelines, Comparative effectiveness studies, and Expert reports)
4. Pharmacovigilance and Risk Management services

Nº OF PROJECTS AT CHAD (2016-2018)

Year	Nº of Projects		
	Market Access	Drug Safety	Total
2016	21	7	28
2017	22	7	29
2018	21	7	28

RELEVANT PUBLICATIONS

Alves C, Mendes D, Batel Marques F. Statins and risk of cataracts: a systematic review and meta-analysis of observational studies. *Cardiovasc Ther.* 2018; **12**:480. doi:10.1111/1755-5922.12480.

Mendes D, Alves C, Loureiro M, Fonte A, Batel Marques F. Drug-induced hypersensitivity: a 5-year retrospective study in a hospital electronic health records database. *J Clin Pharm Ther.* 2019 Feb; **44**(1):54-61. doi: 10.1111/jcpt.12752.

Penedones A, Batel-Marques F. Methodologic assessment of the systematic reviews of ophthalmic adverse drug reactions published in *Ophthalmology* journals: a systematic review *Ophthalmic Res.* 2018; **60**(2):55-68. doi: 10.1159/000489932.

Mendes D, Alves C, Batel Marques F. Number needed to treat (NNT) in clinical literature: an appraisal *BMC Medicine* 2017; **15**:112. DOI: 10.1186/s12916-017-0875-8.

Alves C, Ribeiro I, Penedones A, Mendes D, Batel Marques F. Risk of Ophthalmic Adverse Effects in Patients Treated with MEK Inhibitors: A Systematic Review and Meta-Analysis *Ophthalmic Res.* 2017; **57**(1):60-69.

DC – DATA CENTRE

Director: **Carlos Domingues**, BSc

Staff: Celina Canguero, Dalila Alves, Hugo Morgado, José Monteiro, Marta Ventura, Patrícia Silva, Telmo Miranda, Torcato Santos



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 and that power is always 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 Data Centre asset-protection.

Presently Information Technology Unit maintains more than 30 servers, either virtual or physical supported on different operating systems and technologies. 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 GAMP5 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 Data Centre 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 studies.

Contacts

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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
- EVICR.net webinar platform

Nº OF PROJECTS AT DC (2016-2018)

Year	Nº of Projects/ Services
2016	11
2017	15
2018	16

5

ORGANIZATIONAL UNITS

ADMINISTRATION

CEO: Cecília Martinho

Staff: Laura Seco, Mara Miraldo, Marco Santos, Marta Ventura, Paulo Barros, Tânia Melro



The Administrative Services is responsible for the management of AIBILI and to perform all the necessary 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.

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QUALITY MANAGEMENT UNIT (QMU)

Staff: Cecilia 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.

The Quality Management System (QMS) has 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 9001:2015, ICH-GCP Guidelines, requirements for Certification of ECRIN Data Centres as

well as regulatory requirements, statutory and legal, applicable to AIBILI activities.

Currently the QMS is being adapted to the new General Data Protection Regulation (EU) 2016/679. 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.

Internal auditing is a guarantee that procedures are followed at AIBILI and the QMS is in improvement to enhance customer satisfaction by meeting customers' requirements.

AIBILI's Quality Management Unit also provides consultancy services in helping other healthcare institutions to implement quality systems ISO 9001 and ICH-GCP compliant due to its long and vast experience in this field.

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TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER UNIT (UTT)

Staff: Cecília Martinho, Daniel Fernandes, Paulo Barros

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

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

The Translational Research and Technology Transfer Unit is responsible for promoting AIBILI and its Centres, and is the main contact point for establishing partnership and collaborations with other institutions.

AIBILI is member of the Health Cluster Portugal (HCP) whose 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

AIBILI is part of the Ophthalmology sub-cluster 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.



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INFORMATION TECHNOLOGY UNIT (IT)

Staff: Celina Canguero, Hugo Morgado, Marta Ventura, Patrícia Silva, Telmo Miranda, Torcato Santos, José Monteiro

The Information Technology Unit is responsible for the management and maintenance of AIBILI Data Centre, IT 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 (<https://studies.corc.pt/>); the Clinical Data Management System that is used in the development of eCRFs for each clinical study; the PhVC Manager – Extedo that is used for pharmacovigilance in clinical studies 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's Data Centre houses EVICR.net website (www.evicr.net), EVICR.net Educational Programme webinar platform (https://cloud.aibili.pt/evicr-net_webinars) and also supports other administrative/office information systems.

AIBILI Data Centre is certified by ECRIN - European Clinical Research Infrastructure Network (www.ecrin.org) and is part of the ECRIN Data Centre Network. AIBILI Data Centre can provide safe, secure, compliant and efficient management of clinical research data.



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6

ETHICS COMMITTEE

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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 n° 97/95 of 10 May, repealed by Law n° 80/2018, 15 October.

In 2018, AIBILI Ethics Committee has reviewed and approved one ophthalmological clinical study and was kept informed of the approval of three new clinical trials 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.

MEMBERS

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)

Vice-President

Cristina Cordeiro, MD, MSc
(Coordinator of the Coimbra Forensic Pathology Unit of the National Institute of Legal Medicine and Invited Assistant at the Faculty of Medicine, University of Coimbra)

Secretary

Margarida Caramona, PhD
(Emeritus Professor at the Faculty of Pharmacy, University of Coimbra)

José Moura Pereira, MD

(Ophthalmologist at the University Hospital of Coimbra)

Maria Elizabeth Batista Geraldes, MD

(Endocrinologist at the University Hospital of Coimbra)

Paulo Simões, BSc

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

Filomena Maria Ferreira Ramos Mena, BSc

(Nurse at the National Institute of Forensic Medicine, Coimbra)

PARTNERSHIPS



ARSC – Health Administration of the Centre Region of Portugal

ARSC (www.arscentro.min-saude.pt) regulates the organization and functioning of healthcare institutions and services in the Centre Region of Portugal.

The Protocol between AIBILI and ARSC is of great relevance as the area of primary healthcare is a major research interest of AIBILI as screening and prevention are priorities for AIBILI research particularly in imaging diagnostics.

Since 2011, AIBILI-CORC is the Reading Centre for fundus images of Screening Programme for Diabetic Retinopathy in the Centre Region of Portugal.



i3S – Institute for Research and Innovation in Health of the University of Porto

The i3S consortium (www.i3s.up.pt), headed by the Porto University, brings together institutions and researchers from several schools of the Porto University. This wide participation of schools, research institutions and hospitals in a research

institute is unique in Portugal and is a valuable asset for science and technology development, while creating an environment that feeds real breakthrough research and translation of discoveries into the clinic.

The partnership between AIBILI and i3S will increase the participation in innovation and translational projects as well as to have a more complete and robust value chain for their clients, particularly, for companies.



INFARMED - National Authority of Medicines and Health Products, I.P.

INFARMED, IP (www.infarmed.pt) is a Government agency accountable to the Health Ministry, that evaluates, authorises, regulates and controls human medicines as well as health products,

namely, medical devices and cosmetics for the protection of Public Health.

AIBILI has a protocol with INFARMED to pursue with their tasks and achieving their objectives in the framework of the national strategy for the development of the pharmaceutical sector and for clinical research. Since 2008 that AIBILI-CHAD has been responsible for a Pharmacovigilance Unit of the National Pharmacovigilance System contracted with INFARMED, IP.



INFOCUS Clinical Research

INFOCUS (www.infocusclinical.com/) is an ophthalmology focused full-service contract research organization (CRO) based in the USA.

AIBILI and INFOCUS are currently providers of ophthalmology clinical research development support services, respectively, in Europe and North America and are evaluating themselves to execute and integrate global programs.



Portugal's Biotechnology Industry Organization
Associação Portuguesa de BioIndústria

P-BIO – Portugal's Biotechnology Industry Organization

P-BIO (<http://p-bio.org/pt/>) is the only association that brings together the vast majority of companies linked to the biotechnology and life sciences sector. P-BIO seeks to develop an environment

that is favourable to the creation and growth of start-ups, promoting their corporate development domestically and internationally.

The partnership with AIBILI will allow P-BIO companies to have access to differentiated support to evaluate the economic viability of medicines, value strategy design, regulation and translation of technology, market access and effectiveness after commercialization.

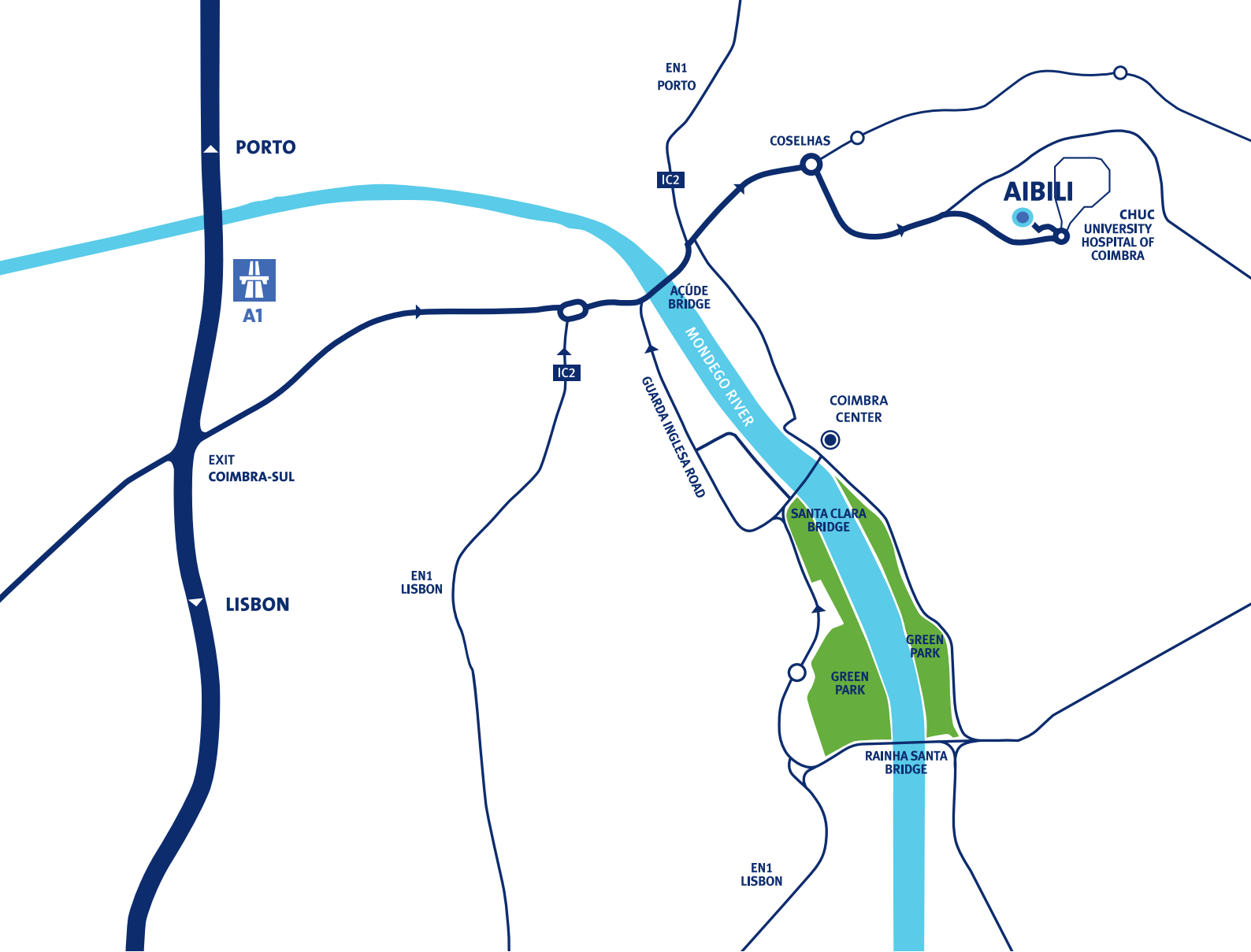


PtCRIN – Portuguese Academic Clinical Research Infrastructures Network

PtCRIN (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. PtCRIN is the Portuguese member of ECRIN-ERIC.

AIBILI is a founding member of the PtCRIN.



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