

**ANNUAL
REPORT**

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ANNUAL REPORT

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MESSAGE FROM THE PRESIDENT

AIBILI - Association for Innovation and Biomedical Research on Light and Image, was founded more than thirty years ago. Its main goals were to contribute with innovative solutions in the areas of ophthalmology, neurosciences, imaging, and pharmacology and to develop tools to improve health care delivery. The scientific work performed at AIBILI has been published regularly in the best international scientific journals and has led to the development of new products. AIBILI is recognised internationally and has a leading role in European eye research by coordinating a network of more than 80 clinical research centres -EVICR.net.

AIBILI is a translational research centre, particularly dedicated to the development of new biomarkers of disease progression and response to treatment. AIBILI has been recognised as an Interface Centre by the Portuguese Ministry of Economy and is the only one in the health sector. I can say that the main objectives set thirty years ago have been generally fulfilled and I am convinced that in the next thirty years AIBILI will continue to pursue its path on research and innovation in the

health sector, contributing to the development of scientific knowledge, international collaboration, and healthcare.

The year of 2021 was a particularly difficult year as we had to adapt to the pandemic situation. However, it turned out to be a new challenge. The need to adapt to working remotely and to find new solutions showed AIBILI's ability to overcome hurdles while maintaining the levels of excellence by which we are guided.

Our Strategic Scientific Research Program has been improved and adapted to our scientific activity, showing unequivocally that we have lines of research in which we intend to continue to differentiate. As our objective is to keep up with the permanent innovation, we intend to continue to improve our collaborations with other research centres, namely with partnerships that make it possible to take advantage of the mutual potential, in the sense of continuing to contribute to obtaining more knowledge and solutions for the promotion and improvement in quality of life.

Conceição Lobo
President



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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 an Interface Centre of the National Portuguese Network of the Economy Ministry. It is a private not-for-profit organisation, founded in 1989, established to support technology transfer and translational research in the health area.

AIBILI main areas of activity are:

- Performance of Clinical Studies
- 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
- Data Centre

AIBILI is ISO 9001:2015 certified for all its activities. Clinical research is performed in accordance with ICH - Good Clinical Practice (GCP) Guidelines and national and European regulatory requirements, as well as legislation applicable to the protection of personal data. AIBILI Data Centre is certified by ECRIN - European Clinical Research Infrastructures Network since 2016.

AIBILI is located in the Coimbra University Health Campus 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 56 including medical doctors, researchers, engineers, pharmacologists, technicians, project managers, statisticians data managers, study coordinators and administrative personnel. Another 50 professionals collaborate regularly in research activities.

In order to promote science and technology advancement and bring potential new treatments and diagnostic tools to the market, AIBILI has assumed an integrated Strategic Scientific Research Program 2020-2025 with five main Research Programs: Diabetic Retinopathy; Age-Related Macular Degeneration; Imaging Biomarkers; Drug Evaluation; and Translational Vision. The outcome of this Strategic Scientific Research Plan will be a key element to enable AIBILI to maintain its excellence in health innovation: by increasing the number and quality of research projects, as well as their funding; to promote AIBILI as an added-value to clinical development and innovation; to promote technology transfer and translational research, and to stimulate novel national and international collaborations, focusing on the improvement of health research and life quality.

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.

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INTERFACE CENTRE IN THE HEALTH SECTOR



AIBILI is an Interface Centre in the Health Sector of the National Technology Network of the Economy Ministry. 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 solutions to the health market.

In order to promote research of excellence and science innovation, AIBILI has established the following priorities:

- Promote the assessment to real-world data focused on the risks and benefits of health technologies by conducting network meta-analysis and economic assessment studies;
- Increase AIBILI's technological strength through the qualification of human resources, the use of state-of-the-art equipment and research collaborations.
- Maintain a critical position in clinical and translational research allowing the creation of new knowledge in collaboration with other reference institutions and participation in international consortia;
- Increase research in the areas of diabetes and neurology, taking advantage of the articulation with primary health care units and the established capacities to study the retina-brain relationship;
- Develop new imaging biomarkers to support the diagnosis and identification of disease stages and facilitate the analysis for risk of development and progression of disease;

With these priorities and participation in international reference networks the following Strategic Scientific Research Program on the quality management system, AIBILI is positioned to achieve excellence in research and innovation that will contribute to society through the contribution of improvements in clinical practice.



BIOTECHNOLOGY AND LIFE SCIENCES FOCUS: HUMAN HEALTH

FINANCIADO POR



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

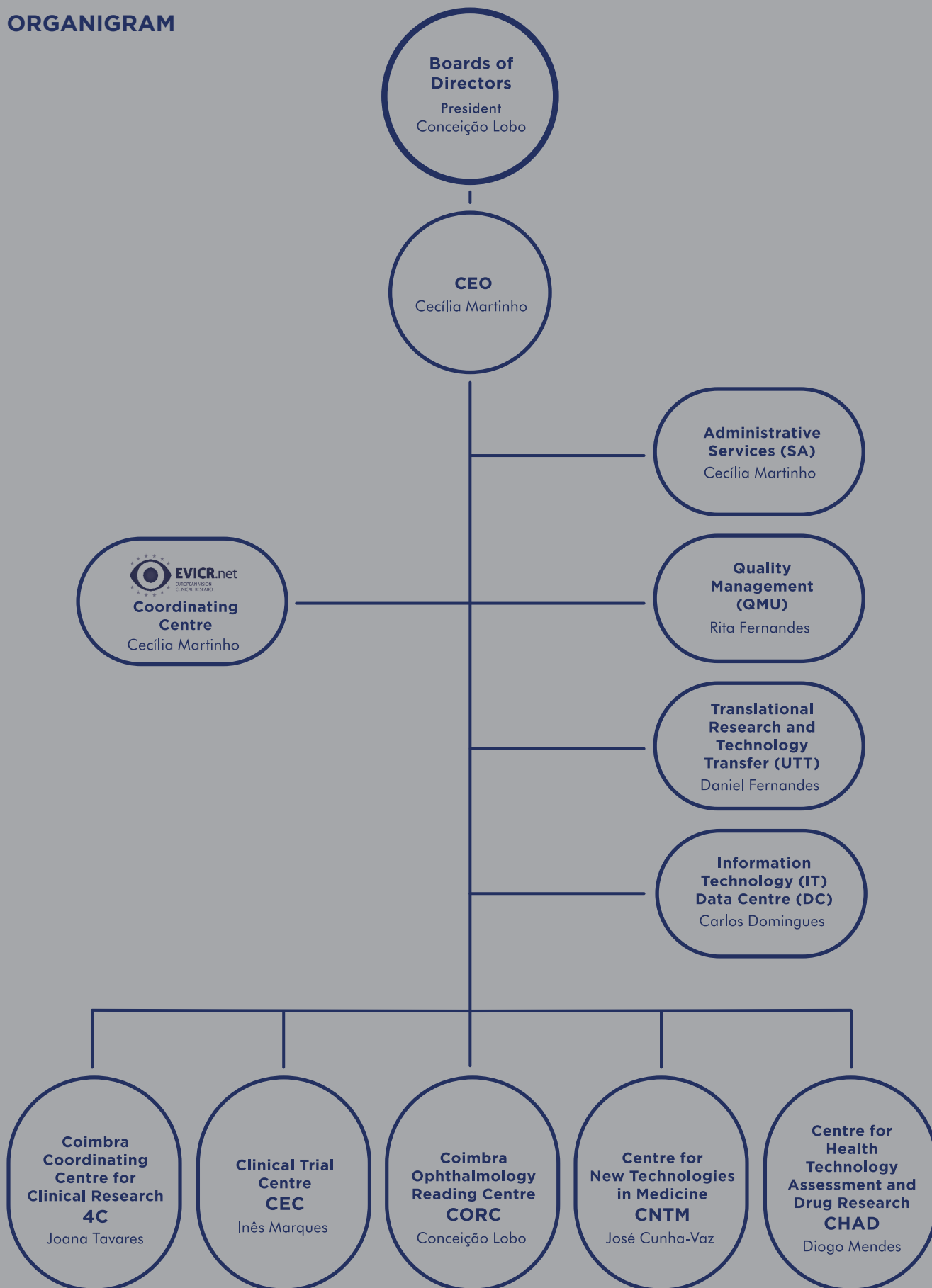
- Alcon Portugal - Prod. e Equip. Oftalmológicos, Lda.
- BIAL - Portela & C^ª, SA
- Cecília Martinho
- Centro de Oftalmologia da Universidade de Coimbra
- Conceição Lobo
- Francisco Batel Marques
- Fundação Champalimaud (Honorary Associate)
- Hospital CUF Coimbra / José de Mello Saúde
- Laboratórios Pfizer, Lda.
- Novartis Farma, SA
- Universidade de Coimbra (Honorary Associate)

BOARD OF DIRECTORS

(2020-2023)

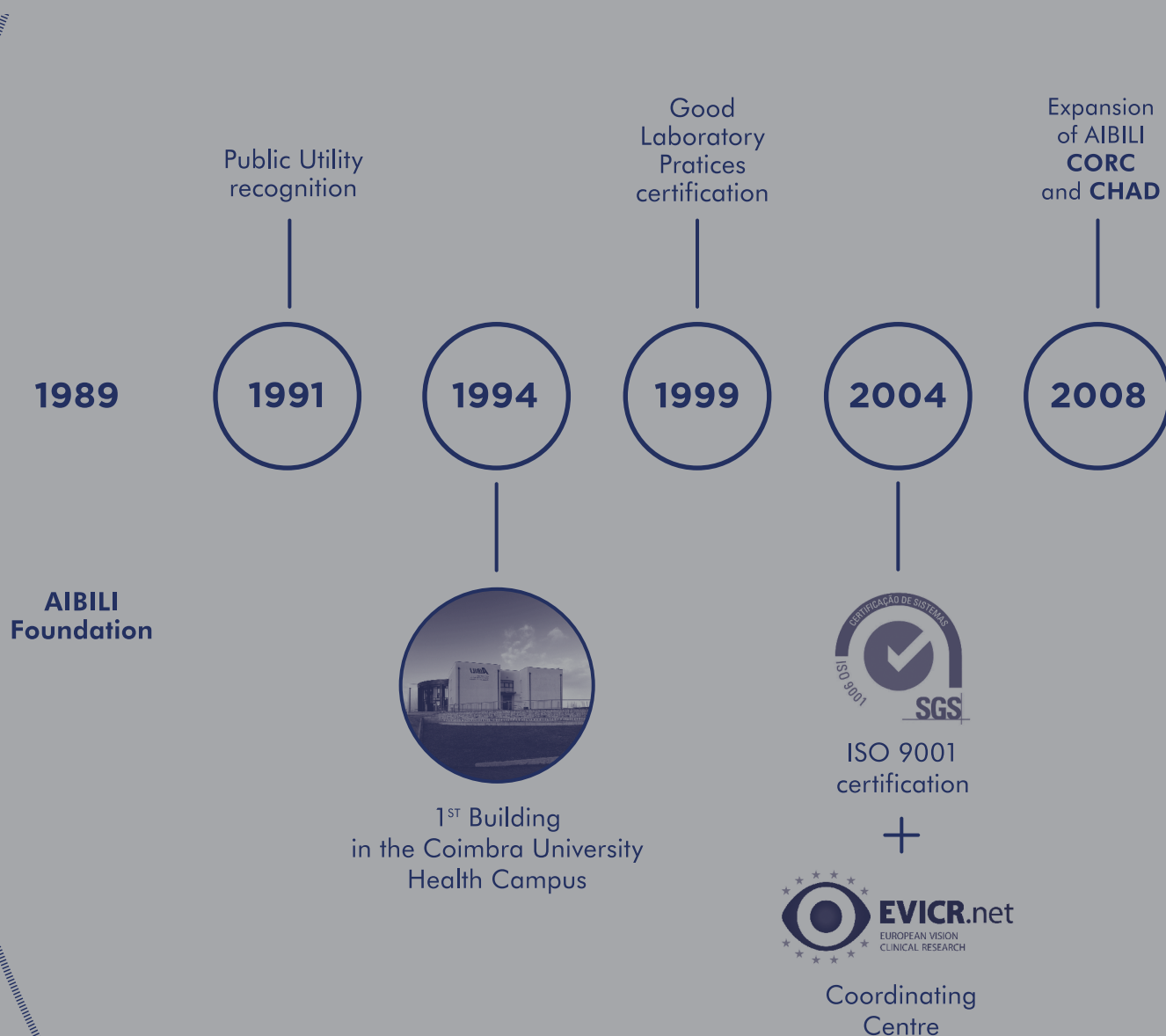
- Conceição Lobo, President
- Francisco Batel Marques, Vice-President
- Nuno Pires (Rep. BIAL - Portela & C^ª, SA)
- António Parreira (Rep. Fundação Champalimaud)
- Gonçalo Pimpão (Rep. Laboratórios EDOL - Produtos Farmacêuticos, S.A.)
- Américo Figueiredo (Rep. Serviço de Dermatologia do Centro Hospitalar e Universitário de Coimbra)
- Cecília Martinho, CEO
- José Cunha-Vaz, Honorary President

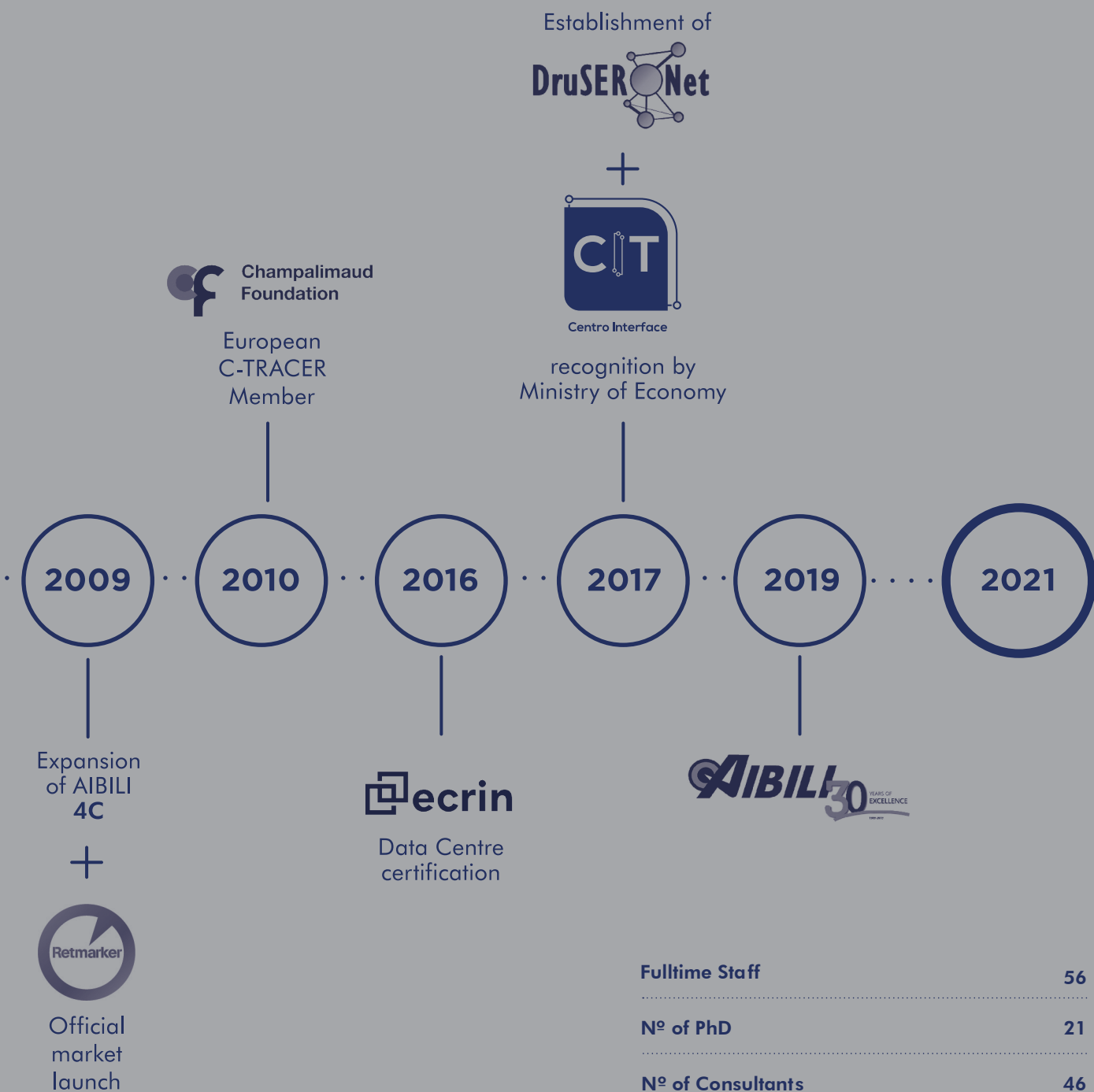
ORGANIGRAM



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AIBILI IN NUMBERS





Fulltime Staff	56
Nº of PhD	21
Nº of Consultants	46
Nº of Ongoing studies, services, projects, contracts	137
Nº of Patents	3 (USA) + 1 (Europe)
Nº of European Union funded projects (ongoing)	2
Nº of Publications (2020 -2021)	65
Nº of Publications / PhD (2020-2021)	3

3

AIBILI RESEARCH CENTRES AND UNITS

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)
- Data Centre (DC)

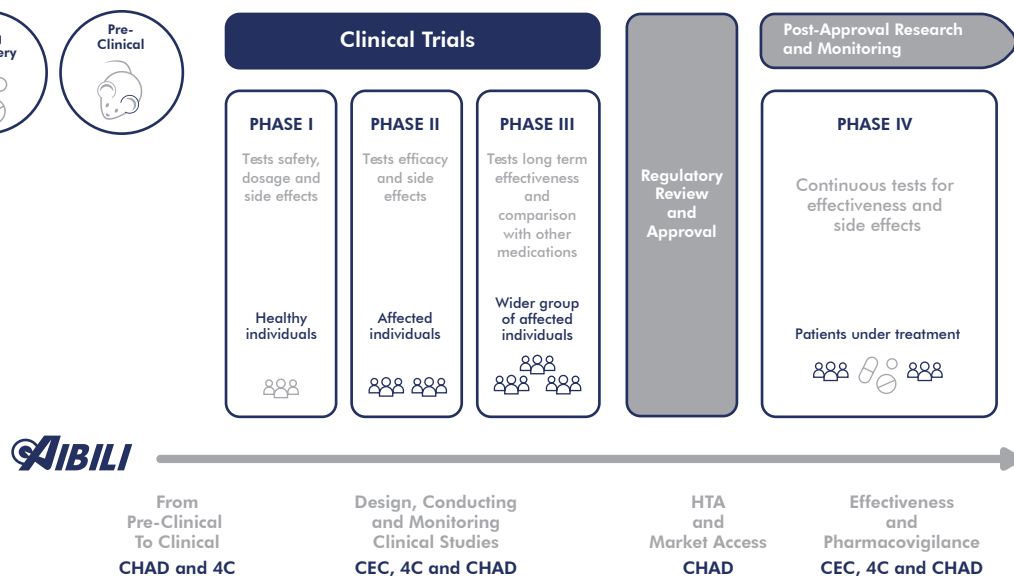
Organizational Units are:

- Administration (SA)
- Quality Management Unit (QMU)
- Translational Research and Technology-Transfer Unit (UTT)
- Information Technology Unit (IT)

In Vitro and In Vivo Study



Clinical Development



4C - COIMBRA COORDINATING CENTRE FOR CLINICAL RESEARCH



Director: Joana Tavares, PhD

Staff: Ana Fernandes, Beatriz Melício, Cátia Francisco, Cecília Martinho, Conceição Lobo, Daniel Fernandes, Diana Tavares, Fábio Mesquita, Laura Seco, Inês Aires, Inês Tavares, Liliana Carvalho, José Cunha-Vaz, Paulo Faria, Pier Basile, Rita Coimbra, Rita Fernandes, Sónia Ferreira, Sónia Simões, Sónia Sousa

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:



PRE-STUDY	IN-STUDY	POST-STUDY
<ul style="list-style-type: none"> • Study Design • Statistical Planning • Development of Protocol and Informed Consent • eCRF Development ¹ • Database Validations and Implementation ¹ • MF and Site File development • Clinical Centre Selection • SOPs Development • Submission to RAs • Insurance and Contracts • Monitoring Planning 	<ul style="list-style-type: none"> • Study Coordination • IMP Management • eCRF Management and Support ¹ • Data Management ¹ • Monitoring • Pharmacovigilance ² 	<ul style="list-style-type: none"> • Data Base Lock • Biostatistics • Final Report • Regulatory Affairs • Publication • Archiving
		ecrin ¹ DATA CENTRE ² CHAD

Contacts

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Nº of Clinical Studies Coordinated by 4C (2019-2021)

Year	Coordination of Clinical Studies (nº)			Total
	Investigator Initiated	Industry Sponsored	Other	
2019	14	2	4	20
2020	13	2	4	19
2021	15	3	5	23

Representative Publications (maximum 5)

Madeira M, Marques IP, Ferreira S, Tavares D, Santos T, Santos AR, Figueira J, Lobo C, Cunha-Vaz J.: **Retinal Neurodegeneration in Different Risk Phenotypes of Diabetic Retinal Disease.** *Frontiers in Neuroscience*. 2021 December; doi: 10.3389/fnins.2021.800004.

Ribeiro L, Marques IP, Coimbra R, Santos T, Madeira MH, Santos AR, Barreto P, Lobo C, Cunha-vaz J. **Characterization of One-Year Progression of Risk Phenotypes of Diabetic Retinopathy.** *Ophthalmol Ther*. 2021 December; doi: org/10.1007/s40123-021-00437-z.

Silva R, Arias L, Nunes S, Farinha C, Coimbra R, Marques JP, Cachulo M, Figueira J, Barreto P, Madeira M, Pires I, Sousa J, Distefano L, Rosa P, Carneiro A, Vaz-Pereira S, Meireles A, Cabrera F, Bures A, Mendonça L, Fernandez-Vega-Sanz A, Barrão S, Koh A, Cheung CMG, Cunha-Vaz J, Murta JG, for the EVICR.net ATLANTIC Study Group: **Efficacy and Safety of Intravitreal Aflibercept Treat and Extend for Polypoidal Choroidal Vasculopathy in the ATLANTIC Study: A Randomized Clinical Trial.** *Ophthalmologica* 2021 July; doi: 10.1159/000518235.

Marques IP, Kubach S, Santos T, Mendes L, Madeira MH, Sisternes L, Tavares D, Santos AR, Lewia W, Lobo C, Durbin MK, Cunha-Vaz J.: **Optical Coherence Tomography Angiography Metrics Monitor Severity Progression of Diabetic Retinopathy—3-Year Longitudinal Study.** *J. Clin. Med*. 2021, 10, 2296. doi: org/10.3390/jcm10112296.

Santos AR, Mendes L, Madeira MH, Marques IP, Tavares D, Figueira J, Lobo C, Cunha-Vaz J.: **Microaneurysm Turnover in Mild Non-Proliferative Diabetic Retinopathy is Associated with Progression and Development of Vision-Threatening Complications: A 5-Year Longitudinal Study.** *J. Clin. Med*. 2021, 10, 2142; doi.org/10.3390/jcm10102142.

Terheyden J, Behning C, Lüning A, Wintergerst L, Basile P, Tavares D, Melício B, Leal S, Weissgerber G, Luhmann U., Crabb D, Tufail A, Hoyng C, Berger M, Schmid M, Silva R, Martinho C, Cunha-Vaz J, Holz F, Finger R, and on behalf of the MACUSTAR consortium: **Challenges, facilitators and barriers to screening study participants in early disease stages-experience from the MACUSTAR study.** *BMC Medical Research Methodology* 2021 March; doi.org/10.1186/s12874-021-01243-8.

CEC - CLINICAL TRIAL CENTRE

Director: Inês Marques, MD, PhD

Staff: Aida Vitorino, Ana Maria Nunes, Ana Rita Santos, Catarina Eloy, Céu Simões, Conceição Lobo, Diana Ramos, Eugénia Cardoso, Filipe Martins, Isabel Pires, Luisa Ribeiro, João Figueira, José Costa, José Cunha-Vaz, Maria da Luz Cachulo, Marcela Pascoal, Marta Lopes, Miguel Amaro, Patrícia Barreto, Patrícia Oliveira, Paulo Marques, Pedro Faria, Rufino Silva, Sandra Pardal, Sílvia Simão



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

Clinical patient-oriented research involves characterizing disease progression and testing new discoveries by carrying out 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, non-interventional, longitudinal studies.

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

CEC has proven expertise with relevant scientific publications in these areas and is a certified Clinical Site of Excellence by the EVICR.net - European Vision Institute Clinical Research Network since 2006.

CEC has experienced and qualified staff and the necessary equipment to perform clinical research according to ICH GCP Guidelines and uses an Electronic Medical Record in its daily routine.



Contacts

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Nº of Investigator Initiated and Industry Sponsored studies performed at CEC (2019-2021)

Year	Nº of Clinical Studies		Total
	Investigator Initiated	Industry Sponsored	
2019	5	13	18
2020	5	10	15
2021	8	10	18

Investigator Initiated Clinical Studies

Diabetic Retinopathy

1. 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
ClinicalTrials.gov n°: NCT03696810
Financial support: Portugal 2020 - 02/SAICT/2017 - Project n° 030375

2. RECOGNISED - Retinal and Cognitive Dysfunction in Type 2 Diabetes: Unraveling the Common Pathways and Identification of Patients at Risk of Dementia
ClinicalTrials.gov n°: NCT04281186
Financial support: European Union - H2020-SC1-BHC-01-2019-847749

3. PROGRESS 10 - Progression of Diabetic Retinopathy. Identification of Signs and Surrogate outcomes -10-year follow-up
ClinicalTrials.gov n°: NCT04650165

4. CHART - Characterization of Retinal disease progression in eyes with NPDR in diabetes Type 2 using non-invasive procedures
ClinicalTrials.gov n°: NCT04636307
Financial support: IIR Grant from Bayer

Age-Related Macular Degeneration

5. 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

6. AMDMetab - Metabolomics: An Integrative Tool for Investigating the Pathogenesis of Age-related Macular Degeneration Network with Massachusetts Eye and Ear Infirmary (MEEI) and the Harvard Medical School, Boston, USA
ClinicalTrials.gov n°: NCT04241536
Financial Support: EURETINA Clinical Research Award

Retinal Degenerative Diseases

7. STAR - Development of a Model for Advanced Screening for Timely Treatment of Age-Related Eye Diseases

8. EYEMARKER - Characterization of potential biomarkers of Eye Disease and Vision Loss
ClinicalTrials.gov n°: NCT02500862

Industry Sponsored Clinical Trials

Diabetic Macular Edema

1. 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

2. A two-year, three-arm, randomized, double-masked, multicentre, phase III study assessing the efficacy and safety of brodalumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL)
EudraCT n°: 2017-004742-23

3. A Multicenter, Open-Label Extension Study To Evaluate The Long-Term Safety And Tolerability Of Faricimab In Patients With Diabetic Macular Edema (Rhine-X)
EudraCT n°: 2020-000402-29

Age-Related Macular Degeneration

4. A Multicenter, Double Masked, Randomized, Dose-Ranging Trial to Evaluate the Efficacy and Safety of Conbercept Intravitreal Injection in Subjects with Neovascular Age-Related Macular Degeneration (PANDA)
EudraCT n°: 2017-004825-34

5. A 52-week multicenter, randomized, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea®, administered intravitreally, in patients with neovascular age-related macular degeneration (MyLight)
EudraCT n°: 2019-004838-41

Glaucoma

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

Neurological Disorders

7. 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

8. Multicenter, non-comparative extension to study AC-058B301, to investigate the long-term safety, tolerability, and control of disease of ponesimod 20 mg in subjects with relapsing multiple sclerosis (OPTIMUM)
EudraCT n°: 2016-004719-10

Oncology

9. Open-label, single-arm trial to evaluate antitumor activity, safety, and pharmacokinetics of SAR408701 used in combination with ramucirumab in metastatic, nonsquamous, non-small-cell lung cancer (NSQ NSCLC) patients with CEACAM5-positive tumors, previously treated with platinum-based chemotherapy and an immune checkpoint inhibitor
EudraCT n°: 2019-003914-15

10. A Phase 3 Multicenter, Open-Label, Randomized, Controlled Study of Oral Infigratinib Versus Gemcitabine With Cisplatin in Subjects With Advanced/Metastatic or Inoperable Cholangiocarcinoma With FGFR2 Gene Fusions/Translocations: the PROOF Trial (PROOF)
EudraCT n°: 2018-004004-19

Representative Publications (maximum 5)

Madeira MH, Marques IP, Ferreira S, Tavares D, Santos T, Santos, AS, Figueira J, Lobo C, Cunha-Vaz J. **Retinal Neurodegeneration in Different Risk Phenotypes of Diabetic Retinal Disease**. *Frontiers in Neuroscience*, 21 December 2021. doi: 10.3389/fnins.2021.800004.

Ribeiro L, Marques IP, Coimbra R, Santos T, Madeira MH, Santos AR, Barreto P, Lobo C, Cunha-Vaz J. **Characterization of One-Year Progression of Risk Phenotypes of Diabetic Retinopathy**. *Ophthalmol Ther*. 5 December 2021. doi: 10.1007/s40123-021-00437-z.

Vujosevic S, Cunha-Vaz J, Figueira J, Löwenstein A, Midena E, Parravano M, Scanlon PH, Simó R, Hernández C, Madeira MH, Marques IP, Martinho AC, Santos AR, Simó-Servat O, Salongay RP, Zur D, Peto T.: **Standardisation of Optical Coherence Tomography Angiography Imaging Biomarkers in Diabetic Retinal Disease**. *Ophthalmic Res*. 2021 Jul 30. doi: 10.1159/000518620.

Marques IP, Kubach S, Santos T, Mendes L, Madeira MH, de Sisternes L, Tavares D, Santos AR, Lewis W, Lobo C, Durbin MK, Cunha-Vaz J.: **Optical Coherence Tomography Angiography Metrics Monitor Severity Progression of Diabetic Retinopathy-3-Year Longitudinal Study**. *J Clin Med*. 2021 May 25;10(11):2296. doi: 10.3390/jcm10112296.

Santos T, Warren LH, Santos AR, Marques IP, Kubach S, Mendes LG, Sisternes L, Madeira MH, Durbin M, Cunha-Vaz JG.: **Swept-source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR**. *Br J Ophthalmol*. 2020 Dec 22: bjophthalmol-2020-317890. doi: 10.1136/bjophthalmol-2020-317890.

CORC – COIMBRA OPHTHALMOLOGY READING CENTRE



Director: Conceição Lobo, MD, PhD

Staff: Alda Baltar, Ana Paula Pascoal, Ana Raquel Branco, Ana Rita Santos, Carla Sofia Gomes, Catarina Neves, Christian Schwartz, Cláudia Farinha, Cláudio Mendes Ferreira, Diana Ramos, Emmanuel Neves, Inês Marques, Isa Sobral, Isabel Pires, João Gil, João Pedro Marques, José Cunha-Vaz, José Filipe Costa, Jorge Simão, Lara Portugal, Márcia Ferreira, Marco Marques, Maria Filipa Ponces, Mariana Costa, Maria da Luz Cachulo, Marta Lopes, Miguel Raimundo Renata Castanheira, Rui Pita, Sílvia Simão, Telmo Miranda

The Coimbra Ophthalmology Reading Centre (CORC) is a Central Reading Centre for multinational and multicentric clinical studies as well as for the Diabetic Retinopathy Central and South Region of Portugal Screening Programme.

CORC focus its activities on grading of ophthalmic exams for characterization and quantification of ophthalmic disease, mainly of the posterior segment/retinal diseases.



Contacts

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Posterior Segment / Retinal Diseases

- Diabetic Retinopathy (DR)
- Age-related Macular Degeneration (AMD)
- Retinitis Pigmentosa (RP)
- Retinal Vein Occlusion (RVO)

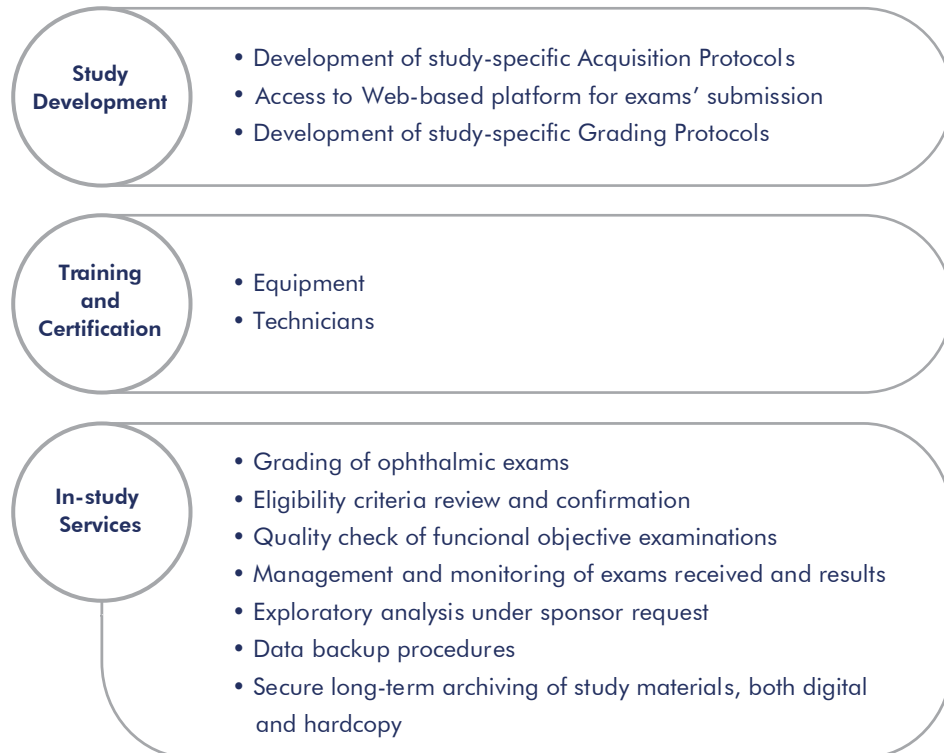
Anterior Segment Diseases

- Neurotrophic Keratitis
- Dry Eye

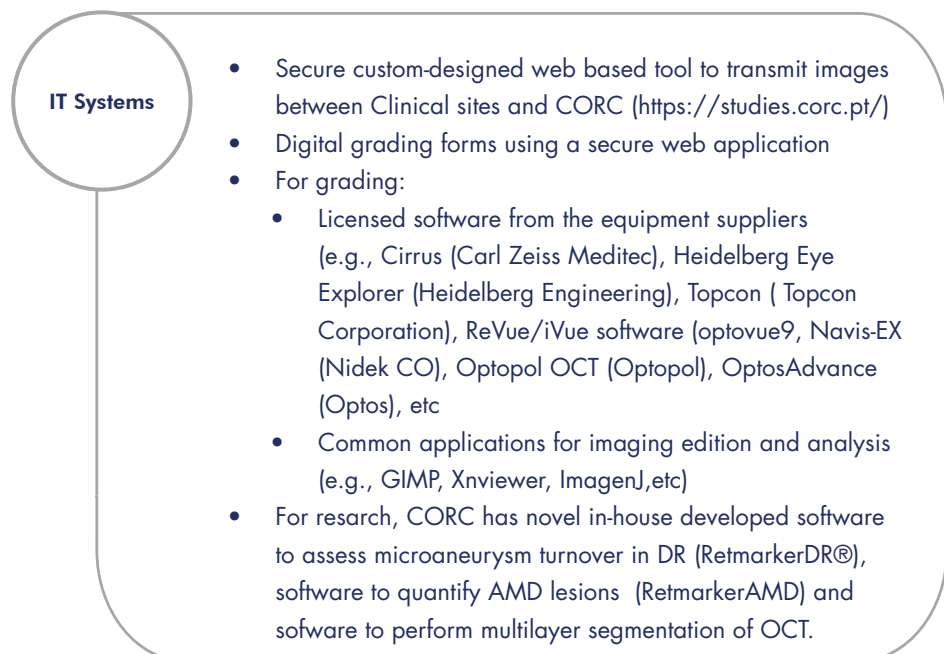
Ophthalmic Exams

- Retinal Fundus Images
 - Fundus photography (FP)
 - Fluorescein Angiography (FA)
 - Ultrawide field (UWF) imaging (UWF FP and UWF FA)
 - Indocyanine-green Angiography (ICG)
 - Fundus Autofluorescein (FAF)
- Optical Coherence Tomography (OCT)
- Optical Coherence Tomography Angiography (OCTA)
- Anterior Segment Photography
- Functional examinations (Quality check): perimetry, Microperimetry, erg

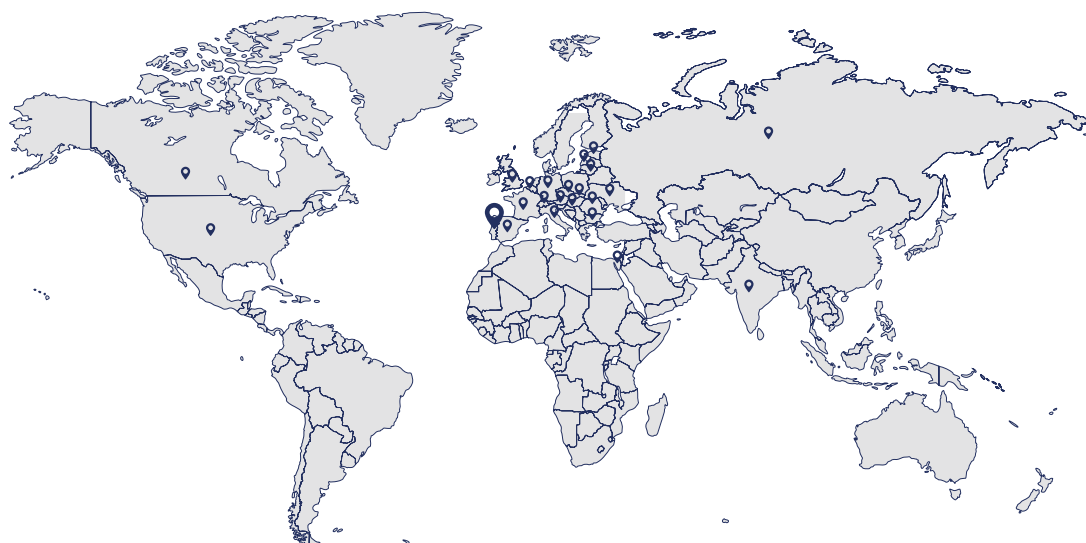
CORC provides the following services:



CORC uses the following IT Systems:



Receive and Grade Exams from



- | | | |
|------------------|-------------|---------------|
| 📍 AUSTRIA | 📍 HUNGARY | 📍 ROMANIA |
| 📍 BELGIUM | 📍 INDIA | 📍 RUSSIA |
| 📍 BULGARIA | 📍 ISRAEL | 📍 SLOVAKIA |
| 📍 CANADA | 📍 ITALY | 📍 SPAIN |
| 📍 CZECH REPUBLIC | 📍 LATVIA | 📍 SWITZERLAND |
| 📍 ESTONIA | 📍 LITHUANIA | 📍 UK |
| 📍 FRANCE | 📍 POLAND | 📍 UKRAINE |
| 📍 GERMANY | 📍 PORTUGAL | 📍 USA |

Nº of Projects per scientific area at CORC (2019-2021)

Year	Nº of Projects			Total
	Diabetic Retinopathy	AMD	Other	
2019	8	8	2	18
2020	9	5	2	16
2021	13	4	3	20

Representative Publications (maximum 5)

Ribeiro L, Marques IP, Coimbra R, Santos T, Madeira MH, Santos AR, Barreto P, Lobo C, Cunha-Vaz J. **Characterization of One-Year Progression of Risk Phenotypes of Diabetic Retinopathy.** *Ophthalmol Ther.* 2021 Dec 5. doi: 10.1007/s40123-021-00437-z.

Mendes L, Marques IP, Cunha-Vaz J. **Comparison of Different Metrics for the Identification of Vascular Changes in Diabetic Retinopathy Using OCTA.** *Front Neurosci.* 2021 Nov 30;15:755730. doi: 10.3389/fnins.2021.755730.

Farinha C, Silva AL, Coimbra R, Nunes S, Cachulo ML, Marques JP, Pires I, Cunha-Vaz J, Silva R. **Retinal layer thicknesses and neurodegeneration in early age-related macular degeneration: insights from the Coimbra Eye Study.** *Graefes Arch Clin Exp Ophthalmol.* 2021 Sep;259(9):2545-2557. doi: 10.1007/s00417-021-05140-0.

Simão JM, Farinha CV, Marques JP, Nunes S, Pires IM, Cachulo ML, Figueira JP, Murta JN, Silva RM. **Polypoidal Choroidal Vasculopathy in Caucasians: Morphological Findings from Multimodal Retinal Imaging.** *Ophthalmologica.* 2021;244(4):315-325. doi: 10.1159/000515295.

Silva R, Arias L, Nunes S, Farinha C, Coimbra R, Marques JP, Cachulo ML, Figueira J, Barreto P, Madeira MH, Pires I, Sousa JC, Distefano L, Rosa P, Carneiro Â, Vaz-Pereira S, Meireles A, Cabrera F, Bures A, Mendonça L, Fernandez-Vega-Sanz A, Barrão S, Koh A, Cheung CMG, Cunha-Vaz JG, Murta J; EVICR.net ATLANTIC Study Group. **Efficacy and Safety of Intravitreal Aflibercept Treat and Extend for Polypoidal Choroidal Vasculopathy in the ATLANTIC Study: A Randomized Clinical Trial.** *Ophthalmologica.* 2021 Jul 13. doi: 10.1159/000518235.

Marques IP, Kubach S, Santos T, Mendes L, Madeira MH, de Sisternes L, Tavares D, Santos AR, Lewis W, Lobo C, Durbin MK, Cunha-Vaz J. **Optical Coherence Tomography Angiography Metrics Monitor Severity Progression of Diabetic Retinopathy-3-Year Longitudinal Study.** *J Clin Med.* 2021 May 25;10(11):2296. doi: 10.3390/jcm10112296.

CNTM - CENTRE FOR NEW TECHNOLOGIES IN MEDICINE

Director: José Cunha-Vaz, MD, PhD

Staff: Celine Canguero, Luís Mendes, Maria Castro, Rufino Silva, Telmo Miranda, Torcato Santos

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. CNTM is particularly interested in developing non-invasive methodologies that allow repeated observations and measurements in order to identify early alterations that may allow timely therapeutic interventions, e.g., precision medicine.

CNTM has been able to identify novel biomarkers of disease progression, such as microaneurysm turnover in diabetic retinopathy identified automatically by software developed in-house, the Retmarker®, developed in a partnership with Retmarker SA., and fluid quantification in the retinal diseases by identifying non-invasively changes in the Blood-Retinal Barrier in the retina, using a novel patented algorithm, the OCT-Leakage. A major effort is also being made in the development of Optical Coherence Tomography Angiography for diagnosing progression of diabetic retinopathy and to develop methods involving artificial intelligence.



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Research Focus

- Multimodal imaging of retinal disease
- Characterization of capillary closure as the main alteration that identifies diabetic retinopathy progression
- OCT-Leakage. Layer by layer fluid analysis of the retina
- Characterization of prognostic biomarkers of retinal disease progression using artificial intelligence
- Characterization of response to anti-VEGF treatment in Diabetic Macular Edema
- Use of artificial intelligence to improve diagnosis and follow-up of retinal diseases

Nº of Projects at CNTM (2019-2021)

Year	Nº of Projects		Total
	Imaging/ Artificial Intelligence	Diabetic Retinopathy	
2019	6	5	11
2020	8	4	12
2021	9	6	15

Representative Publications (maximum 5)

Cunha-Vaz J. and Mendes L. **Characterization of Risk Profiles for Diabetic Retinopathy Progression.** J Pers Med. 2021 Aug 23;11(8):826. doi: 10.3390/jpm11080826.

Mendes L, Marques IP, Cunha-Vaz J. **Comparison of Different Metrics for the Identification of Vascular Changes in Diabetic Retinopathy Using OCTA.** Front Neurosci. 2021 Nov 30;15:755730. doi: 10.3389/fnins.2021.755730.

Santos T, Warren LH, Santos AR, Marques IP, Kubach S, Mendes LG, Sisternes L, Madeira MH, Durbin M, Cunha-Vaz JG.: **Swept-source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR.** Br J Ophthalmol. 2020 Dec 22: bjophthalmol-2020-317890. doi: 10.1136/bjophthalmol-2020-317890.

Marques IP, Alves D, Santos T, Mendes L, Lobo C, Santos AR, Durbin M, Cunha-Vaz J. **Characterization of disease progression in the initial stages of retinopathy in diabetes type 2. A two-year longitudinal study.** Invest Ophthalmol Vis Sci. 2020 Mar 9;61(3):20. doi: 10.1167/iovs.61.3.20.

Santos AR, Alves D, Santos T, Figueira J, Silva R, Cunha-Vaz JG. **Measurements of retinal fluid by Optical Coherence Tomography 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.

CHAD - CENTRE FOR HEALTH TECHNOLOGY ASSESSMENT AND DRUG RESEARCH



Director: Diogo Mendes, PhD

Staff: Alexandra Escada, Ana Penedones, Carlos Alves, Carlos Fontes Ribeiro, Daniel Fernandes, Daniel Figueiredo, Francisco Batel Marques, Inês Tavares, Joana Abrantes

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 drug reimbursement decisions at ambulatory and hospital settings.

CHAD is a useful resource to work closely with Pharmaceutical Industry in all the different phases of drug development.

CHAD also performs pharmacovigilance services necessary in clinical studies. It has a phar-

macovigilance 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 ICHGCP 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

- Health Technology Assessment, pricing and reimbursement (medicines and medical devices)
- Primary research (Patient-based outcomes and real-world effectiveness studies)
- 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)
- Pharmacovigilance and Risk Management services

Nº of Projects at CHAD (2019-2021)

Year	Nº of Projects		Total
	Market Access	Drug Safety	
2019	16	8	24
2020	15	9	24
2021	24	10	34

Representative Publications (maximum 5)

Mendes D, Abrantes J, Rigueiro G, Pais AF, Penedones A, Alves C, Batel-Marques F. **Real-world intensive safety monitoring of biosimilars rituximab and trastuzumab in a Portuguese oncology hospital.** J Oncol Pharm Pract. 2021 Sep;27(6):1432-1438. doi: 10.1177/1078155220957079.

Alves C, Penedones A, Mendes D, Batel-Marques F. **The Risk of Infections Associated With JAK Inhibitors in Rheumatoid Arthritis: A Systematic Review and Network Meta-analysis.** J Clin Rheumatol. 2021 Apr 24. doi: 10.1097/RHU.0000000000001749.

Alves C, Penedones A, Mendes D, Batel Marques F. **Risk of infections and cardiovascular and venous thromboembolic events associated with JAK inhibitors in rheumatoid arthritis: protocols of two systematic reviews and network meta-analyses.** BMJ Open. 2020 Dec 31;10(12):e041420. doi: 10.1136/bmjopen-2020-041420.

Mendes D, Penedones A, Martins M, Cavadas S, Alves C, Batel Marques F. **Rectus sheath hematoma in patients receiving subcutaneous enoxaparin: A case series of five patients.** Clin Case Rep. 2020; 00: 1– 8. <https://doi.org/10.1002/ccr3.3427>.

DC – DATA CENTRE

Director: Carlos Domingues, BSc

Staff: Celine Cangeiro, Hugo Morgado, José Monteiro, Patrícia Silva, Telmo Miranda, Torcato Santos



AIBILI Data Centre was built specifically to support AIBILI's information systems as well as 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 70 servers, either virtual or physical supported on different operating systems and technologies. There are specific Standard Operating Procedures (SOPs) in place, developed according to IT best practices such as Information Technology Infrastructure Library (ITIL), and project manage-

ment 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 with specific backup policies defined according information value. Long term storage procedures are in place to assure the whole information lifecycle. Information Technology Unit manages over than 80 TB of useful information/data (clinical images and databases, administrative information, project information and long-term storage).

AIBILI Data Centre is certified by ECRIN - European Clinical Research Infrastructure Network (www.ecrin.org) version 3 since April 2016 and recertification (in version 4) was achieved on February 2021. This Data Centre is the only one certified in the Peninsula Iberia. Compliance with ECRIN standards confirms AIBILI capacity to provide appropriate and effective data management services for multinational, randomised controlled studies as well as clinical 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
- eCRF users helpdesk
- CORC platform support and digital grading forms development
- Data export and biostatistics support
- Long Term Storage
- Software development

Nº of Projects at DC (2019-2021)

Year	Nº of Projects
	Projects/Services
2019	15
2020	17
2021	27

ORGANISATIONAL UNITS

Administrative Services

CEO: *Cecília Martinho*, BSc Econ

Staff: Ana Sousa, Laura Seco, Mara Miraldo, Marco Santos, Paulo Barros, Tânia Melro

The Administrative Services (SA) are 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 and in compliance with national legislation and requirements. The Administrative Services establishes a direct liaison between the Board of Directors of AIBILI and its Centres and organisational Units.



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Quality Management Unit (QMU)

Quality Manager: *Rita Fernandes*, BSc

Staff: Rita Fernandes, Marta Ventura

The Quality Management Unit (QMU) is responsible for the Quality Management System (QMS), which is in accordance with ISO 9001:2015, Principles of Good Clinical Practices, requirements for Certification of ECRIN Data Centre and General Data Protection Regulation (EU) 2016/679 as well as other regulatory requirements applicable to AIBILI activities, to ensure improvement through regular support to Unit's activities and internal audits. The new Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use and the Regulation (EU) 2017/745 on medical devices, are being incorporated in AIBILI's Quality Management System. Internal auditing is a guarantee that procedures are followed and the QMS is in improvement to enhance clients satisfaction by meeting customers' requirements.

The QMU assures that the Quality Management System (QMS) is maintained effective and efficient permitting improvement and has the necessary resources to provide the services and meet the needs of its Clients and interested parties.

AIBILI is ISO 9001 certified for the activities of: Research and Development in New Technologies for Medicine with particular emphasis in the Areas of Imaging, Optics and Photobiology; Performance of Clinical Studies; Planning, Coordination, Monitoring of Clinical Research Activities; Health Technology Assessment; Grading of Eye Exams; and Data Centre Activities.

The QMS is progressively in digital format to streamline approvals, records and archiving as well as permanent access to all information.

The QMU performs AIBILI's internal Quality Assurance (QA) as well as external QA services for CORC, 4C and UFC services.

The QMU also performs internal and external training on quality and regulatory requirements applicable to clinical research activities.



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TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER UNIT (UTT)

UTT Manager: Daniel Fernandes, BSc

Staff: Cecília Martinho, Daniel Fernandes, Maria Madeira

The Translational Research and Technology Transfer Unit facilitates the performance of research and development activities and promotes translational activities that allow its evolution into clinical practice. It identifies opportunities for creating new knowledge and transferring technology, supporting contracting with industry and the search for financing programs.

The UTT is also responsible for promoting and publicizing AIBILI activities, being the main point of contact for partnerships and collaborations.

Following the implementation of the AIBILI Strategic Scientific Program 2020-2025, UTT coordinates the activities of the different lines of research, supporting the conceptualization and elaboration of different projects. It also promotes the integration of multidisciplinary concepts from different scientific areas with the aim of creating new knowledge bases that contribute in a relevant way to innovative research developed by AIBILI.



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INFORMATION TECHNOLOGY UNIT (IT)

IT Manager: Carlos Domingues, BSc

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

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 and Grading Forms for each clinical study; as well as the Clinical Management System (CMS) 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 Data Centre also houses EVICR.net website (www.evicr.net), EVICR.net Educational Programme webinar platform (https://cloud.aibili.pt/evicrnet_webinars) and supports other administrative/office information systems.

ETHICS COMMITTEE

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) or medical devices) performed at AIBILI according to the Portuguese Decree Law n° 80/2018 of October 15th.

AIBILI Ethics Committee is available to be called upon National Ethics Committee for Clinical Research (CEIC) request, in case it is needed for the review of ophthalmology clinical trials or studies since it has expertise in this scientific area.

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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 and Secretary

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Members

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Ophthalmologist at the University Hospital of Coimbra

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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

Maria Cecília Martinho, BSc

AIBILI CEO

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RESEARCH AND INNOVATION

Throughout its more than thirty years of existence, AIBILI has created an excellence track record in ophthalmology clinical research, being internationally recognized for its innovation in the area of imaging biomarkers and diagnostics.

With the huge acceleration in innovation in the past years, and the increased complexity in medical needs, it has become crucial to science to escort this acceleration. Researchers must provide more insight on disease understanding and deliver more healthcare solutions to promote and protect human health. Likewise, AIBILI also needs to keep up its pace in innovation.

In order to promote science and technology advancement and bring potential new treatments and diagnostic tools to the market, AIBILI has assumed an integrated Strategic Research Program 2020 - 2025 with five main Research areas:

- Diabetic Retinopathy
- Age-Related Macular Degeneration
- Imaging Biomarkers
- Drug Evaluation
- Translational Vision

AIBILI Strategic Research Program aims to achieve four main goals, to stimulate the complementarity of our dedicated Research areas:

Integrate science and medicine development

- Support the development of precision medicine, biomarkers
- Create integrated evaluation pathways for assessment of medical devices and innovative products

Improve research quality

- Foster innovation in clinical trials
- Exploit digital technology and artificial intelligence (AI)
- Expand benefit-risk assessment and communication

Advance in patient-centred access to medicine

- Contribute to HTA decision-making in innovative medicines
- Promote high-quality real-world data
- Deliver improved products, targeted on earlier stages and precision medicine

Leverage research and innovation

- Foster collaboration between academia and other research institutes to address critical research innovation questions in our dedicated Research Programs
- Contribute to better healthcare and personalized medicine

DIABETIC RETINOPATHY RESEARCH PROGRAM

Coordinator: João Figueira, MD, PhD and Inês Marques, MD, PhD

Research Team: Ana Rita Santos, Conceição Lobo, Inês Marques, Joana Tavares, José Cunha-Vaz, Luis Mendes, Luisa Ribeiro, Maria Madeira, Rita Coimbra, Torcato Santos

Diabetic retinopathy (DR) remains a major cause of blindness as the prevalence of diabetes is expected to approximately double globally between 2000 and 2030. DR progresses over time at different rates in different individuals with only a limited number developing significant vision loss due to the two major vision-threatening complications, clinically significant macular edema and proliferative diabetic retinopathy.

Good metabolic control is important to prevent and delay progression, but whereas some patients escape vision loss even with poor control, others develop vision loss despite good metabolic con-

trol. Our research group has been able to identify three different DR phenotypes characterized by different dominant retinal alterations and different risks of progression to vision-threatening complications. Microaneurysm turnover (MAT) has been validated as a prognostic biomarker of development of clinically significant macular edema, whereas subclinical macular edema identified by Optical Coherence Tomography (OCT) appear to be also a good candidate as organ-specific biomarker of DR. Hemoglobin A1c (HbA1c) remains the only confirmed systemic prognostic biomarker of DR progression.



Contacts

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Research Program Main Goals

Identify new biomarkers of DR progression and their correlation with different risks for development of vision-threatening complications, offering new perspectives for understanding DR and for its personalized management.

Ongoing Projects

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

ClinicalTrials.gov n°: NCT03010397

Sponsor: AIBILI

PROGRESS is a clinical study dedicated to characterize the 5-year progression of mild non-proliferative DR (NPDR), in patients with diabetes type 2, to vision-threatening complications.

Through this study, the predictive risk of ocular and systemic markers was accessed to identify prediction methods for disease development and progression. Moreover, visual acuity and retinal neurodegenerative changes in different stages of DR are explored.

PROGRESS 10 – Progression of Diabetic Retinopathy. Identification of Signs and Surrogate outcomes -10-year follow-up

ClinicalTrials.gov n°: NCT04650165

Sponsor: AIBILI

PROGRESS 10 is the continuation of the PROGRESS study (NCT 03010397), a prospective non-interventional longitudinal

clinical study designed to follow type 2 diabetic individuals with non-proliferative diabetic retinopathy, in a 10-year period of follow-up.

Patients have a complete annual ophthalmological examination, including standard methodologies as color fundus photography (CFP), visual acuity, optical coherence tomography, and also taking advantage of recent and innovative approaches as Spectral domain OCT-angiography (SD-OCTA) and Swept-source OCT (SS-OCTA).

CORDIS - Characterization of retinal vascular disease in diabetes type 2, using novel non-invasive imaging methods

ClinicalTrials.gov n°: NCT03696810

Sponsor: AIBILI

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

The main objective of this project is to better characterize, using new methods, OCTA and OCT-Leakage, the evolution and progression of phenotypes B and C of DR identifying eyes that

show worsening and disease progression to sight-threatening DR (progression phenotypes), allowing for a better characterization of the two main features of the leaky or ischemic progressor phenotypes, using non-invasive methodologies.

RECOGNISED - Retinal and cognitive dysfunction in type 2 diabetes: unravelling the common pathways and identification of patients at risk of dementia

ClinicalTrials.gov Number: NCT04281186

Sponsor: VHIR, Barcelona, Spain

Financial support: Horizon2020 – H2020-SC1-BHC-01-2019-847749

RECOGNISED is a multicentre, multinational study that aims to investigate the common mechanisms involved in the pathogenesis of DR and cognitive impairment in the type 2 diabetes (T2D). The main goal is to use the retina as a tool to identifying individuals with T2D at a higher risk of developing cognitive decline or dementia.

CHART - Characterization of Retinal disease progression in eyes with NPDR in diabetes Type 2 using non-invasive procedures

ClinicalTrials.gov n°: NCT04636307

Sponsor: AIBILI

Financial support: IIR Grant from Bayer

This is a multicentre two-year observational study that aims to better characterize the retinal changes that occur during a 2-years follow-up period in patients with the initial stages of NPDR and at higher risk for sight-threatening complications (ETDRS 35, 43, 47 and 53), allowing better characterization of eyes at risk of progression (phenotypes B and C).

The main aim is to identify biomarkers, obtained using non-invasive procedures, that can predict disease progression and progression to sight-threatening stages of the disease and to characterize the retinal changes that occur in NPDR.

RICHARD - Retinal ischemia characterization in diabetes

ClinicalTrials.gov Number: NCT05112445

Sponsor: AIBILI

Financial support: IIR funding from Boehringer Ingelheim

RICHARD will use these state-of-the-art methodologies to perform a complete, accurate and noninvasive evaluation of retinal ischemic events associated with diabetes, aiming on having a precise characterization of Diabetic Macular Ischemia (DMI) and its microvascular mechanisms, which can have critical importance in clinical practice allowing a more precise medicine.

Representative Publications

Marques IP, Kubach S, Santos T, Mendes L, Madeira MH, de Sisternes L, Tavares D, Santos AR, Lewis W, Lobo C, Durbin MK, Cunha-Vaz J.: **Optical Coherence Tomography Angiography Metrics Monitor Severity Progression of Diabetic Retinopathy-3-Year Longitudinal Study.** J Clin Med. 2021 May 25;10(11):2296. doi: 10.3390/jcm10112296.

Santos, A. R. et al. **Microaneurysm turnover in mild non-proliferative diabetic retinopathy is associated with progression and development of vision-threatening complications: A 5-year longitudinal study.** J. Clin. Med. 10(10):214, (2021). doi: 10.3390/jcm10102142

Cunha-Vaz J. and Mendes L. **Characterization of Risk Profiles for Diabetic Retinopathy Progression.** J Pers Med. 2021 Aug 23;11(8):826. doi: 10.3390/jpm11080826.

Ribeiro L, Marques IP, Coimbra R, Santos T, Madeira MH, Santos AR, Barreto P, Lobo C, Cunha-Vaz J. **Characterization of One-Year Progression of Risk Phenotypes of Diabetic Retinopathy.** Ophthalmol Ther. 5 December 2021. doi: 10.1007/s40123-021-00437-z.

Santos, T. et al. **Swept source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR.** Br. J. Ophthalmol. 2020 Dec 22;bjophthalmol-2020-317890. doi: 10.1136/bjophthalmol-2020-317890.

Figueira J et al. **Guidelines for the Management of Center-Involving Diabetic Macular Edema: Treatment Options and**

Patient Monitorization. Clin Ophthalmol. 2021 Jul 30;15:3221-3230. doi: 10.2147/OPHT.S318026.

Santos, A. R. et al. **Microperimetry and mfERG as functional measurements in diabetic macular oedema undergoing intravitreal ranibizumab treatment.** Eye (2020). doi:10.1038/s41433-020-1054-2.

Marques, I. P. et al. **Different retinopathy phenotypes in type 2 diabetes predict retinopathy progression.** Acta Diabetol. (2020). doi:10.1007/s00592-020-01602-9

Martinho, A. C.-V. et al. **Ocular and Systemic Risk Markers for Development of Macular Edema and Proliferative Retinopathy in Type 2 Diabetes: A 5-Year Longitudinal Study.** Diabetes Care dc201125, (2020).

Marques IP et al, **Retinopathy Phenotypes in Type 2 Diabetes with Different Risks for Macular Edema and Proliferative Retinopathy,** J. Clin. Med. 2020, 9(5), 1433; <https://doi.org/10.3390/jcm9051433>.

Marques IP et al, **Characterization of disease progression in the initial stages of retinopathy in diabetes type 2. A two-year longitudinal study.** Invest Ophthalmol Vis Sci. 2020 Mar 9;61(3):20. doi: 10.1167/iovs.61.3.20.

Marques IP, et al. **Multimodal Imaging of the Initial Stages of Diabetic Retinopathy: Different Disease Pathways in Different Patients.** Diabetes. 2019 Mar;68(3):648-653. doi: 10.2337/db18-1077. Epub 2018 Dec 6. PubMed PMID:30523027.

AGE-RELATED MACULAR DEGENERATION RESEARCH PROGRAM

Coordinator: Rufino Silva, MD, PhD

Stesearch Team: Cláudia Farinha, Joana Tavares, José Cunha-Vaz, Luis Mendes, Maria Madeira, Patrícia Barreto, Rita Coimbra, Torcato Santos

Age-related Macular degeneration (AMD) is the leading cause of adult blindness in developed countries, which affects almost 30% of the older population. In fact, with the aging of population, AMD will become globally an increasingly important and prevalent disease worldwide.

The hallmark of the early phases of AMD are macular drusen and pigmentary changes, and it progresses slowly from early AMD to intermediate AMD (iAMD) and ultimately late-stage AMD with severe manifestation and frequently irreversible lesions. Of note, it is probable that the early and intermediate forms of AMD do not represent a single disease, but rather a collection of subtypes, which ultimately progress to the advanced forms. Therefore, elucidating these subtypes and their underlying pathogenesis will be critical in developing effective therapies for these earlier stages of AMD.

The etiology of AMD is complex, and although genome-wide and gene-candidate studies have been enabled to identify genetic variants associated with AMD pathogenesis, studies on gene-environment interactions have gain increased relevance on the disease onset. Hence, maintenance of healthy diet, with the use of nutritional supplements has raised as a strategic preventive measure for personalized medicine in AMD.

The AMD multifactorial nature is currently well-established; however, how these factors interact to promote the development and progression of this condition remains largely unknown. This leads to a current lack of treatments for dry AMD and to halt its progression to AMD late blinding forms. Identification of progression biomarkers would be a major advance that could greatly improve patient care.



Contacts

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Research Program Main Goals

Contribute to the understanding of the pathophysiology of AMD, and to identify novel targets for future treatments of this condition and innovative diagnosis methods, focusing on:

- Structure and function relation in AMD
- Genomics and metabolomics of AMD
- Lifestyle and genetics interplay in AMD onset and progression
- Drug safety and effectiveness in AMD
- Development of innovative approaches, based on Artificial Intelligence, to facilitate AMD diagnosis

Ongoing Projects

AMD Metab - Metabolomics, Genetics and Environment - A novel integrative approach to Age-Related Macular Degeneration

ClinicalTrials.gov n°: NCT04241536

Sponsor: AIBILI

Financial support: EURETINA Retinal Medicine Clinical Research Award 2020

In collaboration with Massachusetts Eye and Ear Institute and the Harvard Medical School, Boston, USA.

This clinical study will elucidate the role of metabolomics in the understanding of AMD and will also identify potential biological-

ly robust biomarkers that can address the problem of predicting progression. It has the central hypothesis that patients with progression of AMD have a distinct metabolomic profile compared to patients in who AMD remains stable. Likewise, this study seeks to achieve the following aims:

- To characterize the metabolome of AMD progression over six years.
- To evaluate the relationship between metabolomics and genetics in AMD and identify new candidate AMD-metabolite associations.

COIMBRA EYE STUDY - Epidemiological study of the prevalence and incidence of Age-Related Macular Degeneration in Portugal
ClinicalTrials.gov n°: NCT01298674 and NCT02748824
Sponsor: AIBILI

Age-related Macular Degeneration in Portugal - Prevalence, incidence and risk factors in the era of multimodal imaging

The main objective of this clinical study is to take advantage of multimodal evaluation of possible risk factors and biomarkers, demographic factors, genetics and structural markers, to evaluate a possible progression biomarker and infer on an association with fast progressor AMD phenotype or another particular phenotype.

Age-Related Macular Degeneration: Genetic susceptibility, Nutrition and Lifestyle

The purpose of this project is to determine the effect modification on the risk of AMD onset and progression of high-risk-patients due to nutrition and lifestyle. It will assess on what grounds food, nutrients and lifestyle protect or not patients at genetic risk for AMD.

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

Sponsor: AIBILI

Financial support: IIR Grant from Bayer

This was a multicentre clinical study with the aim to compare the efficacy and safety of intravitreal aflibercept (IVA) with sham photodynamic therapy (sPDT) versus IVA with verteporfin photodynamic therapy (sPDT) in a Caucasian population with treatment-naïve PCV, enrolling in a treat and extend regimen. As only 22% of the eyes underwent PDT treatment, the benefit of combined treatment for PCV in Caucasian patients could not be definitively elucidated from this study.

Phenotypic and genotypic characterization of Polypoidal Choroidal Vasculopathy (PCV) in Caucasian populations. A multicenter retrospective study

This clinical study is a continuation of ATLANTIC study and aims to characterize the genetic, anatomical and imaging features of PCV in a large Caucasian population in order to provide a better understanding of this condition in this specific ethnicity.

MACUSTAR - Intermediate AMD: Development of Novel Clinical Endpoints for Clinical Trials in Patients with a Regulatory and Patient Access Intention

ClinicalTrials.gov n°: NCT03349801

Sponsor: UKB, Bonn, Germany

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

MACUSTAR is a multinational clinical study which the major objective of is to develop novel clinical endpoints for clinical trials with a regulatory and patient access intention in the area of functional, structural, and patient-reported outcome measures in patients with intermediate age-related macular degeneration (iAMD). MACUSTAR will also characterize visual impairment in iAMD and its progression, as well as identify risk factors for progression to late-stage AMD.

Representative Publications

Jordan-Yu, J. M. N. et al. **Phenotypic And Genetic Variations Between Asian And Caucasian Polypoidal Choroidal Vasculopathy Eyes.** Br. J. Ophthalmol. 317537, (2020). doi: 10.1136/bjophthalmol-2020-317537.

Farinha et al, **Age-Related Macular Degeneration Staging by Color Fundus Photography vs. Multimodal Imaging—Epidemiological Implications (The Coimbra Eye Study—Report 6)** J. Clin. Med. 2020, 9, 1329; doi:10.3390/jcm9051329.

Laíns I, et al. **Human Plasma Metabolomics in Age-Related Macular Degeneration: Meta-Analysis of Two Cohorts.** Metabolites. 2019 Jul 2;9(7). pii: E127. doi: 10.3390/metabo9070127.

Laíns I, et al **Urine Nuclear Magnetic Resonance (NMR) Metabolomics in Age-Related Macular Degeneration.** J Proteome Res. 2019 Mar 1;18(3):1278-1288. doi: 10.1021/acs.jproteome.8b00877.

Farinha C, et al. **Optical Coherence Tomography Leakage In Neovascular Age-Related Macular Degeneration: Identification of Choroidal Neovascularization Activity by Location and Quantification of Abnormal Fluid Under Anti-Vascular Endothelial Growth Factor Therapy.** Retina. 2019 Jan 24. doi: 10.1097/IAE.0000000000002470.

Terheyden J, Behning C, Lüning A, Wintergerst L, Basile P, Tavares D, Melício B, Leal S, Weissgerber G, Luhmann U., Crabb D, Tufail A, Hoyng C, Berger M, Schmid M, Silva R, Martinho C, Cunha-Vaz J, Holz F, Finger R, and on behalf of the MACUSTAR consortium: **Challenges, facilitators and barriers to screening study participants in early disease stages-experience from the MACUSTAR study.** BMC Medical Research

Methodology 2021 March; doi.org/10.1186/s12874-021-01243-8.

Farinha C et al. **Incidence of Age-Related Macular Degeneration in the Central Region of Portugal: The Coimbra Eye Study - Report 5.** Ophthalmic Res. 2019;61(4):226-235. doi: 10.1159/000496393.

Farinha C et al. **Retinal layer thicknesses and Neurodegeneration in Early Age-related Macular Degeneration – insights from the Coimbra Eye Study.** Graefes Arch Clin Exp Ophthalmol. 2021 Mar 18. doi: 10.1007/s00417-021-05140-0.

Raimundo M, et al. **Adherence to a Mediterranean diet, lifestyle and age-related macular degeneration: the Coimbra Eye Study - report 3.** Acta Ophthalmol. 2018 Dec;96(8):e926-e932. doi: 10.1111/aos.13775.

Laíns I, et al. **Human Plasma Metabolomics Study across All Stages of Age-Related Macular Degeneration Identifies Potential Lipid Biomarkers.** Ophthalmology. 2018 Feb;125(2):245-254. doi: 10.1016/j.ophtha.2017.08.008.

Nunes S, et al. **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. doi: 10.1016/j.nut.2017.12.010.

Laíns I, et al. **Choroidal Changes Associated With Subretinal Drusenoid Deposits in Age-related Macular Degeneration Using Swept-source Optical Coherence Tomography.** Am J Ophthalmol. 2017 Aug;180:55-63. doi: 10.1016/j.ajo.2017.05.021.

IMAGING BIOMARKERS RESEARCH PROGRAM

Coordinator: Conceição Lobo, MD, PhD

Research Team: Ana Rita Santos, João Figueira, José Cunha-Vaz, Luis Mendes, Maria Madeira, Torcato Santos

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.

Fundus Digital Photography, Optical Coherence Tomography (OCT) and Optical Coherence Tomography Angiography (OCTA) are non-invasive examinations that offer extremely promising perspectives as the data collected can be analyzed 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 also a novel AIBILI patented algorithm, the OCT-Leakage.



Contacts

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Research Program Main Goals

Development of new imaging techniques of the eye fundus without disturbing in any way the ocular and body environment. Particular interest is given to 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.

Ongoing Projects

Identification of Capillary Closure in using Optical Coherence Tomography Angiography

Sponsor: AIBILI

Financial Support: Partnership with Carl Zeiss Meditec (CA, USA)

The major goal is to identify reliable methods to quantify retinal vascular alterations, which allow disease characterization and identification of the different disease progression groups. As ultimate goal, we aim on facilitate disease stage identification in clinical practice, as well as to facilitate the identification of patients with higher risk for progression.

OCT-Leakage. Layer by layer fluid analysis of the retina

Sponsor: AIBILI

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.

Retinal-FluidMAPPING - Development and validation of OCT-based Abnormal Retinal FluidMapping

Sponsor: AIBILI

Financial Support: FCT PEX grant - EXPL/EMD-EMD/1402/2021

In this new project we propose to further explore the potential of OCT-Leakage and develop a more refined system to enable 3-dimensional visualization of extracellular fluid accumulation. This will allow mapping of microcystic and cystoid changes and therefore identify the distinctive features that characterize different responses to treatment.

The project Retinal FluidMAPPING has the goal of developing a software prototype tool that maps and quantifies abnormal accumulations of abnormal fluid to be used as a DME prognostic biomarker, facilitating a personalized ophthalmological healthcare and consequent reduction of societal and economic burden of DME.

Ultra-widefield CFP vs ETDRS

This study to be performed is expected to confirm the need for widefield imaging in more advanced stages of DR. Examination protocols are expected to be developed and tested.

The microvascular disease that plays a central role in the evolution of DR is expected to be better characterized by identifying the location and correlations of the different vascular alterations: microaneurysms, capillary closures, haemorrhages, venous abnormalities and neovessel formation.

Artificial intelligence for characterization of retinal biomarkers

The purpose is 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 diseases.

FILTER - Framework to Develop and Validate Automated Image Analysis Systems for Early Diagnosis and Treatment of Eyes at Risk in Blinding Age-Related Diseases

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

FILTER aims the development and validation of a prototype to be used in the screening and management of blinding age-related diseases.

The prototype will allow the detection, characterization, and follow-up of lesions associated with AMD and DR. Novel methods will be developed for the analysis of OCT imaging data and CFP images.

ADRIAN - Development and Validation of a Machine Learning Algorithms for Automated Prediction of Diabetic Retinopathy Progression

Sponsor: Roche, Switzerland

With this collaboration, ROCHE and AIBILI expects to develop and validate a machine learning (ML) algorithm that automatically predict Diabetes Mellitus patients that are at high risk for progression in Diabetic Retinopathy severity and vision-threatening conditions.

Research Contracts and Partnerships

Quantification of Retinal Microvasculature in Retinal Disease

Sponsor: Carl Zeiss Meditec, USA

ADRIAN - Development and Validation of a Machine Learning Algorithms for Automated Prediction of Diabetic Retinopathy Progression

Sponsor: Roche, Switzerland

Representative Publications

Vujosevic S, et al. **Standardisation of Optical Coherence Tomography Angiography Imaging Biomarkers in Diabetic Retinal Disease.** Ophthalmic Res. 2021 Jul 30. doi: 10.1159/000518620.

Santos, T. et al. **Swept source OCTA quantification of capillary closure predicts EDRS severity staging of NPDR.** Br. J. Ophthalmol. British Journal of Ophthalmology 2020 Dec 22;bjophthalmol-2020-317890. doi: 10.1136/bjophthalmol-2020-317890.

Marques IP, et al. **Multimodal Imaging of the Initial Stages of Diabetic Retinopathy: Different Disease Pathways in Different Patients.** Diabetes. 2019 Mar;68(3):648-653. doi: 10.2337/db18-1077. Epub 2018 Dec 6. PubMed PMID:30523027.

Pappuru RKR, et al. **Microaneurysm turnover is a predictor of diabetic retinopathy progression.** Br J Ophthalmol. 2019 Feb;103(2):222-226. doi: 10.1136/bjophthalmol-2018-311887. Epub 2018 Apr 26. PubMed PMID: 29699981; PubMed Central PMCID: PMC6362804.

Santos AR, et al. **Characterization of Initial Stages of Diabetic Macular Edema.** Ophthalmic Res. 2019;62(4):203-210. doi: 10.1159/000499117. Epub 2019 Apr 23. PubMed PMID: 31013506.

Santos AR, Alves D, Santos T, Figueira J, Silva R, Cunha-Vaz JG. **Measurements of retinal fluid by Optical Coherence Tomography 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.

Durbin MK, et al **Quantification of Retinal Microvascular Density in Optical Coherence Tomography Angiography Images in Diabetic Retinopathy,** JAMA Ophthalmol. 2017, vol. 135, N 4, pp 370-376.

Santos AR, et al; **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. Epub 2017 Jun 29. PubMed PMID: 28663190.

Cunha-Vaz J, et al. **Agreement between OCT Leakage and Fluorescein Angiography to Identify Sites of Alteration of the Blood-Retinal Barrier in Diabetes.** Ophthalmol Retina. 2017 Sep - Oct;1(5):395-403. doi: 10.1016/j.oret.2017.02.002. Epub 2017 Mar 29. PubMed PMID: 31047568.

Farinha C, et al. **OCT-Leakage Mapping: A New Automated Method of OCT Data Analysis to Identify and Locate Abnormal Fluid in Retinal Edema.** Ophthalmol Retina. 2017 Nov - Dec;1(6):486-496. doi: 10.1016/j.oret.2017.03.004. Epub 2017 May 10. PubMed PMID: 31047440.

Cunha-Vaz J, et al. **OCT-Leakage: A New Method to Identify and Locate Abnormal Fluid Accumulation in Diabetic Retinal Edema.** Invest Ophthalmol Vis Sci. 2016 Dec 1;57(15):6776-6783. doi: 10.1167/iops.16-19999. PubMed PMID: 27978559.

DRUG EVALUATION RESEARCH PROGRAM

Coordinator: Diogo Mendes, PhD

Research Team: Ana Penedones, Carlos Alves, Daniel Figueiredo, Francisco Batel Marques, Joana Abrantes

The demand 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, safety and economics of drugs R&D and reimbursement.

Research in Centre for Health Technology Assessment and Drug Research (CHAD) is, through several interconnected ongoing projects, aimed at real world outcomes, safety, economics and market access of drugs.



Research Program Main Goals

To strengthen the evaluation of medicines for the benefit of public health, through research and development of methodologies to assess their safety, effectiveness and efficiency.

Contacts

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Projects

DruSER.Net – Drug Safety and Effectiveness Research Network-
Sponsor: AIBILI

The DruSER.Net is a research network of Hospitals and Primary Healthcare Centres, 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.

START-Portugal-Register - The Portuguese survey on anticoagulated patients register

ClinicalTrials.gov n°: NCT03977363

Sponsor: AIBILI

The purpose of the PT-START-Register study is to record the clinical history of patients who initiate anticoagulation prospectively and without interfering with current clinical practice to generate evidence to assess the safety and effectiveness of the various therapeutic options.

Systematic review: role in drug safety and clinical effectiveness assessment

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.

Economic evaluation of ophthalmic medicines: does the results estimated based on pre-marketing evidence correlates with clinical practice?

The main objective of this research is to clarify the role of pharmacoeconomic studies as a tool to inform policy decision making of ophthalmic medicines. The research will also identify, characterize and assess the methodological quality of pharmacoeconomic studies of ophthalmic medicines, and it will evaluate if the results of economic studies reflect the findings from real-world clinical practice evidence.

Network Meta-analysis

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.

Methodologies and metric indices in HTA for market access

The aim of this research is to focus on methodological challenges that are encountered by health technology assessment (HTA) assessors while performing assessments of medicines for market access. Identify which methodology guidelines have been used to determine the therapeutic and economic value of medicines in the context of HTA for reimbursement purposes. Understand the actual role and value of metric indices to make health evaluations as useful and transferable as possible.

Coimbra Pharmacovigilance Regional Centre

The main aim is to validate the post-marketing adverse drug reactions reported to the Coimbra Regional Unit of the Portuguese Pharmacovigilance System, by assessing causality, seriousness and previous knowledge. Different techniques for safety signals generation are being tested and applied.

Covid Vaccine Monitor: Safety monitoring of SARS-CoV-2 vaccines in EU Member States

Sponsor: Universiteit Utrecht, Netherlands

The Coimbra Pharmacovigilance Regional Centre together with two other regional centres (Lisbon and Porto) of the Portuguese Pharmacovigilance System comprise the CLPP Vaccines Network,

which participates in a consortium of 8 European countries (Ireland, Italy, Portugal, Romania, Slovakia, Spain, Switzerland, and the Netherlands) to carry out the Work Package (WP) 1 “Co-hort Event Monitoring of safety of COVID-19 vaccines in special populations (pregnant and lactating women, children and adolescents, immunocompromised, people with history of allergy, people with prior SARS-CoV-2 infection)” of the Covid Vaccine Monitor (CVM) project, which is coordinated by the University of Utrecht. The study is funded by the European Medicines Agency (EMA). The primary aim of the WP1 is to generate and compare incidence rates of patient-reported adverse reactions of different COVID-19 vaccines in special populations.

Representative Publications

Alves C, et al. **Risk of Cardiovascular and Venous Thromboembolic Events Associated With Janus Kinase Inhibitors in Rheumatoid Arthritis: A Systematic Review and Network Meta-analysis.** J Clin Rheumatol. 2021 Nov 3. doi: 10.1097/RHU.0000000000001804.

Alves C, et al. **The Risk of Infections Associated With JAK Inhibitors in Rheumatoid Arthritis: A Systematic Review and Network Meta-analysis.** J Clin Rheumatol. 2021 Apr 24. doi: 10.1097/RHU.0000000000001749.

Alves C, et al. **Risk of infections and cardiovascular and venous thromboembolic events associated with JAK inhibitors in rheumatoid arthritis: protocols of two systematic reviews and network meta-analyses.** BMJ Open. 2020 Dec 31;10(12):e041420. doi: 10.1136/bmjopen-2020-041420.

Mendes D, et al. **Rectus sheath hematoma in patients receiving subcutaneous enoxaparin: A case series of five patients.** Clin Case Rep. 2020 Oct 27;8(12):3432-3439. doi: 10.1002/ccr3.3427.

Mendes D, et al. **Real-world intensive safety monitoring of biosimilars rituximab and trastuzumab in a Portuguese oncology hospital.** J Oncol Pharm Pract. 2021 Sep;27(6):1432-1438. doi: 10.1177/1078155220957079.

Mendes D, et al. **Intensive safety monitoring program of antineoplastic medicines: A pilot study in a Portuguese oncology hospital.** J Oncol Pharm Pract. 2020 Jan;26(1):133-140. doi: 10.1177/1078155219849277.

Ribeiro I, et al. **A Systematic Review of Economic Studies Evaluating Ophthalmic Drugs: An Analysis of the Health-state Utilities.** Ophthalmic Epidemiol. 2020 Oct;27(5):325-338. doi: 10.1080/09286586.2020.1792938.

Penedones A, et al. **Risk of nonarteritic ischaemic optic neuropathy with phosphodiesterase type 5 inhibitors: a systematic review and meta-analysis.** Acta Ophthalmol. 2020 Feb;98(1):22-31. doi: 10.1111/aos.14253.

Mendes D, et al. **Spontaneous reports of hypersensitivity adverse drug reactions in Portugal: a retrospective analysis.** Expert Opin on Drug Safety 2020, DOI: 10.1080/14740338.2020.1743262

Ribeiro I, et al. **An analysis of the effectiveness outcomes of economic studies evaluating ophthalmic drugs: a systematic review.** Acta Ophthalmol. 2020 Jan 30. doi: 10.1111/aos.14362.

Alves C, et al. **Fluoroquinolones and The risk of tendon injury: a systematic review and meta-analysis.** Eur J Clin Pharmacol. 2019 Oct;75(10):1431-1443.

Batel Marques F, et al. **Effectiveness in clinical practice versus efficacy of dipeptidyl peptidase-4 inhibitors in clinical trials for type 2 diabetes: protocol for systematic review.** BMJ Open 2019;9:e032522.

Penedones A, et al. **A comparison between two recommendations to conduct and report systematic reviews on drug's safety.** Syst Rev. 2019 Oct 16;8(1):238.

TRANSLATIONAL VISION RESEARCH PROGRAM

Coordinator: António Francisco Ambrósio, PhD

Research Team: Ana Paula Silva, Ana Raquel Santiago, Henrique Alves, José Cunha-Vaz, Maria Madeira, Rosa Fernandes

AIBILI and the Faculty of Medicine of the University of Coimbra have a historical relationship, particularly with the Coimbra Institute for Clinical and Biomedical Research (iCBR, former IBILI). This represents an excellent and strategic opportunity for the facilitation of Translational Research and of innovation based on knowledge gathered from fundamental research on vision science.

This research area at AIBILI, named 'Translational Vision Research', results from the previous and fruitful collaboration with the Retinal Dysfunction and Neuroinflammation Lab, a Group from iCBR headed by the coordinator of this Program, Francisco Ambrósio.



Research Program Main Goals

To promote innovative translational vision research, not only by translating laboratory science into new therapeutic strategies, but also by finding new biomarkers of disease, disease progression and response to therapy.

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Projects

Biomarkers of disease, disease progression and response to therapy.

With a clear translational perspective, and with the aim of bridging the gap between fundamental and clinical research and finding new biomarkers, the aim is to analyse ocular fluids (tears, aqueous humour, vitreous humour) and blood, namely at a molecular level, to access proteins, microRNAs, mitochondrial DNA and antimicrobial peptides (AMPs).

New links between tears composition and Diabetic Retinopathy

Cross-sectional, non-interventional study including healthy controls and T2D patients without and with NPDR or PDR from both genders and between 40-75 years, which aims to evaluate changes in tear protein profiles that can act as early biomarkers for diagnosis Diabetic Retinopathy onset and be useful do predict or monitor its progression. Further this study aims to establish associations between changes in the composition and stability of the tear fluid, as well as, with DR progression.

The retina as a window to the brain or a mirror of the brain

Taking advantage of the communication between retina and brain, we will assess structural, functional, cellular and molecular changes in the retina and will try to establish correlations with changes occurring in the brain in the context of Alzheimer's disease, and Attention Deficit Hyperactivity Disorder (ADHD).

Development of new potential therapeutic strategies for retinal diseases

Target the unmet need for novel potential advanced therapeutic strategies to retinal degenerative diseases, focusing on testing the efficacy of molecular entities that have been selected based on our studies focused on the mechanism of disease, and new delivery routes, such as biodegradable implants or microparticles loaded with drugs of interest.

Representative Publications

- Ramos Rego I, Santos Cruz B, Ambrósio AF, Alves CH. **TRAP1 in Oxidative Stress and Neurodegeneration.** *Antioxidants* (Basel). 2021 Nov 19;10(11):1829. doi: 10.3390/antiox10111829.
- Aires ID, Ribeiro-Rodrigues T, Boia R, Ferreira-Rodrigues M, Girão H, Ambrósio AF, Santiago AR. **Microglial Extracellular Vesicles as Vehicles for Neurodegeneration Spreading.** *Biomolecules*. 2021 May 21;11(6):770. doi: 10.3390/biom11060770.
- Rodrigues-Neves AC, Carecho R, Correia SC, Carvalho C, Campos EJ, Baptista FI, Moreira PI, Ambrósio AF. **Retina and Brain Display Early and Differential Molecular and Cellular Changes in the 3xTg-AD Mouse Model of Alzheimer's Disease.** *Mol Neurobiol*. 2021 Jul;58(7):3043-3060. doi: 10.1007/s12035-021-02316-x.
- Campos A, Campos EJ, Martins J, Ambrósio AF, Silva R. **The value of choroidal thickness in diabetic macular oedema is contradictory.** *Acta Ophthalmol*. 2021 Mar;99(2):e281-e282. doi: 10.1111/aos.
- Campos A, et al. **Choroidal and retinal structural, cellular and vascular changes in a rat model of Type 2 diabetes.** *Biomed Pharmacother*. 2020 Dec;132:110811. doi: 10.1016/j.biopha.2020.110811
- Ferreira-Silva J, et al. **Activation of Adenosine A3 Receptor Inhibits Microglia Reactivity Elicited by Elevated Pressure.** *Int J Mol Sci*. 2020 Sep 30;21(19):7218. doi: 10.3390/ijms21197218
- Campos A, Campos EJ, Martins J, Rodrigues FSC, Silva R, Ambrósio AF. **Inflammatory cells proliferate in the choroid and retina without choroidal thickness change in early Type 1 diabetes.** *Exp Eye Res*. 2020 Oct;199:108195. doi: 10.1016/j.exer.2020.108195. Epub 2020 Aug 22.
- Aires ID, Ribeiro-Rodrigues T, Boia R, Catarino S, Girão H, Ambrósio AF, Santiago AR. **Exosomes derived from microglia exposed to elevated pressure amplify the neuroinflammatory response in retinal cells.** *Glia*. 2020 Dec;68(12):2705-2724. doi: 10.1002/glia.23880. Epub 2020 Jul 9. PMID: 32645245
- Socodato R, Portugal CC, Canedo T, Rodrigues A, Almeida TO, Henriques JF, Vaz SH, Magalhães J, Silva CM, Baptista FI, Alves RL, Coelho-Santos V, Silva AP, Paes-de-Carvalho R, Magalhães A, Brakebusch C, Sebastião AM, Summavielle T, Ambrósio AF, Relvas JB. **Microglia Dysfunction Caused by the Loss of Rhoa Disrupts Neuronal Physiology and Leads to Neurodegeneration.** *Cell Rep*. 2020 Jun 23;31(12):107796. doi: 10.1016/j.celrep.2020.107796. PMID: 32579923
- Boia R, et al. **Activation of adenosine A3 receptor protects retinal ganglion cells from degeneration induced by ocular hypertension.** *Cell Death Dis*. 2020 May 27;11(5):401. doi: 10.1038/s41419-020-2593-y
- Salobar-García E, Rodrigues-Neves AC, Ramírez AI, de Hoz R, Fernández-Albarral JA, López-Cuenca I, Ramírez JM, Ambrósio AF, Salazar JJ. **Microglial Activation in the Retina of a Triple-Transgenic Alzheimer's Disease Mouse Model (3xTg-AD).** *Int J Mol Sci*. 2020 Jan 27;21(3):816. doi: 10.3390/ijms21030816. PMID: 32012676
- Aires ID, et al. **Intravitreal injection of adenosine A2A receptor antagonist reduces neuroinflammation, vascular leakage and cell death in the retina of diabetic mice.** *Sci Rep*. 2019 Nov 20;9(1):17207. doi: 10.1038/s41598-019-53627-y.
- Chiquita S, et al. **Retinal thinning of inner sub-layers is associated with cortical atrophy in a mouse model of Alzheimer's disease: a longitudinal multimodal in vivo study.** *Alzheimers Res Ther*. 2019 Nov 13;11(1):90. doi: 10.1186/s13195-019-0542-8
- Boia R, et al. **Porous poly(E-caprolactone) implants: A novel strategy for efficient intraocular drug delivery.** *J Control Release*. 2019 Dec 28;316:331-348. doi: 10.1016/j.jconrel.2019.09.023. Epub 2019 Nov 9. PMID: 31715277

5

INTERNATIONAL NETWORKING

EVICR.net - EUROPEAN VISION INSTITUTE CLINICAL RESEARCH NETWORK



AIBILI is the Coordinating Centre of EVICR.net, that is responsible for the management of the Network, coordination of multinational clinical research studies as well as developing training activities in ophthalmology clinical research.

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 Standard Operating Procedures (SOPs) ICH - GCP compliant.

At present, EVICR.net has 88 Clinical Ophthalmological Research Centres members from 14 European countries.

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). 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 organisational 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 EVICR.net certified Clinical Site of Excellence.

Scientifically it is organised 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.

Chairman: Prof. Hendrik Scholl, CS n°110, University Hospital Basel, University Eye Clinic, Basel, Switzerland.

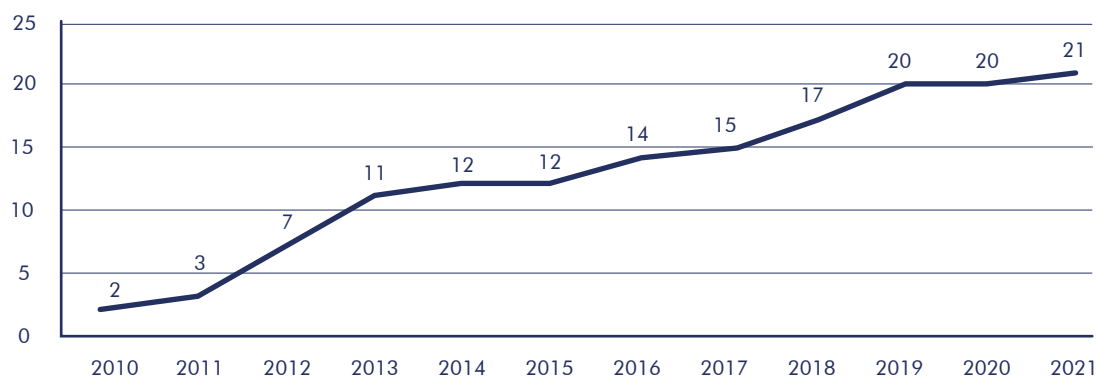
CLINICAL STUDIES AND REGISTRIES

AIBILI as EVICR.net Coordinating Centre, assumes the 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 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.

EVICR.net MULTINATIONAL CLINICAL RESEARCH STUDIES (2010-2021)

Number of Multinational Clinical Research Studies



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 2021 there were eight ongoing multinational clinical research studies of which 3 are European Union funded.

More information:
www.evicr.net

Ongoing Clinical Studies and Activities

Age-Related Macular Degeneration

- ATLANTIC (IIR, Industry grant)
- MACUSTAR (IIR, EU funded – IMI2)
- MADEOS (External-sponsored)

Retinal Dystrophies

- IRD Survey (Industry Collaboration)

Diabetic Retinopathy

- RECOGNISED (IIR, EU funded – H2020)
- CHART (IIR, Industry Grant)

Anterior Segment

- REDCAKE (IIR, Flemish grant)
- ANIRIDIA-NET (EU funded - COST)

EDUCATIONAL PROGRAMME

EVICR.net has developed a continual training and educational programme with webinars on ophthalmology clinical research. The Educational Programme is organised in modules each with three webinars of one hour.

Currently the following modules are available at www.evicr.net/webinars/webinars/ to the whole community:

REPRESENTATIVE PUBLICATIONS

Lorenz B, Tavares J, van den Born LJ, Marques JP, Scholl HPN. **Current management of Inherited Retinal Degenerations (IRD) patients in Europe. Results of a multinational survey by the European Vision Institute Clinical Research Network EVICR.net.** Ophthalmic Res. 2021 Jan 19. doi: 10.1159/000514540.

Lorenz B, Tavares J, van den Born LJ, Marques JP, Scholl HPN, The EVICR.net Group. **Current management of patients with RPE65 mutation-associated inherited retinal degenerations (IRDs) in Europe. Results of a multinational survey by the European Vision Institute Clinical Research Network EVICR.net.** 2021 Mar 8. doi: 10.1159/00051568.

Silva R, Arias L, Nunes S, Farinha C, Coimbra R, Marques JP, Cachulo ML, Figueira J, Barreto P, Madeira MH, Pires I, Sousa JC, Distefano L, Rosa P, Carneiro A, Vaz-Pereira S, Meireles A, Cabrera F, Bures A, Luís Mendonça, Fernandez-Vega Sanz A, Barrão S, Koh A, Cheung CMG, Cunha-Vaz J, Murta J, EVICR.net ATLANTIC Study Group. **Efficacy and safety of Intravitreal Afibercept Vs Verteporfin Photodynamic Therapy in a Caucasian Population with Polypoidal Choroidal Vasculopathy: A Randomized Clinical Trial.** Ophthalmologica. 2021 Jul 13. doi: 10.1159/000518235.

Terheyden JH, Behning C, Lüning A, Wintergerst L, Basile PG, Tavares D, Melicio BA, Leal S, Weissgerber G, Luhmann UFO, Crabb DP, Tufail A, Hoyng C, Berger M, Schmid M, Silva R, Martinho CV, Cunha-Vaz J, Holz FG, Finger RP; MACUSTAR consortium. **Challenges, facilitators and barriers to screening study participants in early disease stages-experience from the MACUSTAR study.** BMC Med Res Methodol. 2021 Mar 17;21(1):54. doi: 10.1186/s12874-021-01243-8.

Vujosevic S, Cunha-Vaz J, Figueira J, Löwenstein A, Midena E, Parravano M, Scanlon PH, Simó R, Hernández C, Madeira MH, Marques IP, Martinho AC, Santos AR, Simó-Servat O, Salongcay RP, Zur D, Peto T. **Standardisation of Optical Coherence Tomography Angiography Imaging Biomarkers in Diabetic Retinal Disease.** Ophthalmic Res. 2021 Jul 30. doi: 10.1159/000518620.

Phase **First step - General** **Second Step - Scientific**

Educational Programme Module	Available						Now Available		
	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	Unmet needs in Glaucoma	Retinal Dystrophies		
Webinars	Webinar #1	Webinar #4	Webinar #4	Webinar #8	Webinar #11	Webinar #14	Webinar #17	Webinar #20	Webinar #23
	How to setup a clinical research study	DME definition, classification and imaging	DME definition, classification and imaging	Landmark clinical trials in glaucoma	Dry eye syndrome: signs and symptoms	Patient compliance & IOP telemetry	Inherited Retinal Dystrophies: Overview Causative Genes and Diagnostic Approach	Macular Dystrophies	Genetic Diagnostics in IRDs
	Webinar #2	Webinar #5	Webinar #5	Webinar #9	Webinar #12	Webinar #15	Webinar #18	Webinar #21	
	Clinical research organisation	Predicting progression and treatment response	Predicting progression and treatment response	Risk factors in glaucoma	Diagnosis in dry eye syndrome	Non-IOP dependent strategies	Retinitis Pigmentosa and Gene Therapy	Functional Diagnostics of The Retina in IRDs	
	Webinar #3	Webinar #6	Webinar #7	Webinar #10	Webinar #13	Webinar #16	Webinar #19	Webinar #22	
	SOPs – quality and certification	Treatment of DME	Anti-VEGF treatment of DME	Glaucoma Who to treat and when	Treatment of dry eye syndrome	Surrogate markers and outcome measures & Early diagnosis	Differential Diagnostics of Juvenile and Childhood Genetic Diseases of The Retina	Retinal imaging in IRDs	

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.

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 in Coimbra, Portugal and the Institute for Vision at the Federal University of S. Paulo in S. Paulo, Brazil.

More information:

[www.first.fchampalimaud.org/en/
champalimaud-research/c-tracer](http://www.first.fchampalimaud.org/en/champalimaud-research/c-tracer)

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 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 clinical research in ophthalmology, 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 whereas, ECRIN provides support in the submission and coordination at national level. The MACUSTAR clinical study is an example of this collaboration where the overall clinical study coordination is performed by EVICR.net under the leadership of Prof. Frank Holz, UKB, Bonn, Germany (Sponsor), and the submission and monitoring activities are performed by ECRIN.

More information:

<https://www.ecrin.org>

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 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, is member of EATRIS and has capacities in the Biomarkers and Imaging and Tracing platforms.

The logo for EATRIS, featuring the word "eatris" in a bold, lowercase, sans-serif font.

European infrastructure
for translational medicine

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

ERN-EYE - EUROPEAN REFERENCE NETWORK ON RARE EYE DISEASES

The European Reference Network on Rare Eye Diseases (ERN-EYE) is led by Prof. Hélène Dollfus (Strasbourg, France) and is composed of 29 health care providers (HCP) in 13 full members countries and 15 HCPs in 7 affiliated partners countries across European Union. ERN-EYE is organised in thematic groups: 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 its long 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.



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

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PARTNERS



ARSC – HEALTH ADMINISTRATION OF THE CENTRE REGION OF PORTUGAL

ARSC 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 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 Centre Region of Portugal Screening Programme for Diabetic Retinopathy.



FMUC – FACULTY OF MEDICINE OF THE COIMBRA UNIVERSITY

The Faculty of Medicine of the University of Coimbra (FMUC) is one of the most important schools of medicine in Portugal due to its vast research areas. The partnership between AIBILI and FMUC allows AIBILI to coordinate clinical research from FMUC investigators.



Escola Superior de Enfermagem de Coimbra

ESEnFC - NURSING SCHOOL OF COIMBRA

ESEnFC is a public institution of national and international reference, dedicated to the education of nurses in health education, research and innovation. AIBILI and ESEnFC signed a partnership agreement for the development of clinical research activities that brings together two institutions in the city of Coimbra. This partnership includes the promotion of training activities focused on clinical research, as well as strengthening the international presence through the networks in which both institutions are involved.



Health Cluster Portugal Pólo de Competitividade da Saúde

HCP – HEALTH CLUSTER PORTUGAL

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.



ICBR – COIMBRA INSTITUTE FOR CLINICAL AND BIOMEDICAL RESEARCH

Coimbra Institute for Clinical and Biomedical Research (iCBR), formerly IBILI, is a multidisciplinary research unit from the Faculty of Medicine, University of Coimbra (FMUC). Research at iCBR aims to investigate molecular and cellular mechanisms underlying the pathophysiology of chronic diseases, to identify innovative therapeutic strategies and disease biomarkers, as well as to unveil and implement new approaches to promote the quality of life and wellness.

The partnership between AIBILI and iCBR aims on filling the gaps between Pre-Clinical and Clinical Research, setting the ground for the development of innovative research projects, translating basic science into new therapeutic strategies, but also by using human samples to find new biomarkers of disease, disease progression and response to therapy.



INFARMED - NATIONAL AUTHORITY OF MEDICINES AND HEALTH PRODUCTS, I.P.

INFARMED, IP 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 collaborate in the framework of the national strategy for the development of clinical research in the pharmaceutical sector. Since 2008 that AIBILI-CHAD has been responsible for a Pharmacovigilance Unit of the National Pharmacovigilance System contracted with INFARMED, IP.



I3S – INSTITUTE FOR RESEARCH AND INNOVATION IN HEALTH OF THE UNIVERSITY OF PORTO

The i3S merges three institutes and researchers from several schools of the Porto University, thus consolidating an extensive collaboration between all institutions. 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 increases 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.



INFOCUS CLINICAL RESEARCH

INFOCUS 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 together they are able to provide a global ophthalmology clinical research support to industry.



HOSPITAL CUF COIMBRA - JOSÉ DE MELLO SAÚDE

The CUF Coimbra Hospital provides access to excellent health services, both inpatient and outpatient with a comprehensive and innovative offer in diverse medical-surgical areas.

The partnership between AIBILI and CUF Coimbra Hospital main goal is the coordination and development of clinical research facilitating the exchange of scientific and technical knowledge and taking advantages of the expertise and resources of each institution.

BIO – PORTUGAL'S BIOTECHNOLOGY INDUSTRY ORGANIZATION

P-BIO 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 allows 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 as well as to the coordination and overall management of clinical research studies.



PTCRIN – PORTUGUESE ACADEMIC CLINICAL RESEARCH INFRASTRUCTURES NETWORK

PtCRIN 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 and is a Clinical Trial Unit as well as a Clinical Research Centre. AIBILI has the only ECRIN Certified Data Centre in the Iberian Peninsula since 2016 and was recently recertified by ECRIN (2021).

UA – AVEIRO UNIVERSITY

The UA is a public foundation under private law whose mission is to contribute to and develop graduate and postgraduate education and training, research and cooperation with society. This partnership with AIBILI allows to cooperate in clinical research activities as well as to students from the Master in Medical Statistics of UA to perform internships at AIBILI.

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