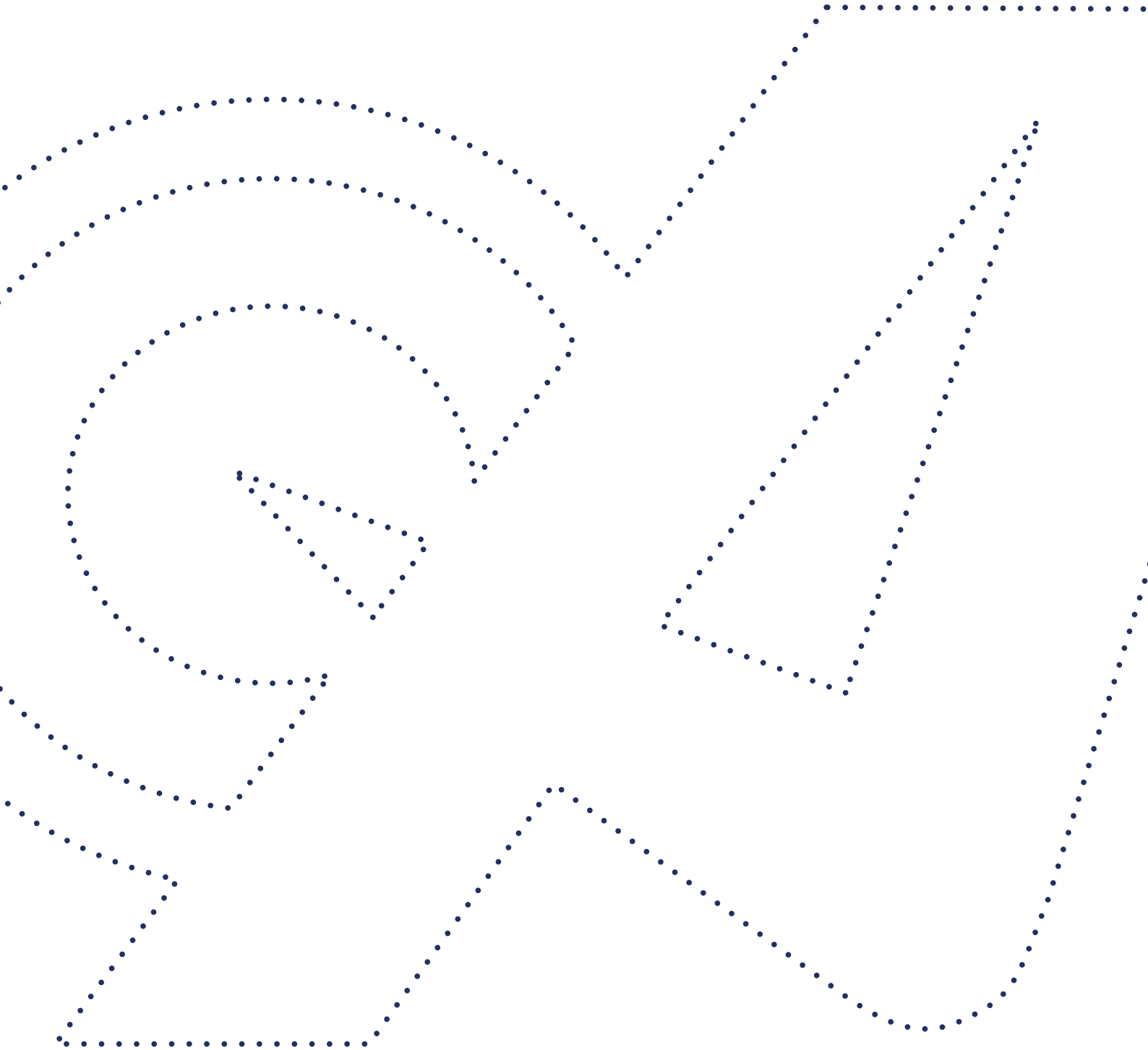
ANNUAL REPORT
2020

AIBILI



Association for Innovation
and Biomedical Research
on Light and Image

ANNUAL REPORT
2020

AIBILI

CONTENTS

MESSAGE FROM THE PRESIDENT

AIBILI was created 31 years ago, from a dream of Professor José Cunha-Vaz to establish in Portugal a reference ophthalmology research institution. His brilliant mind and his ability to envision the future allowed him to make that dream a reality. Several units started their activity, namely the Clinical Trials Centre (CEC) and the Centre of New Technologies for Medicine (CNTM) and over the years they have grown, with the aim of supporting translational research and technology transfer in the health area. Other units have emerged precisely to respond to all aspects of clinical research, such as the Coordinating Centre for Clinical Research (4C), the Ophthalmology Reading Centre (CORC), the Centre for Health Technology Assessment and Drug Research (CHAD), and support units as the IT/Data Centre, the Quality Management and the Translational Research/Technology Transfer Unit. All these are interconnected and very well established to meet one common objective, which is to enable the institution to contribute to scientific knowledge in the areas of ophthalmology, neurosciences, imaging and pharmacology and to develop tools to improve health care delivery. Thus, AIBILI has stood out and has been recognized nationally and internationally in its different aspects. At national level, AIBILI was recognized as an Interface Centre by the Portuguese Ministry of Economy, being the only one in the health sector. At the international level, AIBILI has a leading role in the coordination of the EVICR.net, a European network of 96 ophthalmology clinical research centres from 14 countries, additionally is an active partner in joint projects and publications with reference centres in Europe and the United States of America.

The year of 2020 was a challenging year, and at AIBILI a transition year which make us look to the future with ambition. For me, this challenge started when I assumed the position of President of AIBILI, very aware of the enormous responsibility, but also confidant that with the help of an excellent team which has been built over the years, it is possible to continue the pathway of research and innovation in the Health Sector, maintaining the levels of excellence, contributing to the development of scientific knowledge and bring it to the market. Our Strategic Scientific Research Program is illustrative of our scientific activity and shows the different lines of research in which we intend to remain active, with well-defined objectives and adapted to the need to keep up with the acceleration of innovation that has occurred in recent years. With the connection with other research groups and establishing collaborations in projects, we intend to promote the interaction of different research areas, which allow us to have the contribution of multidisciplinary teams, to obtain more knowledge on the understanding of the disease and development of solutions to promote and improve the quality of life.

Conceição Lobo
President

1 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:

- Coordination of clinical trials at both national and multinational levels
- Performance of clinical studies
- Centralized grading of eye examinations
- Research and development of new technologies for medicine in the area of imaging
- Health technology assessment
- 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.

AIBILI is located in the area of the Health Campus of Coimbra University since 1994 and has its own building with 1.454 m2 and state-of-the-art equipment.
Regarding human resources it has a permanent staff of 59 including medical doctors, researchers, engineers, pharmacologists, technicians, project managers, statisticians data managers, study coordinators and administrative personnel. Another 60 professionals collaborate regularly in research activities.

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.

Contacts

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www.aibili.pt

INTERFACE CENTRE IN THE HEALTH SECTOR

Centro Interface

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 products to the market in the health area.

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

- 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
- 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

With these priorities and participation in international reference networks, together with the quality management system implemented, AIBILI is positioned to achieve excellence in research and innovation that will contribute to society through the promotion of improvements in clinical practice.

BIOTECHNOLOGY AND LIFE SCIENCES FOCUS: HUMAN HEALTH

FINANCIADO POR

FITEC Fundo de Inovação, Transferência de Tecnologia e Economia Circular

PROGRAMA INTERFACE

Programa Nacional de Reformas

REPÚBLICA PORTUGUESA

ASSOCIATES

Founding Associates

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

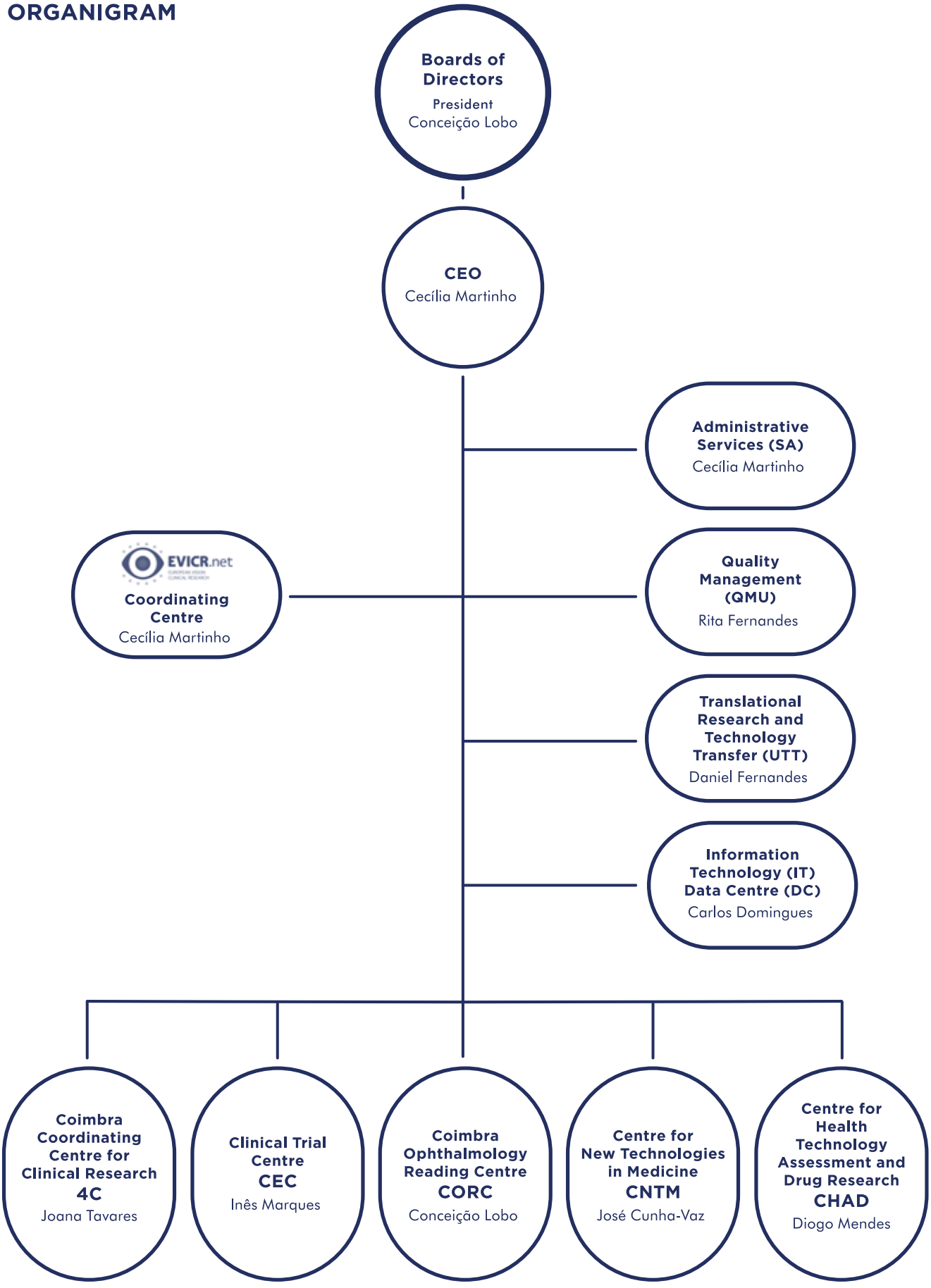
Other Associates

- Alcon Portugal - Prod. e Equip. Oftalmológicos, Lda.
- BIAL - Portela & Cª., SA
- 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 & Cª, 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


Boards of Directors
President
Conceição Lobo
CEO
Cecília Martinho
Administrative Services (SA)
Cecília Martinho
EVICR.net
Coordinating Centre
Cecília Martinho
Quality Management (QMU)
Rita Fernandes
Translational Research and Technology Transfer (UTT)
Daniel Fernandes
Information Technology (IT) Data Centre (DC)
Carlos Domingues
Coimbra Coordinating Centre for Clinical Research
4C
Joana Tavares
Clinical Trial Centre
CEC
Inês Marques
Coimbra Ophthalmology Reading Centre
CORC
Conceição Lobo
Centre for New Technologies in Medicine
CNTM
José Cunha-Vaz
Centre for Health Technology Assessment and Drug Research
CHAD
Diogo Mendes

2 AIBILI IN NUMBERS

1989 — **AIBILI Foundation**

1991 — Public Utility recognition

1994 — 
1ST Building in the Coimbra University Health Campus

1999 — Good Laboratory Pratices certification

2004 — ISO 9001 certification
+
Coordinating Centre

2008 — Expansion of AIBILI **CORC** and **CHAD**

Establishment of DruSER Net + CIT Centro Interface recognition by Ministry of Economy

Champalimaud Foundation European C-TRACER Member

2009 Expansion of AIBILI **4C** + Retmarker Official market launch

2010

2016 ECRIN European Clinical Research Infrastructure Network Data Centre certification

2017

2019 AIBILI 30 Years of Excellence

2020

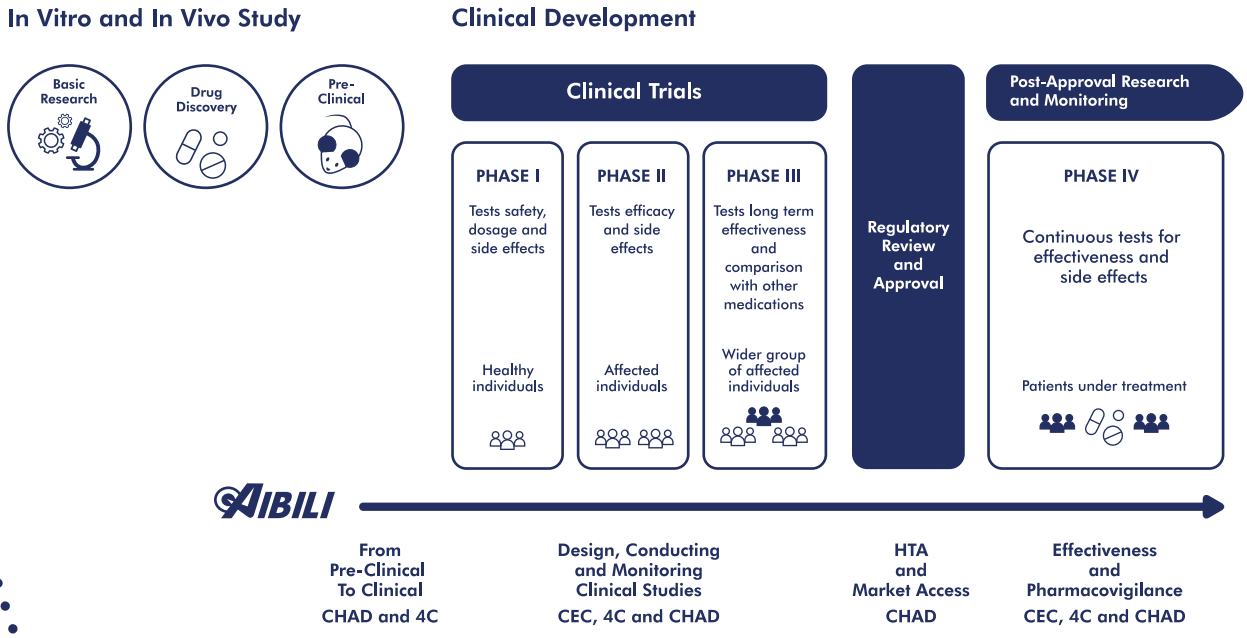
Fulltime Staff	**59**
Nº of PhD	**21**
Nº of Consultants	**42**
Nº of Ongoing studies, services, projects, contracts	**108**
Nº of Patents	**3 (USA) + 1 (Europe)**
Nº of European Union funded projects (ongoing)	**2**
Nº of Publications (2019-2020)	**84**
Nº of Publications / PhD (2019-2020)	**4,7**

3 AIBILI RESEARCH CENTRES AND UNITS

AIBILI is organised in Research Centres and Organisational 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)

Organisational Units are:
- Administrative Services (SA)
- Quality Management Unit (QMU)
- Translational Research and Technology Transfer Unit (UTT)
- Information Technology Unit (IT)



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, Laura Seco, Liliana Carvalho, José Cunha-Vaz, Maria Viegas Nascimento, Paulo Faria, Pier Basile, Rita Coimbra, Rita Fernandes, Sónia Simões

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:

Contacts
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E-mail: jftavares@aibili.pt

PRE-STUDY	IN-STUDY	POST-STUDY
• Study Design	• Study Coordination	• Data Base Lock
• Statistical Planning	• IMP Management	• Biostatistics
• Development of Protocol and Informed Consent	• eCRF Management and Support [1]	• Final Report
• eCRF Development [1]	• Data Management [1]	• Regulatory Affairs
• Database Validations and Implementation [1]	• Monitoring	• Publication
• MF and Site File development	• Pharmacovigilance [2]	
• Clinical Centre Selection		
• SOPs Development		
• Submission to RAs		
• Insurance and Contracts		
• Monitoring Planning		

ECRIN

1 **DATA-CENTRE** 2 **CHAD**

Nº of Projects Coordinated by 4C (2018-2020)

	Coordination of Clinical Studies (nº)			
Year	Investigator Initiated	Industry Sponsored	Other	Total
2018	16	2	3	21
2019	14	2	4	20
2020	**13**	**2**	**4**	**19**

Representative Publications

De Breuk A, Acar IE, Kersten E, Schijvenaars MMVAP, Colijn JM, Haer-Wigman L, Bakker B, de Jong S, Meester-Smoor MA, Timo Verzijden, Missotten TOAR, Monés J, Biarnés M, Pauleikhoff D, Hense HW, Silva R, Nunes S, Melo JB, Fauser S, Hoyng CB, Ueffing M, Coenen MJH, Klaver CCW, den Hollander AI, EYE-RISK Consortium. **Development of a Genotype Assay for Age-Related Macular Degeneration: The EYE-RISK Consortium** Ophthalmology. 2020 Jul 24;S0161-6420(20)30725-9. doi: 10.1016/j.ophtha.2020.07.037.

Terheyden J, Holz F, Schmitz-Valckenberg S, Lüning A, Schmid M, Rubin G, Dunbar H, Tufail A, Crabb D, Binns A, Sánchez C, Hoyng C, Margaron P, Zakaria N, Durbin M, Luhmann U, Zamiri P, Cunha-Vaz J, Martinho C, Leal S, Finger R. on behalf of the MACUSTAR consortium. **Clinical study protocol for a low-interventional study in intermediate age-related macular degeneration developing novel clinical end-points for interventional clinical trials with a regulatory and patient access intention – MACUSTAR)**. Trials. 2020 Jul 18;21(1):659. doi: 10.1186/s13063-020-04595-6.

Farinha C, Cachulo ML, Coimbra R, Alves D, Nunes S, Pires I, Marques JP, Costa J, Martins A, Sobral I, Barreto P, Laíns I, Figueira J, Ribeiro L, Cunha-Vaz J, Silva R. **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.

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.

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

CEC - Clinical Trial Centre

Director: **Inês Marques**, MD

Staff: Aida Vitorino, Ana Maria Nunes, Ana Rita Santos, Andreia Santos, Catarina Eloy, Céu Simões, Conceição Lobo, Eugénia Cardoso, Filipe Martins, Isabel Pires, Luisa Ribeiro, João Figueira, José Costa, José Cunha-Vaz, Maria da Luz Cachulo, Maria Viegas Nascimento, Marcela Pascoal, Marta Lopes, Miguel Amaro, Patrícia Barreto, Patrícia Martins 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 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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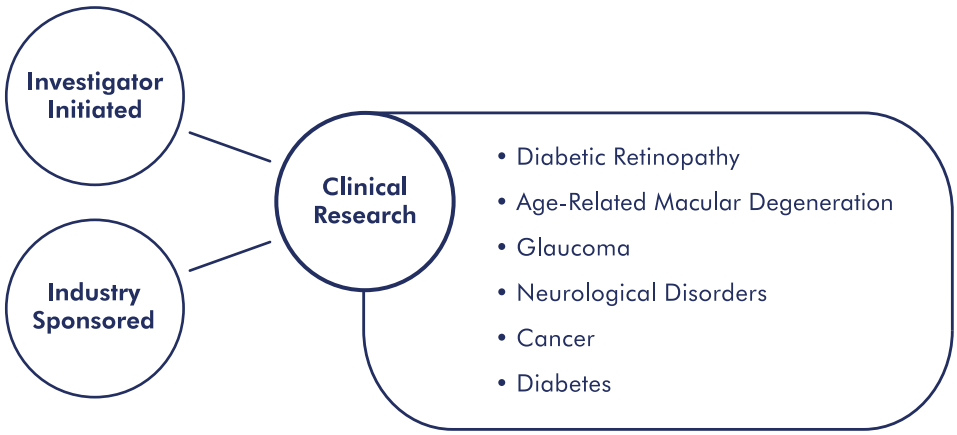

Nº of Investigator Initiated and Industry Sponsored studies performed at CEC (2018-2020)

	N° of Clinical Studies		
Year	Investigator Initiated	Industry Sponsored	Total
2018	6	15	21
2019	5	13	18
2020	**5**	**10**	**15**

Investigator Initiated 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 nº: NCT03696810
Financial support: Portugal 2020 - 02/SAICT/2017
Project nº 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 nº: NCT04281186
Financial support: European Union
H2020-SC1-BHC-01-2019-847749

Age-Related Macular Degeneration

3. MACUSTAR - Intermediate AMD: Development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention
ClinicalTrials.gov nº: NCT03349801
Financial Support: European Union and EFPIA - Innovative Medicines Initiative 2 Joint Undertaking - Grant Agreement nº 116076

Retinal Degenerative Diseases

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

5. EYEMARKER - Characterization of potential biomarkers of Eye Disease and Vision Loss
ClinicalTrials.gov nº NCT02500862

Industry Sponsored Clinical Trials

Diabetic Macular Edema

1. 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 nº: 2017-005105-12

2. Two-year, three-arm, randomized, double-masked, multicentre, phase III study assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual impairment due to diabetic macular edema (KESTREL)
EudraCT nº: 2017-004742-23

3. A randomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of orally administered BI 1467335 for 12 weeks with a 12 week follow up period in patients with non-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN)
EudraCT nº: 2016-002971-91

4. Multicenter, Open-Label Extension Study To Evaluate The Long-Term Safety And Tolerability Of Faricimab In Patients With Diabetic Macular Edema (Rhone-X)
EudraCT nº: 2020-000402-29

Age-Related Macular Degeneration

5. An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD) (AZURE)
EudraCT nº: 2012-003763-22

6. 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 nº: 2017-004825-34

Glaucoma

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

Neurological Disorders

8. 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 nº: 2012-003056-36

9. 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 nº: 2016-004719-10

Oncology

10. 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 nº: 2019-003914-15

Representative Publications

Martinho AC-V, Marques IP, Messias AL, Santos T, Madeira MH, Sousa DC, Cunha-Vaz J. **Ocular and systemic risk markers for development of Macular Edema and Proliferative Retinopathy in type 2 diabetes. A five-year longitudinal study**, Diabetes Care. 2020 Nov 6;dc201125. doi: 10.2337/dc20-1125.

Marques IP, Madeira MH, Messias AL, Santos T, Martinho AC-V, Figueira J, Cunha-Vaz J. **Different retinopathy phenotypes in type 2 diabetes predict retinopathy progression**, Acta Diabetologica (2020) DOI: 10.1007/s00592-020-01602-9).

Santos AR. Raimundo M, Alves D, Lopes M, Pestana S, Figueira J, Cunha-Vaz J, **Microperimetry and mFERG as Functional Measurements in Diabetic Macular Edema Undergoing Intravitreal Ranibizumab Treatment**; Eye (2020) https://doi.org/10.1038/s41433-020-1054-2.

Marques IP, Madeira MH, Messias AL, Santos T, Martinho AC-V, Figueira J, Cunha-Vaz J. **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.

Farinha C, Cachulo ML, Coimbra R, Alves D, Nunes S, Pires I, Marques JP, Costa J, Martins A, Sobral I, Barreto P, Laíns I, Figueira J, Ribeiro L, Cunha-Vaz J, Silva R. **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.

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.

CORC – COIMBRA OPHTHALMOLOGY READING CENTRE

Director: **Conceição Lobo**, MD, PhD

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

Contacts
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The Coimbra Ophthalmology Reading Centre (CORC) focus its activities in grading retinal diseases of fundus images and OCT images of the retina, as well as functional evaluations of the retina using mfERG and visual fields.
It serves as central Reading Centre for a series of multinational/multicentric clinical studies, mainly in Diabetic Retinopathy (DR) and Age-related Macular Degeneration (AMD). CORC is also the central Reading Centre for the Diabetic Retinopathy Screening Programme of the Central Region of Portugal since 2011.

CORC has a secure custom-designed web-based tool to transmit images between Clinical Sites and CORC (*www.studies.corc.pt*). This system is hosted in the AIBILI´s Data Centre.

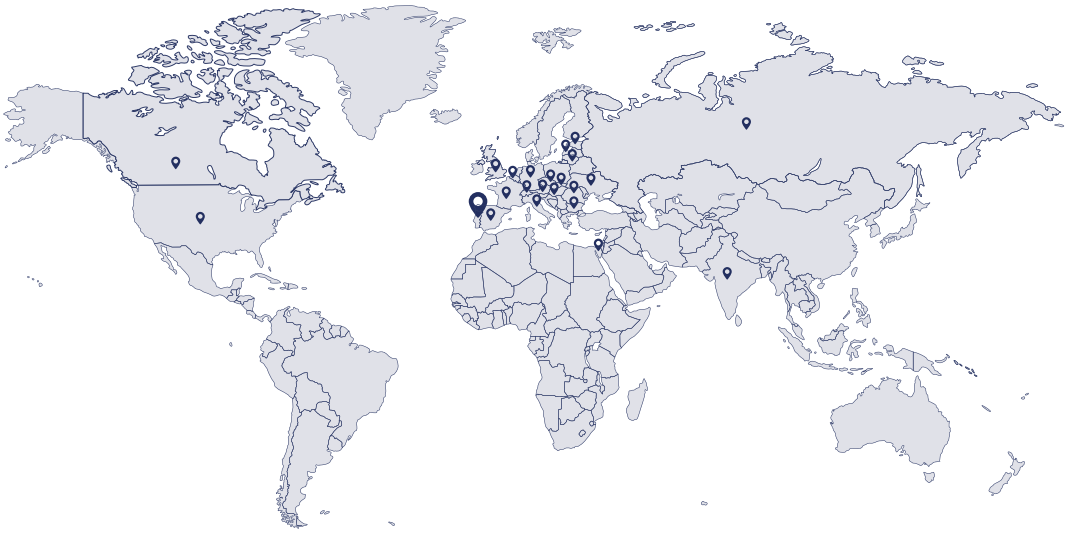
For grading purposes CORC uses licensed software from the equipment suppliers, such as Cirrus HD-OCT (Carl Zeiss Meditec), Heidelberg Eye Explorer (Heidelberg Engineering), RETIsystem (Roland Consult), Topcon OCT (Topcon Corporation), Revue-Optovue, Nidek OCT, Imagenet Review Software (Topcon Corporation), RETIsystem (Roland Consult) for eletrophysiology exams, as well as other common applications for imaging edition and analysis (GIMP, XnViewer, ImageJ, etc). For research, CORC has novel in-house developed software to assess microaneurysm turnover in DR (RetmarkerDR®), classify and quantify AMD lesions (RetmarkerAMD) and perform OCT segmentation of the retinal layers. We also have own software to perform structural OCT segmentation layer-by-layer and qualitative and quantitative analysis of OCTA images.

Study Development
- Development of study-specific Acquisition Protocols
- Provide Web-based platform for exams' submission
- Development of study-specific Grading Protocols

Training and Certification
- Equipment
- Technicians

In-study Services
- Grading of ophthalmic exams: Retinal Fundus images – CFP, FFA, ICGA, FAF, OCT, OCTA, UWF imaging (FI and FA), mfERG, Visual Fields and Anterior Segment images
- Exploratory analysis under request of the sponsor
- Eligibility criteria review and confirmation
- Management and monitoring of exams received and results
- Data backup procedures and disaster recovery plan
- Secure long-term archiving of study materials

Receive and Grade Exams from



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

Nº of Projects per scientific area at CORC (2018-2020)

	N° of Projects			
Year	Diabetic Retinopathy	AMD	Other	Total
2018	10	7	1	18
2019	8	8	2	18
2020	**9**	**5**	**2**	**16**

Representative Publications

Farinha C, Cachulo ML, Coimbra R, Alves D, Nunes S, Pires I, Marques JP, Costa J, Martins A, Sobral I, Barreto P, Laíns I, Figueira J, Ribeiro L, Cunha-Vaz J, Silva R. **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.

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.

Marques JP, Pires J, Simão J, Marques M, Gil JQ, Laíns I, Alves D, Nunes S, Cachulo ML, Miller JB, Vavvas DG, Miller JW, Husain D, Silva R. **Validation of RetmarkerAMD as a semiautomatic grading software for AMD.** Eye (Lond). 2019 Oct 23. doi: 10.1038/s41433-019-0624-7.PubMed PMID: 31645672.

Marques IP, Alves D, Santos T, Mendes L, Santos AR, Lobo C, Durbin M, Cunha-Vaz J. **Multimodal Imaging of the Initial Stages of Diabetic Retinopathy: Different Disease Pathways in Different Patients.** Diabetes. 2019 Mar;68(3):648-653. doi: 10.2337/db18-1077. Epub 2018 Dec 6. PubMed PMID: 30523027.

Farinha C, Cachulo ML, Alves D, Pires I, Marques JP, Barreto P, Nunes S, Costa J, Martins A, Sobral I, Laíns I, Figueira J, Ribeiro L, Cunha-Vaz J, Silva R. **Incidence of Age-Related Macular Degeneration in the Central Region of Portugal: The Coimbra Eye Study – Report 5.** Ophthalmic Res. 2019;61(4):226-235. doi: 10.1159/000496393. Epub 2019 Mar 1. PubMed PMID: 30820012.

CNTM - CENTRE FOR NEW TECHNOLOGIES IN MEDICINE

Director: **José Cunha-Vaz**, MD, PhD

Staff: Celina Cangueiro, Luis Mendes, Maria Castro, Rufino Silva, Sofia Rodrigues, 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®, 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 been made in the development of Optical Coherence Tomography Angiography for diagnosing progression of diabetic retinopathy and to use 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 (2018-2020)

	N° of Projects		
Year	Imaging/ Artificial Intelligence	Diabetic Retinopathy	Total
2018	7	3	10
2019	6	5	11
2020	**8**	**4**	**12**

Representative Publications

Santos T, Lewis W, Santos AR, Marques IP, Kubach S, Mendes L, Sisternes L, Madeira MH, Durbin MK, Cunha-Vaz J. **Swept source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR**, British Journal of Opthalmology2020 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.

Farinha C, Santos T, Santos AR, Lopes M, Alves D, Silva R, Cunha-Vaz J.: **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.

Marques IP, Alves D, Santos T, Mendes L, Santos AR, Lobo C, Durbin M, Cunha-Vaz J: **Multimodal Imaging of the Initial Stages of Diabetic Retinopathy. Different Disease Pathways in Different Patients.** Diabetes. 2018 Dec 6. pii: db181077. doi: 10.2337/db18-1077.

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, Joana Abrantes, Maria Viegas Nascimento, Óscar Lourenço

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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 pharmacovigilance software fully compliant with the regulations, directives, and the general guidance related to electronic reporting of adverse events (US FDA 21 CFR part 11 and EMA's Good Pharmacovigilance Practice (GVP) Guidelines) for this purpose, as well as SOPs ICH-GCP compliant to perform pharmacovigilance clinical research. It has a license to use MedDRA, a standardised international medical terminology designed for use in safety monitoring of medicinal products through all phases of the development cycle (i.e., from clinical trials to post-marketing surveillance) that supports ICH electronic communication within the E2B Individual Case Safety Report.

Since 2008 CHAD has been responsible for a Pharmacovigilance Unit of the National Pharmacovigilance System which is contracted with the National Authority of Medicines and Health Products (INFARMED, IP).

Main Activities

- 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 (2018-2020)

	N° of Projects		
Year	Market Access	Drug Safety	Total
2018	21	7	28
2019	16	8	24
2020	**9**	**15**	**24**

Most recent publications

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.

Ribeiro I, Batel Marques F, Mendes D, Alves C. **A Systematic Review of Economic Studies Evaluating Ophthalmic Drugs: An Analysis of the Health-state Utilities.** Ophthalmic Epidemiology 2020 ju 20, doi:10.1080/09286586.2020.1792938.

Mendes D, Oliveira AR, Alves C, Batel Marques F. **Spontaneous reports of hypersensitivity adverse drug reactions in Portugal: a retrospective analysis.** Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2020.1743262.

Ribeiro I, Batel Marques F, Alves D, Alves C. **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.

DC – DATA CENTRE

Director: **Carlos Domingues**, BSc

Staff: Celina Cangueiro, Hugo Morgado, José Monteiro, Patrícia Silva, Telmo Miranda, Torcato Santos

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

Presently Information Technology Unit maintains more than 60 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 management standards such as recommended by the Project Management Institute (PMI). All changes in the production environment are preceded by testing and validation processes, according to GAMP5 V-model and methodology. This Unit is responsible to guarantee the safety and integrity of the data and images collected all in compliance with GCP Guidelines and applicable national legislation. AIBILI specific SOPs for Information Technology and Data Centre also comply with US FDA 21 CFR part 11 (Guidance for Electronic Records) and ISO 27001 (Information Security Management). Regular internal audits and penetration tests are performed to ensure the safety and integrity of data.

All this information is categorized and specific backup policies are defined according information value. Long term storage procedures are in place to assure the whole information lifecycle. Information Technology Unit manages over than 60 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 a recertification to version 4 is ongoing. 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.

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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-IT platform support and digital grading forms development
- Data export and biostatistics support
- Long Term Storage
- EVICR.net webinar platform
- Software development

Nº of Projects at DC (2018-2020)

	Nº of Projects
Year	Projects/Services
2018	16
2019	15
2020	**17**

ORGANISATIONAL UNITS

ADMINISTRATIVE SERVICES

CEO: **Cecília Martinho**

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

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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.

QUALITY MANAGEMENT UNIT (QMU)

Quality Manager: Rita Fernandes

Staff: Cecília Martinho, Marta Ventura, Rita Fernandes

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

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 was in paper and is now being transposed into digital format to streamline approvals, records and archiving as well as access to management information. The Quality Management Unit (QMU) is responsible for the management of the digital QMS implementation, users training and regular support on the digital Document ´s Management System.
The QMU has a Personal Data Protection Committee which is responsible for promoting compliance and awareness of applicable personal data protection laws and the implementation of personal data protection procedures, their monitoring and compliance.

The QMU performs Quality Assurance services for CORC, 4C and CHAD services.
The QMU also performs internal and external training on quality and regulatory requirements applicable to health research activities.

TRANSLATIONAL RESEARCH AND TECHNOLOGY TRANSFER UNIT (UTT)

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UTT Manager: Daniel Fernandes

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 actions 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 publicising the activities developed at AIBILI, being the main point of contact for partnerships and collaborations. During 2020 AIBILI participated in the EATRIS and EIT-Health events where AIBILI's activities were disseminated.

Following the implementation of the AIBILI Strategic Scientific Research Plan 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.

INFORMATION TECHNOLOGY UNIT (IT)

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IT Manager: Carlos Domingues

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

The Information Technology Unit is responsible for the management and maintenance of AIBILI Data Centre, 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 (www.studies.corc.pt); the Clinical Data Management System that is used in the development of eCRFs for each clinical study; the PhVC Manager – Extedo that is used for pharmacovigilance in clinical studies by CHAD as well as the Clinical Trial Management System (CTMS) used for the management of multiple multinational clinical studies by 4C. There are also other administrative information systems supported in AIBILI's Data Centre. AIBILI's Data Centre houses EVICR.net website (www.evicr.net), EVICR.net Educational Programme webinar platform (www.cloud.aibili.pt/evicrnet_webinars) and also supports other administrative/office information systems.
AIBILI Data Centre is certified by ECRIN - European Clinical Research Infrastructure Network *(www.ecrin.org)* and is part of the ECRIN Data Centre Network. AIBILI Data Centre can provide safe, secure, compliant and efficient management of clinical research data.

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's) or medical devices) performed at AIBILI according to the Portuguese Law nº 97/95 of 10 May.

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

Margarida Duarte Ramos Caramona, PhD

Emeritus Professor at the Faculty of Pharmacy, University of Coimbra

Members

José António Moura Pereira, MD

Ophthalmologist at the University Hospital of Coimbra

Maria Elizabete Batista Geraldes, MD

Endocrinologist at the University Hospital of Coimbra

Paulo Simões, BSc

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

Filomena Maria Ferreira Ramos Mena, BSc

Nurse at the National Institute of Forensic Medicine, Coimbra

Maria Cecília Martinho, BSc

AIBILI CEO

4 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, since 2019 AIBILI has assumed an integrated ***Strategic Scientific Research Plan*** with five main Research Programs:

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

AIBILI Strategic Scientific Research Plan aims to achieve four main goals, and stimulate the complementarity of our dedicated Research Programs:

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

DIABETIC RETINOPATHY RESEARCH PROGRAM

Coordinator: **João Figueira**

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

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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 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 control. 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 biomarkers of DR. Haemoglobin A1c (HbA1c) remains the only confirmed systemic prognostic biomarker of DR progression.

The identification of different phenotypes of DR with different risks for development of vision-threatening complications opens new avenues for the comprehension of DR onset.

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 nº: NCT 03010397
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 will be accessed to identify prediction methods for disease development and progression. Moreover, visual acuity and retinal neurodegenerative changes in different stages of DR will be explored.

CORDIS - Characterization of retinal vascular disease in diabetes type 2, using novel non-invasive imaging methods
ClinicalTrials.gov nº: NCT03696810
Sponsor: AIBILI
Financial support: Portugal 2020 - 02/SAICT/2017 - Project nº 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 n°: NCT04281186
Financial support: European Union 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
Sponsor: AIBILI
ClinicalTrials.gov n°: NCT04636307
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.

Representative Publications

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.

AGE-RELATED MACULAR DEGENERATION RESEARCH PROGRAM

Coordinator: **Rufino Silva**

Research Team: Cláudia Farinha, José Cunha-Vaz, Luis Mendes, Maria Luz Cachulo, 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 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 aetiology 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, an healthy diet and the use of nutritional supplements created the environment for prevention and personalized medicine in this area.

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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
Sponsor: AIBILI
ClinicalTrials.gov nº: NCT04241536
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 biologically 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 nº: 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 nº: 2015-001368-20
Sponsor: AIBILI
Financial support: IIR Grant from Bayer

This is 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-naive PCV, enrolling in a treat and extent regimen.

- ***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
Sponsor: UKB, Bonn, Germany
ClinicalTrials.gov nº: NCT03349801
Financial Support: European Union and EFPIA - Innovative Medicines Initiative 2 Joint Undertaking - Grant Agreement nº 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-elated 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.

IMAGING BIOMARKERS RESEARCH PROGRAM

Coordinator: **Conceição Lobo**

Research Team: Ana Rita Santos, José Cunha-Vaz, João Figueira, 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. 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 information collected can be analysed automatically. The analysis of the data can also be tailored to specific purposes, allowing validating imaging biomarkers of disease. These imaging biomarkers may give information on retinal and eye disease but also may serve as indicators of systemic disease, such as brain degenerative diseases and circulatory disorders.
Our group has been able to identify biomarkers of disease progression, such as microaneurysm (MA) 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.

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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

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

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.

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

Santos T, et al. **Swept source OCTA quantification of capillary closure predicts ETDRS severity staging of NPDR**, British Journal of Opthalmology2020 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.

Santos AR, et al. **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. PubMed PMID: 29077605.

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.

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.

DRUG EVALUATION RESEARCH PROGRAM

Coordinator: **Diogo Mendes**

Research Team: Alexandra Escada, Ana Penedones, Carlos Alves, Daniel Figueiredo, Francisco Batel-Marques, Joana Abrantes, Maria Viegas Nascimento

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.

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

Contacts
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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.

Projects

DruSER.Net – Drug Safety and Effectiveness Research Network
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
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.

ESSENCE - The Effectiveness, Safety and Patient Experience on Oncology Treatments: Achieving Real-World Evidence
The main objective of ESSENCE Study is to assess whether the outcomes of patients with breast, lung and ovarian cancer treated under real-world conditions reflect the results obtained from clinical trials.
This study also aims to identify the healthcare resources consumption and associated costs implicated in the treatment of cancer patients in routine clinical practice.

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

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.

Representative Publications

Alves C, Penedones A, Mendes D, Bater 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 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.

Penedones 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.

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.

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.

TRANSLATIONAL VISION RESEARCH PROGRAM

Coordinator: **António Francisco Ambrósio**

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

AIBILI and the Faculty of Medicine of the University of Coimbra have an historical relationship, particularly with the Coimbra Institute for Clinical and Biomedical Research (iCBR, former IBILI) which represents a critical opportunity in the facilitation of translational research and of innovation from the laboratory to clinical research in vision.

To (re)active this research area at AIBILI, named 'Basic and Translational Vision Research' in collaboration with the Retinal Dysfunction and Neuroinflammation Lab from iCBR is one of our priorities and strategies to reinforce our translational research in this specific area.

Contacts
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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.

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

Boia R, et al. **Treatment with A2A receptor antagonist KW6002 and caffeine intake regulate microglia reactivity and protect retina against transient ischemic damage**. Cell Death Dis. 2017, 8(10):e3065. doi: 10.1038/cddis.2017.451.

Aires ID, et al. **Blockade of microglial adenosine A2A receptor supresses elevated pressure-induced inflammation, oxidative stress, and cell death in retinal cells**. Glia. 2019, 67(5):896-914. doi: 10.1002/glia.23579.

Boia R, et al. **Porous poly(ε-caprolactone) implants: a novel strategy for efficient intraocular drug delivery**. J. Control. Release. 2019. 316:331-348. doi:10.1016/j.jconrel.2019.09.023.

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, 11(1):90. doi: 10.1186/s13195-019-0542-8.

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, 9(1):17207. doi: 10.1038/s41598-019-53627-y.

6 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 SOPs ICH - GCP compliant.
At present, EVICR.net has 96 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 Standard Operating Procedures (SOPs) according to ICH - GCP Guidelines.
Once a member, the Clinical Site adopts/harmonises EVICR.net SOPs with the help of the Coordinating Centre in order to become a 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.

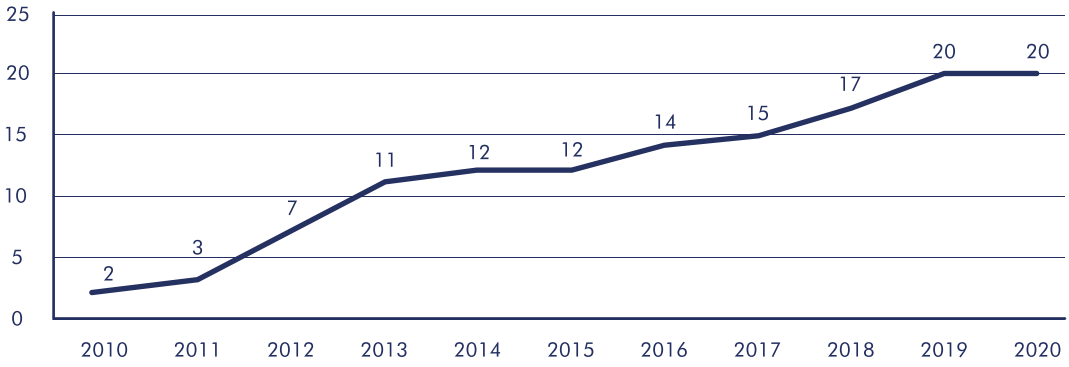
Chairman: Prof. Hendrik Scholl, University Hospital Basel, University Eye Clinic, Basel, Switzerland

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 within EVICR.net.

Multinational Clinical Research Studies (2010-2020)

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 2020 there were eight ongoing multinational clinical research studies of which 3 are European Union funded.

More information:
www.evicr.net

Ongoing Projects 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)
- IRIS (Industry-sponsored)

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

Educational Programme

The 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/:*

Module	Multinational Clinical Research Organisation	Diabetic Macular Edema Understanding and Management	Diabetic Macular Edema, Imaging, Biomarkers and Anti-VEGF Management	Glaucoma Risk Factors and Management	Unmet needs in Glaucoma	Dry Eye Diagnosis and Treatment
WEBINARS	**WEBINAR #1**	**WEBINAR #4**		**WEBINAR #8**	**WEBINAR #14**	**WEBINAR #11**
	How to setup a clinical research study	DME definition, classification and imaging		Landmark clinical trials in glaucoma	Patient compliance & IOP telemetry	Dry eye syndrome: signs and symptoms
	S. Nunes	*J. Cunha-Vaz*		*E. Normando*	*R. Patel*	*J. Gil*
	WEBINAR #2	**WEBINAR #5**		**WEBINAR #9**	**WEBINAR #15**	**WEBINAR #12**
	Clinical research organisation	Predicting progression and treatment response		Risk factors in glaucoma	Non-IOP dependent strategies	Diagnosis in dry eye syndrome
	L. Ribeiro	*J. Cunha-Vaz*		*F. Cordeiro*	*S. Balendra*	*J. Gil*
	WEBINAR #3	**WEBINAR #6**	**WEBINAR #7**	**WEBINAR #10**	**WEBINAR #16**	**WEBINAR #13**
	SOPs – quality and certification	Treatment of DME	Anti-VEGF treatment of DME	Glaucoma Who to treat and when	Surrogate markers and outcome measures & Early diagnosis	Treatment of dry eye syndrome
	C. Martinho R. Fernandes	*J. Cunha-Vaz*	*J. Cunha-Vaz*	*S. Gandolfi*	*T. Yap*	*E. Costa*

Representative Publications

Jiménez-Garcia M, Dhubhghaill SN, Koppen C, Varsanno D, Rozema JJ and the REDCAKE Study Group. **Baseline Findings in the Retrospective Digital Computer Analysis of Keratoconus Evolution (REDCAKE) Project.** Cornea. 2021 Feb 1;40(2):156-167. doi: 10.1097/ICO.0000000000002389.

Jordan-Yu, JMN, Teo K, Fan Q, Gan JC, Leopoldo AK, Nunes S, Farinha C. Barreto P, Melo JB, Carreira I, Murta JN, Silva R, Cheung CMG, **Phenotypic And Genetic Variations Between Asian And Caucasian Polypoidal Choroidal Vasculopathy Eyes.** Br. J. Ophthalmol. 317537, (2020). doi: 10.1136/bjophthalmol-2020-317537.

Terheyden J.H. Schmitz-Valckenberg S. Crabb D. Dunbar H. Luhmann U. Behning C. Schmid M. Pires I. Cunha-Vaz J. Tufail A. Weissgerber G. Leal S. Holz F.G. Finger R.P. **Use of composite endpoints in early and intermediate age-related macular degeneration clinical trials - state-of-the-art and future directions.** Ophthalmologica. 2020 Dec 7. doi: 10.1159/000513591.

Hernandez C, Porta M., Bandello F., Grauslund J., Harding S., Aldington S., Egan P., Frydkjaer-Olsen U., García-Arumí J., Gibson J., Lang G., Lattanzio R., Massin P., Midena E., Ponsati B., Ribeiro L., Scanlon P., Cunha-Vaz J, Simó R. **The Usefulness of Serum Biomarkers in the Early Stages of Diabetic Retinopathy: Results of the EUROCONDOR Clinical Trial.** J. Clin. Med. 2020, 9, 1233; doi:10.3390/jcm9041233.

Rosenblatt A, Udaondo P, Cunha-Vaz J, Sivaprasad S, Bandello F, LanzettaP, Kodjikian L, Goldstein M, Wilner ZH, Loewenstein A, for the ARTES study group: **A Collaborative Retrospective study on the Efficacy and Safety of intravitreal dexamethasone implant (Ozurdex) inpatients with Diabetic Macular Edema (DME). The European DME Registrar Study (ARTES).** Ophthalmology (2019), doi:10.1016/j.ophtha.2019.10.005.

C-TRACER - CHAMPALIMAUD TRANSLATIONAL CENTRE FOR EYE RESEARCH

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 at S. Paulo, Brazil.

More information:
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 in ophthalmology clinical research, is an Affiliate Partner of ECRIN-ERIC. Thus, EVICR.net serves as a resource to ECRIN-ERIC in the area of vision and ophthalmology multinational clinical research, particularly by providing scientific and medical expertise, access to patients and research capacity whereas ECRIN provides support in submission and monitoring activities. The MACUSTAR clinical study is as 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:
www.ecrin.org

EATRIS - EUROPEAN INFRASTRUCTURE FOR TRANSLATIONAL MEDICINE

EATRIS is a client driven, non-profit organisation 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.

More information:
www.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 healthcare providers from 13 European countries. 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:
www.ern-eye.eu

PARTNERS

7

ARSC – Health Administration of the Centre Region of Portugal

ARSC regulates the organisation and functioning of healthcare institutions and services in the Centre Region of Portugal.
The Protocol between AIBILI and ARSC is of great relevance as the area of primary healthcare is a major research interest of AIBILI as screening and prevention are priorities for AIBILI research particularly in imaging diagnostics.
Since 2011, AIBILI-CORC is the Reading Centre for fundus images of Screening Programme for Diabetic Retinopathy in the Centre Region of Portugal.

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 courses focused on clinical research, as well as the strengthening of the international presence through the networks in which both institutions are involved.

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.

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.
During 2020 AIBILI participated in the brainstorm session of the Meetings with Health Innovation and was responsible for the organisation of one of the HCP Autumn webinars dedicated Data Management in Clinical Research.

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 aim on filling the gaps between Pre-Clinical and Clinical Research, setting the ground for the development of innovative 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 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 consortium, headed by the Porto University, brings together institutions and researchers from several schools of the Porto University. This wide participation of schools, research institutions and hospitals in a research institute is unique in Portugal and is a valuable asset for science and technology development, while creating an environment that feeds real breakthrough research and translation of discoveries into the clinic.

The partnership between AIBILI and i3S 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 organisation (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 has as main goal 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. During 2020 a first workshop on "Good Clinical Practices" was performed bringing together the different stakeholders in clinical research.

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 within PtCRIN. AIBILI has the only ECRIN Certified Data Centre in Portugal since 2016.

P-BIO – Portugal's Biotechnology Industry Organisation

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.
During 2020 AIBILI participated in the presentation of the White Book of Rare Diseases and Orphan Drugs in Portugal which Prof. Batel Marques has coordinated.

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 will allow students from the Master in Medical Statistics of UA to perform an internship at AIBILI.

FINANCIADO POR

DESIGN: **3LM***

AIBILI

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