
QUALITY MANUAL



NP EN ISO 9001:2015
ISO/IEC 27001:2022 – being implemented.
Good Clinical Practices
ECRIN Requirements for Data Centre Certification
General Data Protection Regulation (EU) 2016/679

Ver. 39
22/04/2024

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I – PROMULGATION

This Quality Manual describes the Quality Management System of AIBILI in accordance with the requirements of ISO 9001, ISO/IEC 27001, Principles of Good Clinical Practices whenever a clinical study is performed, requirements for Certification of ECRIN Data Centre when performing IT and Data Management services within clinical studies and Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 when processing personal data and on the free movement of such data.

AIBILI Board of Directors demonstrates the leadership and commitment with respect to AIBILI's Information Security Management System (ISMS) and delegates in the President and in the Management Committee the formal approval of the Quality Policy and Quality Manual.

AIBILI staff is responsible for the implementation, maintenance, and improvement of AIBILI's QMS.

III– GENERAL INFORMATION OF AIBILI

- Ensure to the client and other interested parties, a high quality service that meets their needs and expectations in compliance with the standard ISO 9001, ISO/IEC 27001, Principles of Good Clinical Practices whenever a clinical study is performed, requirements for Certification of ECRIN Data Centres when performing Data Centre activities, Legislation applicable to the protection of personal data, in particular Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and Portuguese Law n°58/2019 of 8th August, as well as regulatory requirements, statutory and legal, applicable to AIBILI activities;
- Ensure the transfer of basic science to clinical practice and the health market through translational research, thus contributing to the development of the country;
- Maintain adequate and updated technical resources, infrastructure and work environment that allow an effective and efficient response to the needs and expectations of Client as well as to ensure compliance with Client requirements;
- Ensure adequate and continual training of personnel to maintain and improve their competence to carry out the activities for which they are responsible;
- Promote awareness to all personnel of the Quality Management System, the use of the process approach and risk-based thinking, ensure the confidentiality, integrity and availability of information stored, processed and transmitted, through the application of administrative, management, legal and technological controls, so that, in its daily activities, they meet Client and other interested parties requirements and participate in the processes of continual improvement;
- Promote partnership with other interested parties relevant to the quality management system to achieve mutual benefits and continuity;
- Regularly review the performance of the processes and the impact on Client and interested parties, particularly their satisfaction, to implement actions to achieve the improvement of services and the efficiency and effectiveness of the Quality Management System.

THE MANAGEMENT COMMITTEE

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

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

AIBILI is a Technology and Innovation Centre (CTI) in the health area of the National Network of the Economy Ministry. This recognition identifies AIBILI as the facilitating partner between scientific institutions, enterprises, and industry in order to bring novel solutions to the health market.

Our Mission – to be a reference partner with the best resources and quality systems in the field of health technology innovation.

Our Vision – to improve human health and wellbeing by converting basic research knowledge into innovative applications.

Our Values - to perform quality services, in an innovative and collaborative manner, to be internationally renowned.

AIBILI is ISO 9001 certified for the following activities:

- Performance of Clinical Studies,
- Planning, Coordination, Monitoring of Clinical Research Activities,
- Health Technology Assessment,
- Grading of Eye Exams,
- Research and Development in New Technologies for Medicine in the areas of Imaging, Optics and Photobiology,
- Data Centre Activities.

AIBILI Data Centre is certified by ECRIN Data Centre requirements.

AIBILI Data Centre is currently implementing ISO/IEC 27001:2022

Clinical Studies are performed in accordance with ICH Guidelines for Good Clinical Practice (GCP), European and national applicable legislations and regulations.

The processing of personal data and the free movement of such data is performed in accordance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and

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other legislation applicable to the protection of personal data, namely, the Portuguese Law n°58/2019 of 8th August.

AIBILI is located in 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 multidisciplinary staff and some part-time individual collaborations mainly for research activities.

AIBILI is a Champalimaud Translational Centre for Eye Research (C-Tracer) since 2010 and part of the C-Tracers Network. For detailed information consult website: www.fchampalimaud.org.

AIBILI is organized in research centres:

- 4C - Coimbra Coordinating Centre for Clinical Research – academic Clinical Trial Unit / CRO
- CEC - Clinical Trial Centre – Clinical Research Centre / Clinical Site
- CORC - Coimbra Ophthalmology Reading Centre
- CNTM - Centre for New Technologies in Medicine
- DC - Data Centre

The organizational Units are: Administrative Services (SA), the Translational Research and Technology Transfer Unit (UTT), the Information Technology Unit (IT) and the Quality Management Unit (UGQ).

The Quality Management Unit (UGQ) has a Personal Data Privacy Committee which is responsible for promoting compliance and awareness of applicable personal data protection laws, advising on the implementation of data protection standards and monitoring compliance in AIBILI. Any question regarding personal data protection should be addressed to privacy@aibili.pt.

The Quality Management Unit (UGQ) has also a Compliance Committee responsible for managing and processing whistleblower breach reports in a work related context submitted through an internal channel available at www.aibili.pt and for the Gender Equality Plan (GEP) elaboration and monitoring.

UGQ has a Data Access Committee (DAC) responsible for evaluating Data Access Requests to AIBILI in order to re-use data for scientific research (via DAC@aibili.pt).

AIBILI has also an independent Ethics Committee for Clinical Research (CE) to assess the clinical studies as applicable by Law 21/2014 of 16 of April changed by the Law n.º 73/2015 of 27 of July.

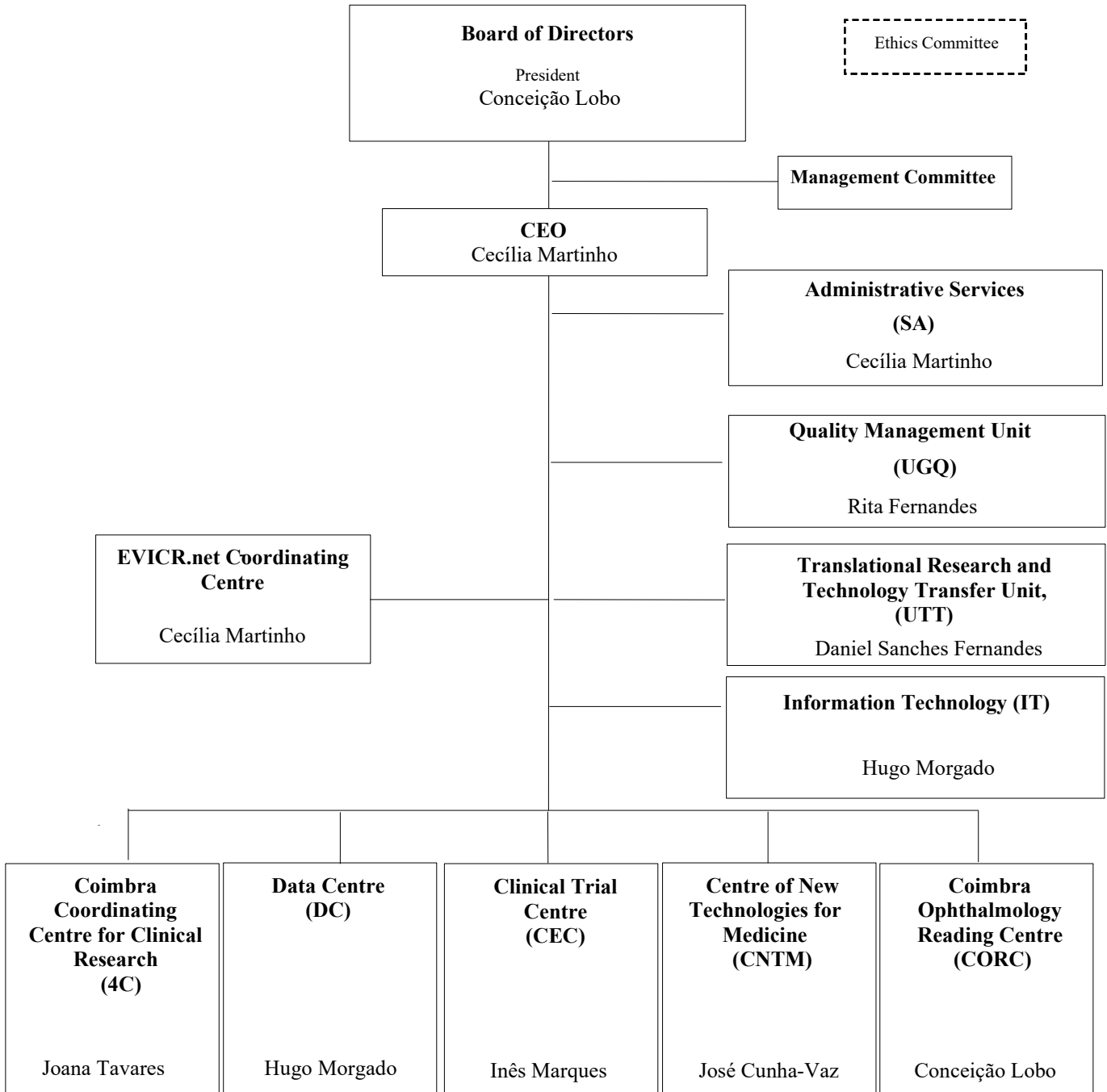
AIBILI Board of Directors delegates their functions on the Management Committee that ensure the development and implementation of the management system and continual improvement of its effectiveness.

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AIBILI has partnerships with national and international institutions, namely with: ULS Coimbra - Local Health Unit of Coimbra, CF - Champalimaud Foundation, FMUC - Faculty of Medicine of the University of Coimbra, i3S – Institute for Research and Innovation in Health of the University of Porto, iCBR - Coimbra Institute for Clinical and Biomedical Research, INFARMED - National Authority of Medicines and Health Products, I.P., Institute for Vision at the Federal University of S. Paulo, S. Paulo, Brazil, IPN - Instituto Pedro Nunes, L.V. Prasad Eye Institute, Hyderabad, India, José de Mello Saúde – Hospital CUF Coimbra, P-BIO – Portugal’s Biotechnology Industry Organization and others.

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. For detailed information, consult website: www.aibili.pt.

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EVICR.net – European Vision Institute Clinical Research Network

AIBILI is the Coordinating Centre of the European Vision Institute Clinical Research Network – EVICR.net, an independent European Economic Interest Grouping (EEIG), established in 2010 in accordance with the Council Regulation (EEC) n.º 2137/85.

EVICR.net is a disease-oriented network of European Ophthalmological Clinical Research Sites, dedicated to perform multinational clinical research in ophthalmology with the highest standards of quality, following the European, International Directives for Clinical Research and ICH-GCP Guidelines. It is mainly dedicated to support multinational Investigator Initiated Research (IIR). Scientifically it is organized by ophthalmology subspecialty Expert Committees. For detailed information consult website: www.evicr.net.

EVICR.net is as a fundamental resource for the development of translational research in the European Union in the area of Ophthalmology and Vision Sciences.

4C - Coimbra Coordinating Centre for Clinical Research

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

- Protocol design and Statistical planning
- Study documents elaboration
- Submission to the Regulatory Authorities
- Coordination and Study implementation
- Monitoring and Quality Control
- Periodic Reports to the Sponsor and/or Regulatory Authorities
- Statistical analysis and Final Study Report
- Medical Writing and Publication support
- Investigational Product Management
- Pharmacovigilance and Risk Management
- Archiving

4C is a qualified resource to work closely with Pharmaceutical Industry by providing support on modelling and conduct cost-effectiveness analysis of drugs and other medical products and therapies

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for market access purposes, aiming at reimbursement either in ambulatory or hospital settings. This activity relies on healthcare policies in practice as well as the orientations provided by the national health national service, being of capital importance to Industry.”

It is also responsible for the Pharmacovigilance Unit of Coimbra of the National Pharmacovigilance System since 2008, contracted with the National Authority of Medicines and Health Products (INFARMED, IP).

DC - Data Centre

AIBILI Data Centre was built specifically to support AIBILI’s information systems but the existing space and environment conditions allow for expansion to store clients/partners data and information.

AIBILI Data Centre services are provided by the Information Technology / Data Centre (IT/DC).

AIBILI Data Centre is certified by ECRIN Data Centre requirements since 2016, meeting the ECRIN requirements for IT and Data Management within Clinical Studies and complies with Good Clinical Practices, Good Practice for Computerised Systems, as well as regulatory requirements, statutory and legal, applicable to AIBILI activities.

AIBILI Data Centre is currently implementing ISO/IEC 27001:2022.

The services provided by AIBILI Data Centre are:

- Design and development of Electronic Case Report Forms (eCRF)
- Development of Digital Grading Forms
- Support Clinical Data Management Application (CDMA)
- Support Reading Center Platforms (studies.corc.pt)
- Users/key-users training
- IT support
- Data Management
- Long Term Data Storage.

Data Centre also provides IT and Data Management services for clinical research studies and Information Security Event and Incident Management.

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CEC - Clinical Trial Centre

The Clinical Trial Centre (CEC) performs clinical patient-oriented research that involves characterizing disease progression and testing new therapies by carrying out controlled research studies in patients, i.e., clinical trials. It has been involved in studies focused on ophthalmology, diabetes and neurology. CEC has excelled in multinational randomized clinical trials and clinical studies with special emphasis in ophthalmology since 1991. CEC has dedicated facilities, qualified and experienced staff and the most updated ophthalmological equipment.

CEC is a certified Clinical Site of Excellence by the EVICR.net - European Vision Institute Clinical Research Network (CS 01), since 2005.

CNTM - Centre of New Technologies for Medicine

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

The goal of CNTM is innovation in eye imaging and transfer these technological innovations to the industry and, therefore to the market, bringing better diagnostic imaging technologies. It works closely with CEC, performing translational research in vision and imaging, and with CORC by developing software tools for grading analysis. The excellence of the work developed in CNTM is well demonstrated by frequent publications in peer reviewed international scientific journals.

CNTM has developed the concept of Multimodal Macula Mapping, the algorithm developed in house, that lead in the product Retmarker® that is available in the market and provides information to monitor the progression of retinal diseases by correlation of sequential fundus imaging and automatic lesion detection. Presently OCT-Leakage, a novel analysis on the permeability of the Blood-Retinal Barrier using non-invasive method was published in the European Patent and in the United States Patent and Trademark bulletins.

The process of technology transfer is really initiated by innovation at the laboratory level well before the development of applications that can be later on tested in clinical studies. This research has led to R&D contracts with Industry.

As the result of the work developed in CNTM the following international patents were granted:

- Ocular Fluorometer for Clinical Use, US Patent n.º 6,013,034. 05/11/1997.

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- Method and Apparatus for Measuring Quantity of a Fluorochrome in a Biological Environment, WO/2008/067525. 20/11/2008.
- System for Analysing Ocular Fundus Images, US Patent n.º 7,856,135. 02/12/2009.
- Method and device for the non-invasive indirect identification of sites of alterations of the Blood-Retinal Barrier, EPO Patent 3 289 565 B1 and US 11,234,591 B2.

CORC – Coimbra Ophthalmology Reading Centre

The Coimbra Ophthalmology Reading Centre (CORC) performs central reading and grading of ophthalmology exams for multinational and multicentric clinical studies. It is also responsible for the Diabetic Retinopathy Screening Programmes of the Central and South Region of Portugal. It receives and grades ophthalmology exams from all over the world, contributing to standardized results and high-quality data for ophthalmic research. By grading several features in different imaging modalities, CORC focus its activities in the characterization and quantification of ophthalmic diseases, mainly in the areas of posterior segment/retinal diseases as Diabetic Retinopathy (DR), Age-related Macular Degeneration (AMD), Retinitis Pigmentosa (RP) and Retinal Vein Occlusion (RVO) and anterior segment diseases as Neurotrophic Keratitis. The variety of imaging modalities that are subject of CORC grading and analysis include retinal fundus images (FP, FA, UWF imaging, ICG, FAF, OCT and OCTA), anterior segment images (Cornea or anterior surface photography) as well as some functional examinations like visual fields, microperimetry and ERG.

CORC uses the following IT systems hosted on AIBILI's Data Centre certified by ECRIN: the CORC imaging Platform (www.studies.corc.pt), a secure custom-designed web-based tool for the transmission of images between Clinical Sites and CORC; and the REDCap software used as CORC Digital Grading Forms Platform to record grading results (Digital Grading Forms).

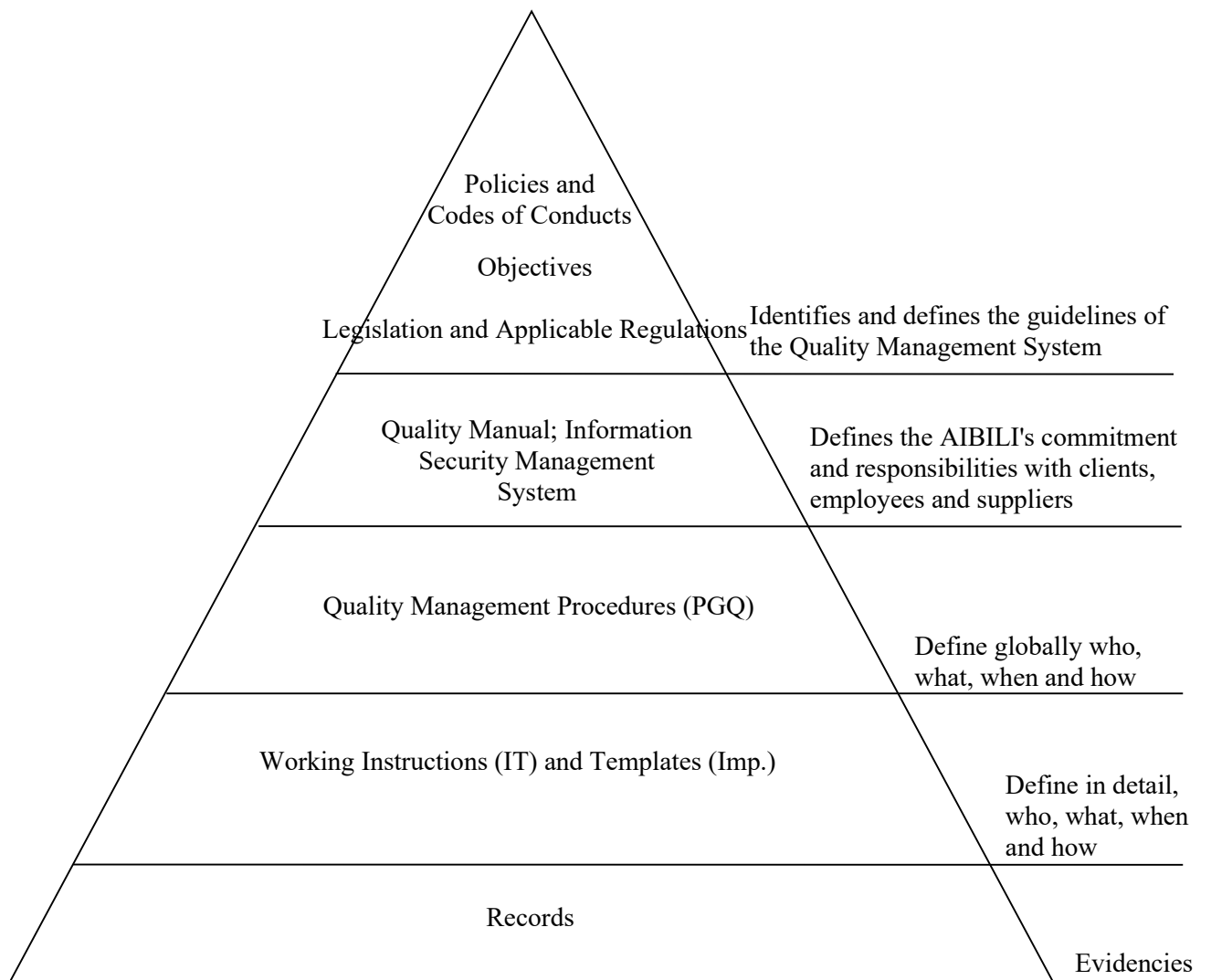
For grading activities, CORC uses licensed software from equipment suppliers (e.g., Cirrus (Carl Zeiss Meditec), Heidelberg Eye Explorer (Heidelberg Engineering), Topcon (Topcon Corporation), ReVue/iVue software (Optovue), Navis-EX (Nidek CO), Optopol OCT (Optopol), OptosAdvance (Optos), Zeiss CLARUS Review (Carl Zeiss Meditec, etc) and other common applications for imaging edition and analysis (e.g., GIMP, XnViewer, ImageJ, etc).

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CORC has all the necessary human resources for its activities, namely Medical Project Coordinators, a vast team of Graders, Study Coordinators, Data Manager and IT Specialist for software/applications development.

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- The AIBILI **Quality Management System (QMS)** is an **integrated system** of several standards, guidelines and regulations, as ISO 9001, ISO/IEC 27001, ECRIN Data Centre requirements, Principles of Good Clinical Practices, GDPR, as well as other regulatory requirements, statutory and legal, applicable to AIBILI activities.
- AIBILI structured its Quality Management System (QMS) and supports it through a hierarchical set of documents that are described below.



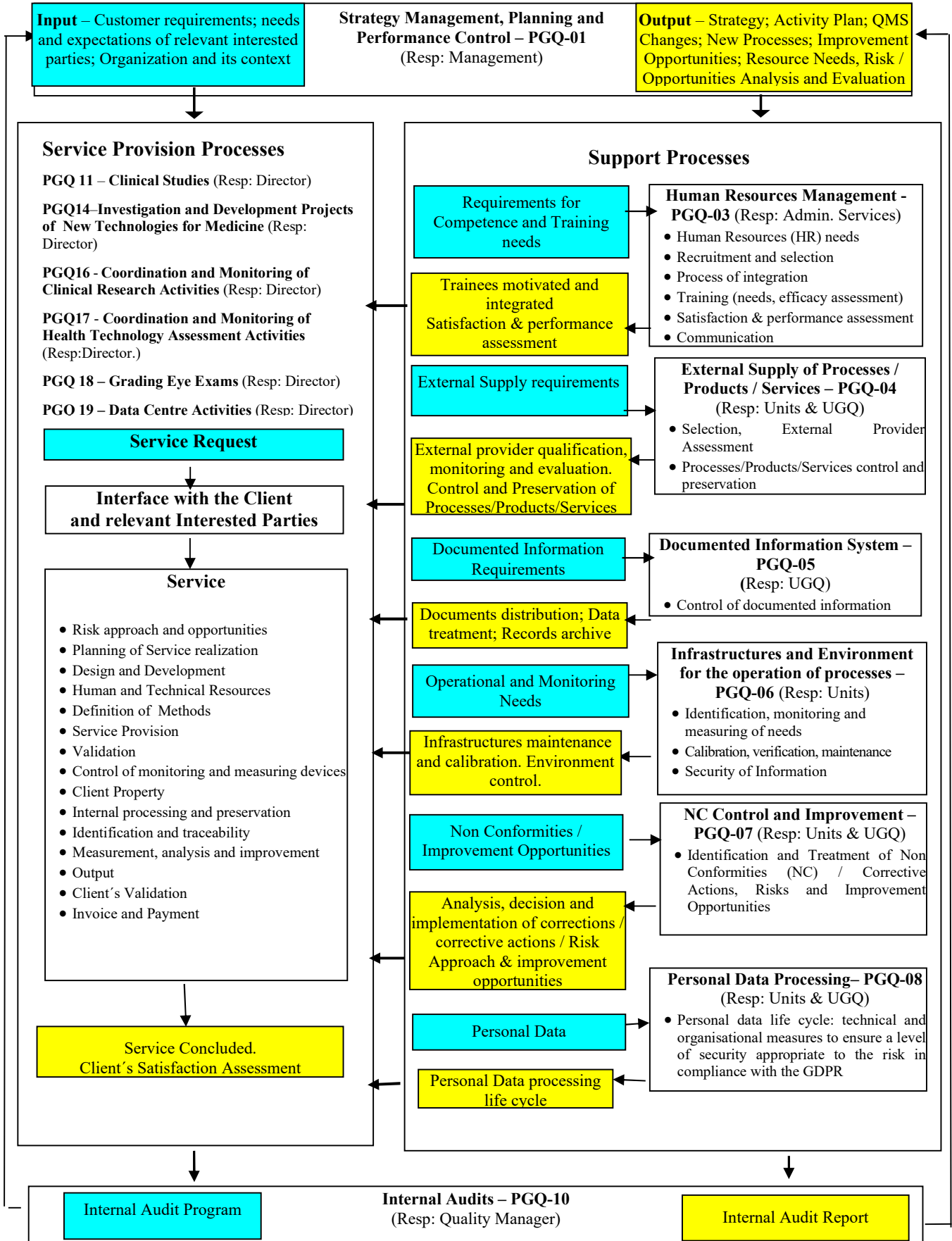
AIBILI Operational Manual is organized by PGQs, ITs and Imp. and structured as stated in Appendix 1.

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The correlations of AIBILI QMS with ISO 9001:2015 are listed in Appendix 2, Principles of Good Clinical Practices in Appendix 3, AIBILI QMS correlation with ECRIN Data Centre requirements is in Appendix 4, GDPR Correlation in Appendix 5. ISO/IEC 27001:2022 is currently being implemented. All this documentation is communicated, including subsequent versions, to whom maybe concerned.

APPENDIX 1 – QUALITY MANAGEMENT SYSTEM – PROCESSES INTERRELATION

The Quality Management System (QMS) is supported by processes with the following interrelation:



APPENDIX 2 - CORRELATION WITH NP EN ISO 9001:2015

Quality Manual and Procedures	Requirements of NP EN ISO 9001:2015																							
	4	5.1	5.2	5.3	6.1	6.2	6.3	7.1	7.2	7.3	7.4	7.5	8.1	8.2	8.3	8.4	8.5	8.6	8.7	9.1	9.2	9.3	10.2	10.3
I - Promulgation	█																							
II - Quality Policy			█																					
III- General Information	█																							
PGQ 01- Strategy Management, Planning and Performance Control	█	█	█		█	█	█			█	█		█							█		█		
PGQ 03-Human Resources Management		█		█				█	█	█														
PGQ 04-External Supply of Processes / Products / Services					█		█	█					█			█	█	█	█					
PGQ 05- Documented Information System												█					█							
PGQ 06- Infrastructures and Environment for the operation of processes								█									█							
PGQ 07- - NC Control & Improvement Management																			█				█	█
PGQ 08- Personal Data Processing	█	█			█		█			█	█	█	█	█	█	█	█	█	█	█	█			
PGQ 10-Internal Audits																						█		
PGQ 11- Clinical Studies	█	█			█	█	█			█	█	█	█	█	█	█	█	█	█	█	█			
PGQ 14- Investigation and Development Projects of New Technologies for Medicine	█	█			█	█	█			█	█	█	█	█	█	█	█	█	█	█	█			
PGQ 16 –Coordination & Monitoring of Clinical Research Activities	█	█			█	█	█			█	█	█	█	█	█	█	█	█	█	█	█			
PGQ 17 – Coordination & Monitoring of Health Technology Assessment Activities	█	█			█	█	█			█	█	█	█	█	█	█	█	█	█	█	█			
PGQ 18 – Grading Eye Exams	█	█			█	█	█			█	█	█	█	█	█	█	█	█	█	█	█			
PGQ 19 – Data Centre Activities	█	█			█	█	█			█	█	█	█	█	█	█	█	█	█	█	█			

Legend:

█ applicable;

□ not applicable

APPENDIX 3 - CORRELATION WITH PRINCIPLES OF GOOD CLINICAL PRACTICES - Law n°21/2014, 16 of April changed by the Law n.°73/2015, 27 of July and Law n° 49/2018 of 14 August

Quality Manual and Procedures	GCP Requirements applicable to AIBILI- Articles of Law n°21/2014, 16 of April and those changed# by the Law n.° 73/2015, 27 of July																																			
	Art.1°	Art.2°	Art. 3°	Art. 4°	Art. 5°	Art. 6°	Art. 7°	Art. 8°	Art. 9°	Art. 10°	Art. 11°	Art. 11°-A	Art. 12°	Art. 13°	Art. 14°	Art. 15°	Art. 16°	Art. 17°	Art. 18°	Art.19°	Art 20, Art 22°	Art. 23°	Art. 25°	Art. 26°	Art. 27° a 31°	Art32	Art33 e 34°	Art. 36° e 37°	Art.38°	Art.39°	Art.40	Art.42	Art.51°	& Art.5°,16,17,21, 24a28,33a39, 43a46,51,52a56		
I - Promulgation	■																																			
II - Quality Policy			■	■																																
III- General Information			■	■																																
PGQ 01- Strategy Management, Planning and Performance Control														■																						
PGQ 03-Human Resources Management									■	■																										
PGQ 04-External Supply of Processes / Products / Services									■	■					■	■																				
PGQ 05- Documented Information System																	■		■	■	■				■											
PGQ 06- Infrastructures and Environment for the operation of processes																																				
PGQ 07- NC Control & Improvement Management									■	■																										
PGQ 08- Personal Data Processing	■		■			■	■	■	■	■						■			■	■	■	■	■	■	■				■							
PGQ 10-Internal Audits																																				
PGQ 11- Clinical Studies*	■							■		■				■		■	■										■									
PGQ 14- Investigation and Development Projects of New Technologies for Medicine *										■											■															
PGQ 16 –Coordination & Monitoring of Clinical Research Activities**											■																									
PGQ 17 – Coordination & Monitoring of Health Technology Assessment Activities										■																										
PGQ 18 –Grading Eye Exams										■																										
PGQ 19 – Data Centre Activities																																				

Note: * Investigator’s Responsibility; ** Sponsor’s Responsibilities; & applicable to Regulatory Authorities.

Legend: ■ applicable; □ not applicable

APPENDIX 4 - CORRELATION WITH ECRIN REQUIREMENTS FOR DATA CENTRE CERTIFICATION - VERSION N^o4

Quality Manual and Procedures	ECRIN Requirements for Data Centre Certification																									
	GE 01	IT 01	IT 02	IT 03	IT 04	IT 05	IT 06	DM 01	DM 02	DM 03	DM 04	DM 05	DM 06	DM 07	DM 08	DM 09	ST 01.01	ST 01.02	ST 01.03	ST 01.04	ST 01.05	ST 01.06	ST 01.07	ST 01.08	ST 01.09	
PGQ19																										
IT 19-01 - Management of Data Centre Services																										
IT 19-02 - Server Management																										
IT 19-03 - Security Access Management																										
IT 19-04 - Business Continuity																										
IT 19-05 - General System Validation																										
IT 19-06 - Extracting and Reporting Data																										
IT 19-07- Data Management																										
IT 19-08 - General Standards																										
IT 19-09 - Local Software Development																										
IT 16-08 - Randomization, Blinding and Unblinding Procedure																										
IT 16-09 - Protocol Deviation and Serious Breach Procedure																										
PGQ03-Human Resources (HR) Management; IT3-3 - Management of HR Competences																										
PGQ07 - Non Conformities Control and Improvement Management; IT 07-01 - Records of Non Conformities Control and Improvement actions																										
PGQ 08- Personal Data Processing																										
PGQ10-Internal Audits; IT10-1- Quality Internal Audits																										

Legend:

applicable ;

not applicable

APPENDIX 5 - CORRELATION WITH GENERAL DATA PROTECTION REGULATION (EU) 2016/679 OF 27th April 2016

Procedures	art.4,5,6,8,9,15,16,17,18,19,20,21,22, 24,25,26,27,28,29,30,31,32,33,34,35, 36,37*,38*,39*,44,45,46,48,49,88,89; considerandos 32,33,39,42,43,58 a 63,65 a 72,74 a 79,82,83,84,85 a 94, 96,97,101 a 115,129,132,156,157,159,169	art.5,12,15,16,17,18,19,20,21, 22,23,30,31,38*,39*,89; considerandos 32,33,39,42,43,58 a 63,65 a 72,82,129,132,156,157,159	art.31,33,34,38*,39 * considerandos 39,58, 59,60,74 a 78,83,85 a 88,97	art.7,13,88	art.8,9, 89	art.28,29,32, considerandos 81,83,95	art.33, 34	considerandos 32,33,38,39, 40 a50,61 a 63	art. 39*
IT 01-04- Procedure for Internal Whistleblower Report									
PGQ 03-Human Resources Management									
PGQ 04-External Supply of Processes / Products / Services									
PGQ 07- Improvement Management									
PGQ 08- Personal Data Processing									
IT 08-1 - Management of personal data processing life cycle									
IT 08-2 - Data Subject Exercise of Rights									
IT 08-3 - Management of Personal Data Breach									
PGQ 10-Internal Audits									
PGQ 11- Clinical Studies									
PGQ 14- Investigation and Development Projects of New Technologies for Medicine									
PGQ 16 –Coordination & Monitoring of Clinical Research Activities									
PGQ 17 – Coordination & Monitoring of Health Technology Assessment Activities									
PGQ 18 – Grading Eye Exams									
PGQ 19 – Data Centre Activities									

Legend:*DPO is not mandatory regarding our activity (art°37). AIBILI has a Personal Data Protection Committee

applicable ;

Not applicable;