association for innovation and biomedical research on light and image

Quality Manual

NP EN ISO 9001:2015

Good Clinical Practices

ECRIN Requirements for Data Centre Certification

General Data Protection Regulation (EU) 2016/679

Ver. nº 38

INDEX

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I – PROMULGATION

This Quality Manual describes the Quality Management System of AIBILI in accordance with the requirements of ISO 9001, 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 the Quality Management System (QMS) and delegates in the President the formal approval of the Quality Policy and Quality Manual.

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

THE BOARD OF DIRECTORS

II – QUALITY POLICY

- 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, 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 nº58/2019 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 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 BOARD OF DIRECTORS

III– GENERAL INFORMATION OF AIBILI

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.

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 other legislation applicable to the protection of personal data, namely, the Portuguese Law nº58/2019 of 8th August.

III– GENERAL INFORMATION OF AIBILI

AIBILI is located in the Health Campus of Coimbra University since 1994 and has its own building with 1.454 m^2 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

AIBILI also has a Data Centre that provides IT and Data Management services for clinical research studies.

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 which is responsible for managing and processing whistleblower breach reports in a work related context submitted through an internal channel available at www.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.

AIBILI has partnerships with national and international institutions, namely with: ARSC – Health Administration of the Centre Region of Portugal, CF - Champalimaud Foundation, FMUC - Faculty of Medicine of the University of Coimbra, i3S – Institute for Research and Innovation in Health of the

III– GENERAL INFORMATION OF AIBILI

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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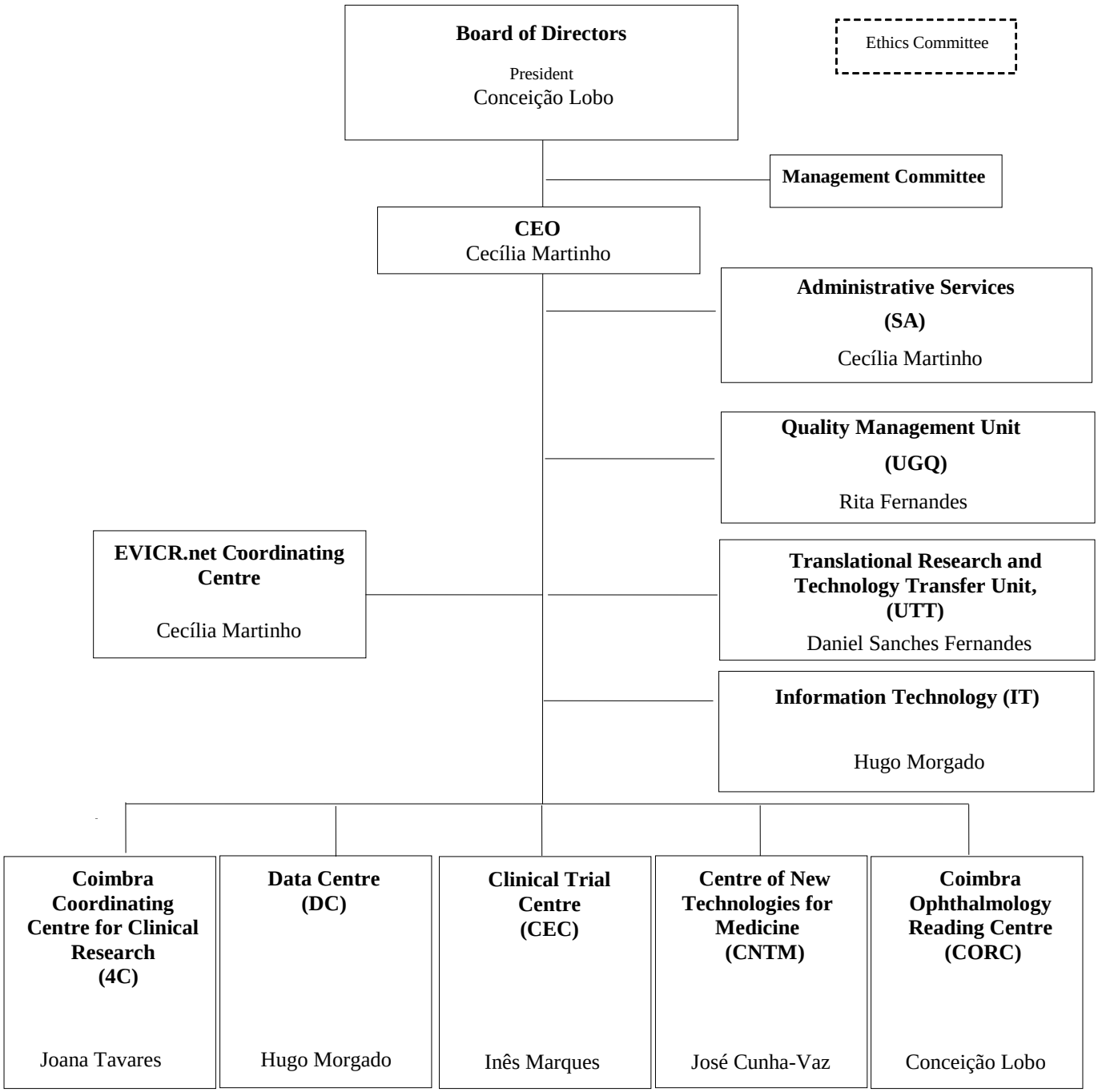

III– GENERAL INFORMATION OF AIBILI

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
- Data Management
- Development of Electronic Data Capture Solutions – with AIBILI Data Centre
- 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

III– GENERAL INFORMATION OF AIBILI

The 4C is a qualified resource to work closely with Pharmaceutical Industry in all the different phases of drug development and also supports industry on evaluation of medicines and other medicinal products for market access purposes, aiming at financing and reimbursement, by providing 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. It is, therefore, of capital importance in both drug reimbursement decisions at both ambulatory and hospital settings.

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 to grow up to store clients/partners data and information. AIBILI Data Centre services are provided by the Information Technology (IT) and 4C.

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.

The services provided by AIBILI Data Centre are: design and development 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 and Long Term Data Storage. Other services, such as data entry might be performed together with other AIBILI Units.

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.
- 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.

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CORC – Coimbra Ophthalmology Reading Centre

The Coimbra Ophthalmology Reading Centre (CORC) serves as a Central Reading Centre for multinational and multicentric clinical studies as well as for the Diabetic Retinopathy Central and South Region of Portugal Screening Programme, mainly in the areas of posterior segment/retinal diseases as Diabetic Retinopathy (DR), and Age-related Macular Degeneration (AMD), Retinitis Pigmentosa (RP), Retinal Vein Occlusion (RVO) and anterior segment diseases as Neurotrophic Keratitis.

CORC focus its activities on grading retinal diseases on fundus images, OCT and OCTA images of the retina for characterization and quantification of ophthalmic disease, functional evaluations of the retina using mfERG and visual fields as well as on grading anterior segment photography.

Since 2011, CORC is the central Reading Centre for the Diabetic Retinopathy Screening Programme of the Central Region of Portugal.

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

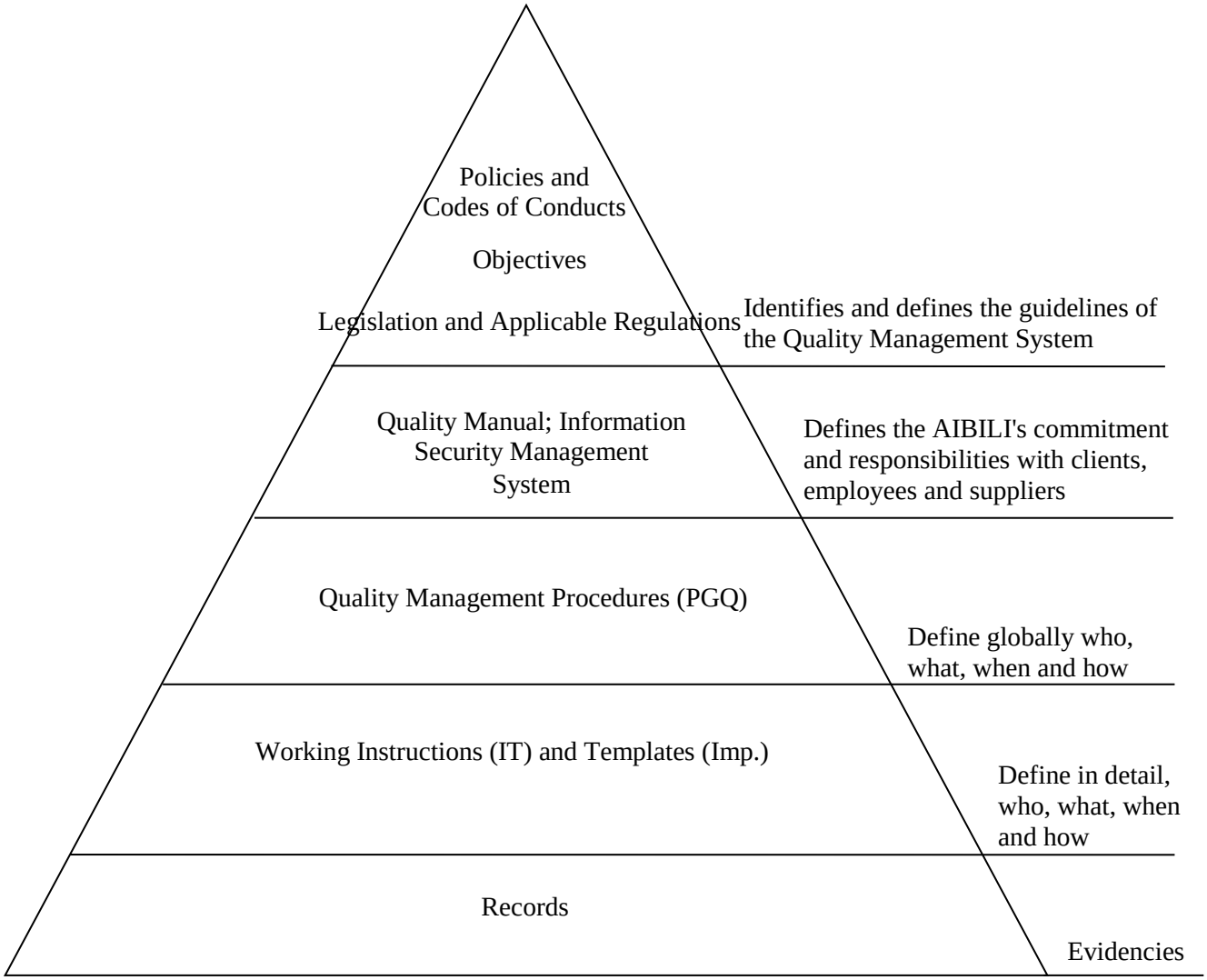
For grading purposes CORC uses licensed software from equipment suppliers and other common applications for imaging edition and analysis.

For research purposes CORC also has novel software programmes, developed in-house, to reliably quantify neovascularization of the retina and leakage, assess microaneurysm turnover in diabetic patients (RetmarkerDR® product), classify and quantify AMD lesions and disease activity in patients with AMD (RetmarkerAMD Research product) and perform segmentation of the retinal layers and quantify cystoid-like spaces on OCT.

CORC has all the necessary human resources for grading retinal images as well as to certify technicians and equipment of the Clinical Sites participating in clinical studies.

III– GENERAL INFORMATION OF AIBILI

AIBILI structured its Quality Management System (QMS) and supports it through a hierarchical set of documents that are described below:



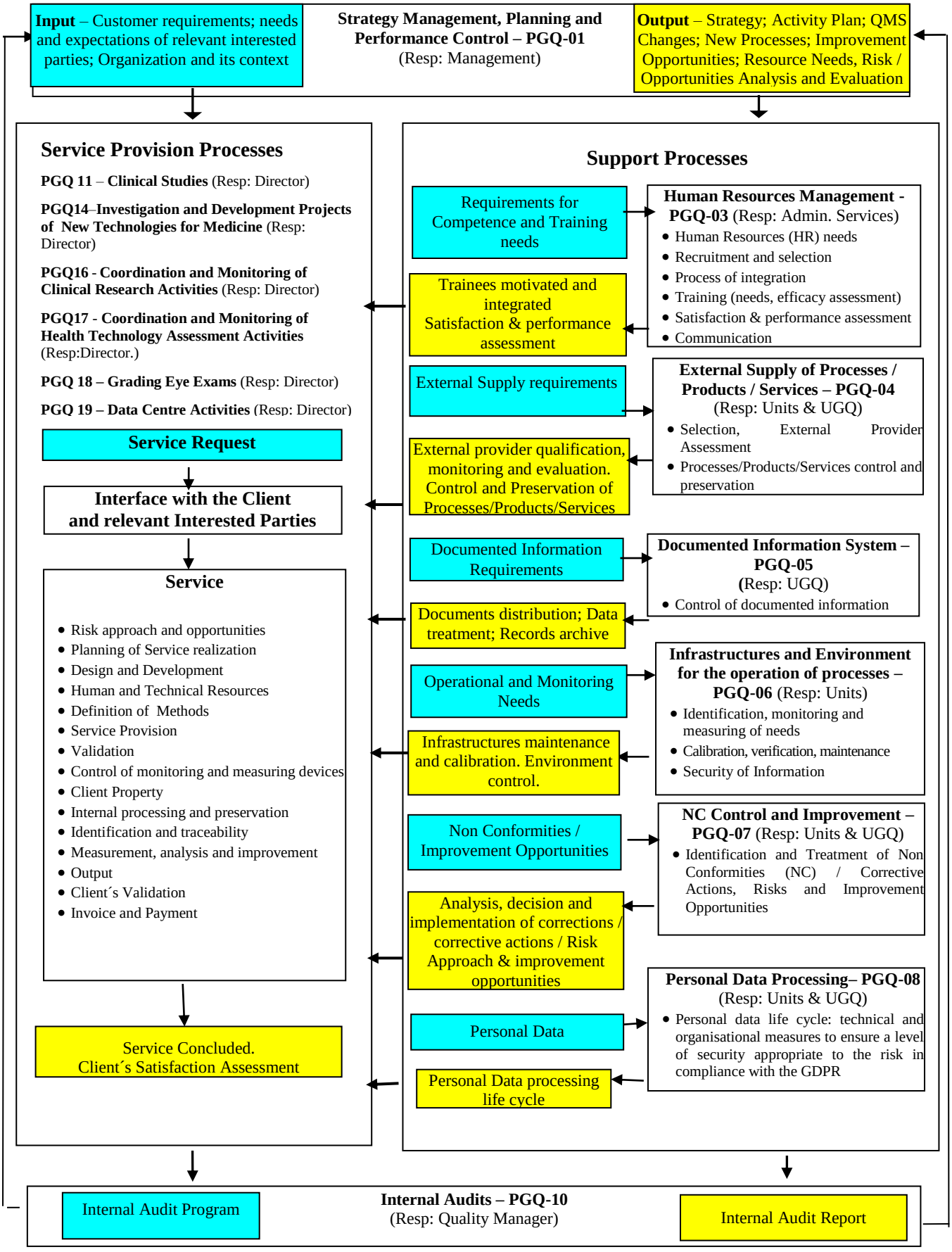
AIBILI Operational Manual is organized by PGQs, ITs and Imp. and structured as stated in Appendix 1.

The correlations of AIBILI QMS with ISO 9001:2015 are listed in Appendix 2 and with Principles of Good Clinical Practices in Appendix 3. Finally, AIBILI QMS correlation with ECRIN Data Centre requirements is also listed in Appendix 4.

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 nº21/2014, 16 of April changed by the Law n.º73/2015, 27 of July and Law nº 49/2018 of 14 August

Quality Manual and Procedures	GCP Requirements applicable to AIBILI- Articles of Law nº21/2014, 16 of April and those changed# by the Law n.º 73/2015, 27 of July																																		
	Art.1º	Art.2º	Art. 3º	Art. 4º	Art. 5º	Art. 6º	Art. 7º	Art. 8º	Art. 9º	Art. 10º	Art. 11º	Art. 11º-A	Art. 12º	Art. 13º	Art. 14º	Art. 15º	Art. 16º	Art. 17º	Art. 18º	Art.19º	Art 20, Art 22º	Art. 23º	Art. 25º	Art. 26º	Art. 27º a 31º	Art32	Art33 e 34º	Art. 36º e 37º	Art.38º	Art.39º	Art.40	Art.42	Art.51º	& Art.5º,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 Responsability; ** Sponsor´s Responsabilities; & applicable to Regulatory Authorities.

Legend: ■ applicable; not applicable

APPENDIX 4 - CORRELATION WITH ECRIN REQUIREMENTS FOR DATA CENTRE CERTIFICATION - VERSION Nº4

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 (artº37). AIBILI has a Personal Data Protection Committee applicable ; Not applicable;