ABBREVIATIONS

AISBL	*Association Internationale Sans But Lucratif* (non-profit international association under Belgian law)
ALLEA	European Federation of National Academies of Sciences and Humanities
BSL	Bio-Safety Level
CCU	Central Coordinating Unit
EC	European Commission
EGE	European Group on Ethics in Science & New Technologies
EMC	Erasmus University Medical Center (ERINHA's Dutch Node)
ERINHA	European Research Infrastructure on Highly Pathogenic Agents
ESF	European Science Foundation
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
FELASA	Federation of European Laboratory Animal Science Association
FoHM	Folkhalsomyndigheten (ERINHA's Swedish Node)
GDPR	General Data Protection Regulation
INSA	Instituto Nacional de Saúde Dr. Ricardo Jorge (ERINHA's Portuguese Node)
INSERM	Institut National de la Santé Et de la Recherche Médicale (ERINHA's French Node)
KUL	Katholieke Universiteit Leuven (ERINHA's Belgian Node)
NNK	Nemzeti Népégészségügyi Központ (ERINHA's Hungarian Node)
OECD	Organisation for Economic Co-operation and Development
OIE	World Organization for Animal Health
OLAW	Office of Laboratory Animal Welfare
PREPARE	Planning Research and Experimental Procedures on Animals: Recommendations for Excellence
RI	Research Infrastructure
RRI	Responsible Research & Innovation

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 824061.

ERINHA ETHICAL GUIDELINES

CONTENTS

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The **E**uropean **R**esearch **IN**frastructure on **H**ighly pathogenic **A**gents (ERINHA) is a pan-European distributed research infrastructure that operates as an International non-profit association under Belgian law (*AISBL - Association Internationale Sans But Lucratif*) with its registered offices in Brussels, a Central Coordinating Unit (CCU) located in Paris, and members in Europe. ERINHA strengthens the European research and development capacities by offering high containment services to researchers, including laboratory experiment services, expertise, and training, and by coordinating or participating to large-scale collaborations to advance research on highly infectious emerging and re-emerging pathogens.

In 2008, the European Strategy Forum on Research Infrastructures (ESFRI) identified a critical need for a relevant and coordinated European Bio-Safety Level 4 (BSL4) capacity to enable the European Union to rise to the challenge of the emergence, re-emergence and globalization of highly pathogenic agents. During two preparatory phases funded by the FP7 and H2020 programmes, the ERINHA and ERINHA2 projects respectively have laid the foundations of the Research Infrastructure (RI) by developing its concept, vision and approach.

ERINHA is currently the only RI of its kind in the European scientific landscape and therefore meets a critical need to bring the European Research Area to the forefront of research excellence, competitiveness, innovation and preparedness.

ERINHA is fully aware of the sensitive nature of its field of expertise and of the responsibilities that come with it. It is therefore of the utmost importance for the infrastructure and its Members to address all ethical issues raised by their activities, especially those related to:

- **Conducting scientific research**
- ***In vivo* work**
- **The use of biological agents**
- **Collecting personal & sensitive data**
- **Responsible Research & Innovation (RRI)**

This document describes the global ethical framework for all ERINHA activities and specifies the regulations that ERINHA Members must comply with at a national level. It will be evolving as new guidelines and policies are being developed.
These guidelines apply to ERINHA and its Members, as well as the Users of the infrastructure, who are expected to endorse and adopt the same level of ethical standards.

1. FUNDAMENTAL ETHICAL PRINCIPLES OF CONDUCTING SCIENTIFIC RESEARCH

European and international ethical guidelines and laws are applicable to any scientific research activity. ERINHA and its Members are not only aware of this framework but unreservedly approve it and commit to strictly comply with it. European and other international guidelines, conventions and laws are added to the specific national legal and ethical requirements applicable in each country where the research is performed.

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1.1 The Ethical Core of Scientific Research: the Nuremberg Code

In 1947, during the Nuremberg trials, a set of ten points, now known as the **Nuremberg Code**, were outlined as the founding ethical principles for legitimate medical research. ERINHA and its Members unreservedly approve these guidelines, which are considered as the universal ethical core of all clinical research and read as follows:

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

1.2 Opinions of the European Group on Ethics in Science & New Technologies

The European Group on Ethics in Science & New Technologies (EGE; formerly known as the "European Group of Advisers on the Ethical Implications of Biotechnology") is an independent advisory body of the President of the European Commission founded in 1991. The EGE Members provide an independent perspective on all ethical questions posed by scientific and technological innovation in relation to European legislation & policies. The EGE gave their recommendations on the **Ethical Aspects of Clinical Research in Developing Countries** (Opinion n°17 presented to the European Commission on 4th February 2003). They highlight the most fundamental guidelines for research ethics, which ERINHA and its Members support and commit to comply with:

- The principle of **respect for human dignity** and the principles of **non-exploitation, non-discrimination and non-instrumentalization**

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- The principle of **individual autonomy** (entailing the giving of free and informed consent, and respect for privacy and confidentiality of personal data)
- The principle of **justice** and the principle of **beneficence and non-maleficence**, namely with regard to the improvement and protection of health
- The principle of **proportionality** (including that research methods are necessary to the aims pursued and that no alternative more acceptable methods are available)

ERINHA and its Members will stay updated on the opinions of the EGE Members and follow their recommendations whenever relevant. (For instance: "Ethical aspects of human tissue banking", N° 11, 21 July 1998; "Ethical aspects of human stem cell research and use", N°15, 14 November 2001, etc.).

1.3 The Standard Codes of Conduct & Ethical Behaviour in Scientific Research

ERINHA and its Members agree unreservedly with the standard codes of conduct and ethical behaviour in scientific research established by the European Science Foundation (ESF) and the European Federation of National Academies of Sciences and Humanities (ALLEA) which outline the **principles of research integrity** and include:

- **Honesty** in communication
- **Reliability** in performing research
- **Objectivity**
- **Impartiality and independence**
- **Openness and accessibility**
- **Duty of care**
- **Fairness** in providing references and giving credit
- **Responsibility** for the scientists and researchers of the future

In addition, these standard codes define the framework of **good research practices** in various contexts (Research Environment; Training, Supervision & Mentoring; Research Procedures, Safeguards, Data Practices & Management; Collaborative Working; Publication & Dissemination; Reviewing, Evaluating & Editing) and address the **possible violations of research integrity** (Fabrication, Falsification, Plagiarism), their consequences, and the ways to handle misconduct. ERINHA and its Members endorse and apply the whole recommendations, which have become ethical references in Europe, including within the scope of the H2020 Programme. They will most likely remain a key element of the ethical framework of the Horizon Europe Programme.

The ongoing implementation of ERINHA's Quality Management System (QMS) is taking all these fundamental aspects into account.

1.4 Article 19 of EU regulation 1291/2013

EU Regulation 1291/2013 establishes the framework of Horizon 2020. More specifically, Article 19 lists areas of research that cannot be funded under the Programme for ethical reasons. It is likely that the framework of Horizon Europe will include similar conditions of eligibility for financing. ERINHA and its Members intend to apply for European funding and therefore commit to never conduct any work that would involve:

- Research activity aiming at human cloning for reproductive purposes

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- Research activity intended to modify the genetic heritage of human beings which could make such changes heritable
- Research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer
- Research involving the use of human embryos or embryonic stem cells

1.5 Additional Ethical References

1.5.1 Additional International Ethical References

In addition to the founding codes & recommendations mentioned above, the main additional international guidelines, key conventions & seminal opinions in relation to biomedical research and that ERINHA and its Members support, include but are not necessarily limited to:

- The Universal Declaration of Human Rights (1948)
- The United Nations Convention on the Rights of the Child (1989)
- The revised Helsinki declaration on Ethical Principles for Medical Research involving Human Subjects as adopted by the 64th WMA General Assembly in 2013
- The Convention on the Protection of Human Rights and the Dignity of Human Beings with regard to the Application of Biology and Medicine, also known as the Convention on Human Rights and Biomedicine (Council of Europe, 1997)
- The International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002 version) prepared by the CIOMS
- The International Ethical Guidelines for Epidemiological Studies (2009 version) prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO)
- The Additional Protocol on the Prohibition of Cloning Human Beings (1998)
- The Guideline for Good Clinical Practice E6 (R1) developed during the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (1996) (Last updated 2016)
- The Ethics of Research in Global Health Emergencies developed by the Nuffield Council on Bioethics (2020)
- The background paper on Pandemics commissioned by the Nuffield Council on Bioethics (2011)
- The background paper on Dual Use in Biology and Biomedicine commissioned by the Nuffield Council on Bioethics (2016)
- The background paper on Scientific Research Integrity commissioned by the Nuffield Council on Bioethics (2013)
- The Ethics of Research Involving Animals developed by the Nuffield Council on Bioethics (2005)
- The Ethical Review of Genome Editing by the Nuffield Council on Bioethics (2016)
- The Ethics and Social Issues of Genome Editing and Human Reproduction developed by the Nuffield Council on Bioethics (2018)
- The Ethics of Research Related to Healthcare in Developing Countries developed by the Nuffield Council on Bioethics (2002)
- The Ethics of the Collection, Linking and Use of Data in Biomedical Research and Health Care developed by the Nuffield Council on Bioethics (2015)

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1.5.2 Additional European Ethical References

At the European level, the ethical guidelines and laws currently in force include, but are not necessarily limited to:

- The Charter of Fundamental Rights of the EU
- The European Convention of Human Rights
- Directive 2005/28/ECC of the European Parliament and of the Council of 8 April 2005, laying down principles and detailed guidelines for good practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Directive 2001/20/EEC of the European Parliament and of the Council of 4th April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, as well as the Guidelines as suggested by the European Science foundation, in European science foundation policy briefing May 2001, on Controlled clinical trials (consolidated version on 7 August 2009)
- Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified microorganisms
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (consolidated version on 26 July 2019)
- Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions
- Directive 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation) (consolidated version on 4 May 2016)

To carry out their duties, ERINHA and its Members will also use the Principles on Good Laboratory Practice published by the Paris Organisation for Economic Co-operation and Development (OECD) (ENV/MC/CHEM (98) 17), as well as the "Guideline on the Clinical Evaluation of Diagnostic Agents" developed by the Committee for Medicinal Use Products for Human Use of the European Medicines Agency (CMPM/EWP/1119/98/Rev).

2. THE ETHICS OF *IN VIVO* WORK

When all other available methods have been fully explored and when strictly necessary, ERINHA and its Members will work with animals to advance research on high-consequence microorganisms known to cause severe pathologies in humans.

The data collected using animal models help identify correlates of infection and provide a very strong (and necessary) framework to inform further clinical studies or preclinical development.

ERINHA and its Members are strongly committed to conduct such research in accordance with the highest ethical standards and respect for animal welfare.

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2.1 Directive 2010/63/EU

The protection and welfare of animals are covered by a wide range of EU legislation. Since 1986, the European Union (EU) has implemented specific legislation that regulates the use of animals for scientific purposes. In 2010, Directive 86/609/EEC was repealed by Directive 2010/63/EU (current consolidated version 26 June 2019) which further strengthened legislation in this area and entered into full force in 2013.
It is one of ERINHA's and its Members' top priorities to perform thoughtfully-designed and humane animal studies in full compliance with **Directive 2010/63/EU**, which focuses on animal welfare, and firmly establishes the **Principle of the Three Rs**, as defined below by the EU, as a legal requirement:

➢ **REPLACEMENT:**

"Replacement can be defined as methods, strategies or approaches which do not involve the use of live animals. Replacement may be achieved through a number of tools or their combinations including:

- *In vitro* systems using tissues, whole cells or parts of cells
- Systems based on biochemical approaches, i.e. using synthetic (macro)molecules as proxies of (reactive) toxicity targets. Such methods are referred to as "*in chimico*"
- Computer-based models and approaches often termed *in silico*
- Use of 'omics' technologies (e.g. transcriptomics, proteomics and metabolomics)
- Non-testing approaches such as 'read-across' technique"

➢ **REDUCTION:**

"The concept of reduction covers any approach that will result in fewer animals being used to achieve the same objective, including maximising the information obtained per animal, reducing the number of animals used in the original procedure and/or limiting or avoiding the subsequent use of additional animals.

The number of animals can also be reduced by performing procedures on animals more than once, where this does not detract from the scientific objective or result in poor animal welfare. However, the benefit of reusing animals should always be balanced against any adverse effects on their welfare, taking into account the lifetime experience of the individual animal. As a result of this potential conflict, the reuse of animals should be considered on a case-by-case basis."

➢ **REFINEMENT:**

"The term refinement signifies the modification of any procedures or husbandry and care practices from the time the experimental animal is born until its death, so as to minimise the pain, suffering and distress experienced by the animal and enhance its well-being.
When an animal experiences pain, suffering or distress, there are often accompanying physiological changes which may increase the variability of scientific results. Refinement therefore is also likely to improve data quality and contribute to Reduction. Refinement can also be achieved by moving from species that are considered more sentient to those less sentient. For example, substituting a non-human primate by the use of a fish or substituting the use of fish with daphnia are both considered methods of refinement as they are likely to reduce the pain, suffering and distress experienced by the animal, however, still requiring the use of live animals."

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The principle of the Three Rs originated in **1959** with the publication of "The Principles of Humane Experimental Technique" by W. M. S Russell and R. L. Burch.

Article 4 of **Directive 2010/63/EU** covers the Principle of Replacement, Reduction and Refinement by stating that:

1. *Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.*
2. *Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.*
3. *Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.*

In addition, Annex III of Directive 2010/63/EU describes the requirements for establishments and for the care and accommodation of animals in a species-specific manner. The document focuses on:

- The physical facilities (general design, holding rooms, procedure rooms, etc.)
- The environment and control thereof (ventilation and temperature, lighting, noise, etc.)
- The care of animals (health, housing and enrichment, handling, feeding, watering, etc.)

The European Parliament resolution of 26 November 2015 on a new animal welfare strategy for 2016-2020 further strengthens that the **Principle of the Three Rs** is to be the new norm in scientific research.

All EU requirements are scrupulously followed and implemented in ERINHA Facilities.

2.2 ERINHA Commitment to Animal Welfare

According to the World Organisation for Animal Health (OIE), the **Five Freedoms** defined by the Brambell Committee in 1965 are guiding principles to ensure animal welfare:

- Freedom from hunger and thirst,
- Freedom from discomfort,
- Freedom from pain, injury or disease,
- Freedom to express normal behaviour, and
- Freedom from fear and distress.

Article 33 of **Directive 2010/63/EU** about Care & Accommodation covers, at least partly, these fundamental principles in the context of scientific research and makes them legal requirements by stating that:

"*Member States shall, as far as the care and accommodation of animals is concerned, ensure that:*

(a) *all animals are provided with accommodation, an environment, food, water and care which are* ***appropriate to their health and well-being****;*
(b) *any restrictions on the extent to which an animal can satisfy its physiological and ethological needs are kept to a minimum;*
(c) *the environmental conditions in which animals are bred, kept or used are checked daily;*

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(d) *arrangements are made to ensure that* ***any defect or avoidable pain, suffering, distress or lasting harm discovered is eliminated as quickly as possible****; and*
(e) *animals are transported under appropriate conditions."*

ERINHA and its Members, of course, comply with all the requirements of Directive 2010/63/EU.

2.2.1 Social Housing

Social interactions are a crucial factor for the well-being of many species. Promoting such interactions fosters natural and non-aggressive interactions between the animals and the expression of species-typical behaviours. Social animals at ERINHA Facilities are therefore harmoniously housed as stable, compatible groups and never kept singly, unless absolutely required (for scientific or veterinary reasons), or unless the species (e.g. hamsters) or type of animal (e.g. adult male mice) is known for its solitary nature. The number of animals never exceeds the maximal capacity recommended by Annex III of EU 2010/63/EU. In addition, the accommodation offers the animals the possibility of expressing their typical behavioural repertoire.

2.2.2 Environmental Enrichment

According to the Federation of European Laboratory Animal Science Association (FELASA), environmental enrichment is "any modification in the environment of the captive animals that seeks to enhance its physical and psychological well-being by providing stimuli meeting the animals' species-specific needs". The key concept behind enrichment is giving animals a degree of choice and control over their environment. Environmental enrichment should promote species-typical behaviour through physical exercise, foraging, and manipulative and cognitive activities. Environmental enrichment is as crucial for animal welfare as an adequate space, and the programmes implemented at ERINHA Facilities thoroughly address the specific social, structural, sensory and cognitive needs of each species.

2.2.3 Positive Reinforcement Training

According to the Code of Practice for the Housing and Care of Animals bred, supplied or used for scientific purposes (Section 3, Chapter 1, Paragraph 4.11), "*the quality of care animals are given may influence not only breeding success, growth rate and welfare but also the quality and outcome of experimental procedures.* ***Accustoming animals to competent and confident handling during routine husbandry and procedures reduces stress both to animals and personnel.*** *For some species, for example dogs and non-human primates, a training programme to encourage co-operation during procedures can be beneficial to the animals, the animal care staff and the scientific programme. For certain species, social contact with humans should be a priority. However, in some cases, handling should be minimised (e.g. wild animals)*. Full programmes of "positive reinforcement training" are challenging to implement in high-containment facilities due to the fact that contacts between humans and animals are minimized for biosafety reasons. However, only outstanding, sufficiently trained and qualified staff is allowed to handle the animals and to carry out the protocols with veterinary advice and support when needed. Animal handling is performed in compliance with specific standard operating procedures designed in accordance with Directive 2010/63/EU and biosecurity prerequisites. No harsh methods of capture or restraint are ever used; the dexterity of the staff along with the adapted equipment and protocols suffice for the humane, safe and smooth handling

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of the animals. Light sedation is also an appropriate measure to mitigate the distress that scientific procedures can cause to the animals, and warrants safe and secure conditions of work for the operator.

2.2.4 Early Humane Endpoints

The identification of early, humane endpoints for euthanasia is a crucial aspect of refinement in scientific studies that involve animals. Early humane endpoints are always considered at ERINHA facilities, and Members have implemented the necessary measures to mitigate animal pain or distress, and avoid any unnecessary animal suffering. All efforts made to prevent discomfort, distress and pain in laboratory animals have both ethical and scientific benefits, thus being continuously encouraged.

2.2.5 Training & Education

With Article 23 on the Competence of Personnel, **Directive 2010/63/EU** acknowledges that the proper training and education of the personnel involved in breeding, supplying and handling animals for scientific purposes is an integral part of a comprehensive policy to ensure animal welfare in research. It states that:

"The staff shall be adequately educated and trained before they perform any of the following functions:
(a) *carrying out procedures on animals;*
(b) *designing procedures and projects;*
(c) *taking care of animals; or*
(d) *euthanising animals"*

The personnel of ERINHA facilities is highly trained and qualified for handling animals and performing all procedures. Through the research infrastructure and in relation with Article 23, ERINHA Members will be working on harmonizing their practices based on the working document on the development of a common education and training framework to fulfil the requirements under the Directive [2010/63/EU] to ensure that all research performed in ERINHA facilities is consistent and follow the highest ethical standards.

2.3 Additional Guidance to Promote Animal Welfare

In addition to the legal requirements, ERINHA and its Members will try and follow the guidance of the latest **PREPARE guidelines** (Planning Research and Experimental Procedures on Animals: Recommendations for Excellence).

These guidelines were developed by a group of experts from the United Kingdom and Norway, led by the Secretary of Norecopa (Norway's National Consensus Platform for the advancement of the 3Rs) to reduce waste and increase the reproducibility of *in vivo* studies. The guidelines focus on a large number of factors which can influence the validity and outcome of studies on animals, as well as the health and safety of all those concerned. A checklist has been made available to help comply with the PREPARE guidelines.

2.4 Member-Specific National Legislation & Authorisations

As required by **Directive 2010/63/EU**, the *in vivo* work conducted at ERINHA Facilities is always approved by the competent authorities, as well as evaluated and supported

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by the relevant institutional and/or local ethics committee(s) (if applicable. All protocols are evaluated and reviewed by either internal or external ethical bodies, or both, as indicated below for each ERINHA Full & Associate Members:

FACILITY	Internal committee	External committee
KUL, Belgium	Institutional animal welfare committee	No (not required considering the species housed at the facility)
FoHM, Sweden	Institutional animal welfare committee	Yes, independent external regional ethics committee
NNK, Hungary	Institutional animal welfare committee	Yes, independent external regional ethics committee
ERASMUS, Netherlands	Institutional animal welfare committee	Yes, independent external ethics committee advising the competent authority (Central Authority for Scientific Procedures on Animals, CCD) on project licenses.
INSA, Portugal	Institutional animal welfare committee – advised by an independent body without any decision-making power	No (not required considering the species housed at the facility)
INSERM, France	No, external ethical review only	Yes, independent external regional ethics committee (IEREC) and French ministry of research

Animal studies can only be carried if three types of licenses are simultaneously in place:

- one for the establishment,
- one for the project, and
- personal licenses of those carrying out animal studies.

All necessary authorisations are kept on file, including:

- Copies of the relevant project licenses for all animal experiments (including the work with genetically modified animals when applicable).
- General information on the nature of the experiments, and the procedures to ensure animal welfare and adherence to the 3Rs principle.
- Copies of the training certificates/personal licenses of the staff involved in animal experiments.
- An individual history file for selected species (dogs, cats, non-human primates) as required by Article 31 of **Directive 2001/63/EU**.

The staff in charge of the animal studies follow all appropriate health and safety procedures in accordance with the relevant local and national guidelines or applicable laws.

2.4.1 Katholieke Universiteit Leuven (KUL), Belgium

Animal housing and caretaking at KUL comply with the Belgian and EU laws, guidelines and policies for animal experimentation, i.e. the **Belgian Royal Decree of 29 May 2013 regarding the protection of laboratory animals** (available online in Flemish)**, and Directive 2010/63/EU** (Flemish version here). The laboratory for Virology and Chemotherapy at KUL is authorized by FOD Volksgezondheid, Brussels, Belgium

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(License: LA1210186) and by the Brussels Environmental Service (IBGE-BIM, file number: LABO 94-0453) to conduct infection experiments in mice and hamsters. The animal work at KUL is officially covered by permits with reference N° AMV/30112018/SBB/219.2018/0892.

KUL is also one of the signatory institutes of the Transparency Agreement on Animal Research in Belgium.

2.4.2 Institut National de la Santé Et de la Recherche Médicale (INSERM), France

Animal housing and caretaking at INSERM comply with the French and EU laws. Both French scientific structures and experimenters must obtain an agreement to conduct animal work (renewable every five years). INSERM is approved for animal experimentation and breeding, and for work using non-human primates (Agreement n° D69387 0502 through decree n°SPA-2017-058, June 2017).

France has had extensive legislation that covers the use of animal for scientific purposes for a long time; the use of alternative methods, for instance, has been a legal requirement since 1976 (Law 76-629). The transposition of **Directive 2010/63/EU** into French national laws is reflected by:

- Law No. 2010/ 788, 12 July 2010
- Order 2012/10, 05 January 2012
- Decree 2013-118 which updates articles R214-87 to R214-137 of the French rural code
- Four orders from 01 February 2013 that each establishes specific conditions for the use of animal for scientific purposes (Order No. 1, Order No. 2, Order No. 3 & Order No. 4)

2.4.3 Nemzeti Népégészségügyi Központ (NNK), Hungary

Animal housing and caretaking at the National Biosafety Laboratory (NBL) at NNK comply with the Hungarian and EU laws, guidelines and policies for animal experimentation, i.e. **Act No. XXVIII of 1998 on animal protection** (revised and expanded on several occasions) is the basic legislation that regulates the use of animals for scientific purposes in Hungary. **Directive 2010/63/EU** (IRÁNYELV) has been transposed into national laws through Ordinance 40/2013 (II.14.) (Hungarian version) and Ordinance 98/2014 (III.25.) (Hungarian version) of the Hungarian Government.

The NBL also complies with the Institutional Ethical Code on Animal Experiments, which regulates the design and conduct of *in vivo* research projects, the environmental conditions, the persons involved in animal handling and caretaking, as well as the necessary trainings and certificates.

The NBL is approved for animal experimentation and breeding, and for experimentation using mice, quails and hamsters (registration number 18/2/2015, administration number PEI/001/1230-2/2015, May, 2015).

2.4.4 Erasmus University Medical Center (EMC), the Netherlands

Animal housing, husbandry, care and use at ERASMUS MC is compliant with the Dutch and EU laws, guidelines and policies for the protection of animals used for research. In the Netherlands, an establishment licence and a project licence are required to carry out studies involving animals. ERASMUS has an establishment licence (10100) and holds

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project licences for using a variety of animal models, including NHPs in infectious/emerging diseases research. It holds OLAW (Office of Laboratory Animal Welfare) Assurance Approval F16-00046 (A5051-01).

All legislation regarding animals is the responsibility of the Minister of LNV (Agriculture, Nature and Food quality).

The Netherlands is a leading country with regards to animal protection and welfare. The founding piece of legislation in the country for animal welfare is the 2011 Animals Act (no English translation available), which prohibits causing pain or injury to domestic animals without reasonable purpose. The Act is based on the **Five Freedoms** defined by the Brambell Committee 1965, as recommended by the World Organization for Animal Health (OIE) and described in Section 2.2.1 (freedom from hunger and thirst, freedom from discomfort, freedom from pain, injury or disease, freedom to express normal behaviour, and freedom from fear and distress).

With regards to the use of animals for scientific purposes, the requirements of **Directive 2010/63/EU** were incorporated into the Dutch legislation (no official English translations are available) through:

- Act on animals used for scientific purposes (Wet op de dierproeven, 2014);
- Decree on animals (to be) used in scientific procedures (Dierproevenbesluit, 2014);
- Regulation on animals (to be) used in procedures (Dierproevenregeling, 2014).

2.4.5 Instituto Nacional de Saúde Dr. Ricardo Jorge (INSA), Portugal

Animal housing and caretaking at INSA comply with the Portuguese and EU laws, guidelines and policies for animal experimentation. INSA is approved for experimentation with mice. The institute licence was granted in 2011 by the Portuguese National Authority, in compliance with the national legislation in force at the moment (Decree-Law No. 1005/92).
Decree-Law No. 113/2013 has repealed Decree-Law No. 1005/92 and established provisions for the implementation of **Directive 2010/63/EU** by specifying rules to fully enforce the application of the principles of the 3Rs. It has been recently amended by Decree-Law No. 1/2019. The use of animals for scientific purposes is under the authority of the Direção-Geral de Alimentação e Veterinária (DGAV) and institutional Animal Welfare Bodies. It also follows the FELASA (Federation of European Laboratory Animal Science Associations) guidelines and recommendations concerning animal welfare in the care and use of laboratory animals, and in the design and conduct of research projects in which animals are used, including the proper education and training of the persons involved in all animal work.
More specifically and under Decree-Law No. 113/2013, three types of authorization are required:

- Authorization for breeders, suppliers, and users of animals (permanent except if an inspection reports any breach);
- Authorization for persons performing certain functions (training course on the proper handling of animals recognized by FELASA)
- Authorization for projects that involve the use of animals.

Finally, in the framework of Decree-Law No. 113/2013, all breeders, suppliers and users must appoint in their establishment a body responsible for the welfare of animals whose composition must take into account the provisions of Order No. 2880/2015 (in Portuguese here).

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2.4.6 Folkhalsomyndigheten (FoHM), Sweden

Animal housing and caretaking at FoHM comply with the Swedish and EU laws, guidelines and policies for animal experimentation.

The animal facility at FoHM is supervised and approved by the Swedish Board of Agriculture (Jordbruksverket).

In Sweden, the national regulations, adjusted to fully comply with **Directive 2010/63/EU**, are as follows:

- The Animal Welfare Act (L 1 Djurskyddslagen SFS 2018:1192) (unofficial translation)
- The Animal Welfare Ordinance (L 2 Djurskyddsförordningen SFS 2019:66) (unofficial translation)
- The Swedish Board of Agriculture's Regulations and General Advice of Laboratory Animals (L150 Statens jordbruksverks föreskrifter och allmänna råd om försöksdjur SJVFS 2019:9) https://djur.jordbruksverket.se/amnesomraden/djur/olikaslagsdjur/forsoksdjur.4.7850716f11cd786b52d80001724.html

3. THE ETHICS OF USING BIOLOGICAL AGENTS

The activities of ERINHA Facilities are regulated by Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

According to this Directive, **"Biological agents"** shall be classified into four risk groups, according to their level of risk of disease upon infection:

- **Group 1 biological agent** means one that is unlikely to cause human disease;
- **Group 2 biological agent** means one that can cause human disease and might be a hazard to workers; it is unlikely to spread to the community; there is usually effective prophylaxis or treatment available;
- **Group 3 biological agent** means one that can cause severe human disease and present a serious hazard to workers; it may present a risk of spreading to the community, but there is usually effective prophylaxis or treatment available;
- **Group 4 biological agent** means one that causes severe human disease and is a serious hazard to workers; it may present a high risk of spreading to the community; there is usually no effective prophylaxis or treatment available.

The most dangerous & pathogenic biological agents, i.e. Risk Group 3 & Group 4 biological agents, are the research focus of ERINHA and its Members.

Directive 2000/54/EC aims at protecting workers against risks to their health and safety, including the prevention of such risks, arising or likely to arise from exposure to biological agents at work, by implementing containment measures as stated in the following articles:

- **Article 15(3):**
  In isolation facilities where there are human patients or animals who are, or who are suspected of being, infected with group 3 or group 4 biological agents, containment

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measures shall be selected from those in Annex V column A, in order to minimise the risk of infection.

- **Article 16(1)(a) and (b):**
  The following measures must be taken in laboratories, including diagnostic laboratories, and in rooms for laboratory animals which have been deliberately infected with group 2, 3 or 4 biological agents or which are or are suspected to be carriers of such agents.
  - Laboratories carrying out work which involves the handling of group 2, 3 or 4 biological agents for research, development, teaching or diagnostic purposes shall determine the containment measures in accordance with Annex V, in order to minimise the risk of infection.
  - Following the assessment referred to in Article 3, measures shall be determined in accordance with Annex V, after fixing the physical containment level required for the biological agents according to the degree of risk.
    Activities involving the handling of a biological agent must be carried out:
    - only in working areas corresponding to at least containment level 2, for a group 2 biological agent,
    - only in working areas corresponding to at least containment level 3, for a group 3 biological agent,
    - only in working areas corresponding to at least containment level 4, for a group 4 biological agent.

In other words, laboratories carrying out work involving risk group 2, 3 or 4 biological agents for research, like ERINHA Members, must determine the relevant containment measures in order to minimise the risk of infection of the workers and of spread in the environment.

In the case of activities involving exposure to several groups of biological agents, the risk must be assessed on the basis of the danger presented by all hazardous biological agents present. The assessment must be renewed regularly.

The Members of ERINHA all have adequate facilities and policies to handle these biological agents in research; this is the core ERINHA's expertise.

4. THE ETHICS OF WORKING WITH PATIENT SAMPLES

As part of their research activities, ERINHA and its Members may conduct studies requiring the analysis of samples collected from patients.

ERINHA does not intend to conduct any biobanking activities and, when required, will source such samples from specialized and reputed biobanks such as BBMRI-ERIC that fully comply with all appropriate legislation and ethical guidelines, including patient consent and proper processing of personal and sensitive data.

5. THE ETHICS OF COLLECTING & PROCESSING PERSONAL DATA

ERINHA is the coordinator of ERINHA-Advance, a Horizon 2020-funded project meant to support the first three years of operation of the infrastructure. ERINHA-Advance includes the launch of calls for proposals and therefore the receipt of applications from scientists in the frame of transnational access (TNA) activities. In this respect, ERINHA, through its CCU, will need to process certain **personal data** concerning the applicants. These data must be held in order to process and evaluate applications and to liaise effectively with applicants about their proposals.

The **General Data Protection Regulation (GDPR)** (Regulation (EU) 2016/679 of the

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European Parliament & and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC) came into force on 25 May 2018 and aims to give individuals control over their personal data. ERINHA's policy is to ensure transparency and has therefore developed a data protection policy note that explains how the personal data collected are used and processed, and addresses the following topics:

1. **What is considered personal data?**
2. **What data will ERINHA collect?**
3. **How will ERINHA collect your data?**
4. **How will ERINHA use your data?**
5. **How will ERINHA store your data, and for how long?**
6. **What are your rights regarding data protection?**
7. **How to contact ERINHA?**
8. **How to contact the appropriate authorities?**

This ERINHA's Data Protection Policy is available online at erinha.eu.

6. THE ETHICS OF RESPONSIBLE RESEARCH & INNOVATION

Responsible Research & innovation (RRI) is "*an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation.*"

This approach implies that societal actors (researchers, citizens, policy makers, business, third sector organisations, etc.) work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society.

In practice, this covers matters such as **public engagement in research and innovation, easier access to scientific results, gender equality, ethics, and science education** among others.

The culture of RRI will most likely be consolidated in the next EU Research & Innovation Programme Horizon Europe. ERINHA and its Members will actively engage in actions that support RRI.

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