

IMI2 GA853989 - ERA4TB

European Regimen Accelerator for Tuberculosis

WP9 –Ethics and Data Privacy

D9.1 GEN - Requirement No. 9 (Ethics Plan)

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1. Abstract

WP9 aims to identify and address all the ethical, legal and societal issues raised by the preclinical and clinical research activities in the Project. This document constitutes an initial report to provide an early status on the ethics and data management will be managed for the preclinical and clinical studies developed within the project.

According to Project proposal, this WP aims to define and follow-up all the Ethical and Data Privacy implications to be considered throughout the project in a cross-sectional way.

2. Background

The Ethics Plan is a deliverable (D9.1) of WP9. It will ensure that research integrity is followed across the project and all its activities fulfil ethical and regulatory requirements for preclinical experimentation and clinical trials under the applicable local and EU regulation on ethics and data privacy.

To be able to achieve these objectives we propose at the present document different activities to follow up all ethics issues and data privacy issues that can appear during the project.

Global project ethics plan: Ethics are a pivotal issue to be able to achieve excellence in research. ERA4TB activities will comply with fundamental ethics principles and legislation within the scientific research carried out within this project.

The most common ethical issues include the involvement of patients, privacy and data protection issues and research on animals and non-human primates, misuse/malevolent use, impact on the environment, etc.

In ERA4TB we have paid special attention to ethics regarding:

- FTIH trials
- Biological samples management
- Genetic information management
- Preclinical studies: Research with non-human primates and mice.
- Data protection

According to the Consortium Agreement (CA), an **Ethics Advisory Board (EAB)** will be set up to consult the development of relevant procedures and forms, advise researchers and monitor the ethics issues in ERA4TB and how they are handled. It will be composed of at least five (5) members, including internal members of WP1, 3,7 and 9 and at least one external expert with detailed knowledge of ethical policies at European level. On 4th June 2020, the Steering Committee endorsed the following composition of the EAB:

- Alberto Borobia (WP9)
- Antonio Carcas (WP9)
- Christoph Hölscher (WP3)
- Emma Fernández (WP7)
- Irene Garcia (WP7)
- Jesus Carretero (WP1)
- Patrick O’Meara (WP1)
- Samira Boarbi (WP3)
- Uwe Fuhr (WP7)
- Alberto García-Basteiro (external expert)

Their affiliation to specific ERA4TB WPs and field of expertise is represented in the table below:

	WP1	WP3	WP7	WP9
	Patrick O’Meara Jesus Carretero	Samira Boarbi Christoph Hölscher	Emma Fernandez Irene Garcia Uwe Fuhr	Alberto Borobia Antonio Carcas
Clinical expertise				
FTIH – Regulatory			X	
Trials with healthy volunteers			X	
Regulatory in each country with CTU				
Management of biological samples			X	
Management of genetic samples			X	
Cross-border shipments			X	
Management of genetic information			X	
Personal data management	X		X	
Personal data anonymization processes	X			
Preclinical expertise				
Ethical regulation in animal experimentation		X		
Regulation for each country involved:				
Clinical studies with primates (nonhuman primates): marmosets (Callithrix and Macaca)				
Clinical studies with mice				
Ethical regulation in animal experimentation		X		

The EAB will keep a repository updated with all ethics documents of research activities involving humans and/or animals. A report by the EAB must be submitted to IMI JU at the end of each reporting period.

3. Preclinical ethics plan

Regarding the preclinical ethics plan, WP6 will lead Pharmaceutical Development. Different preclinical species will be used (rodents and non-human primates) to define the best formulation allowing exposure levels needed for efficacy with the required minimum specifications to facilitate transition to next phases.

Regarding research involving animal experimentation, the Project consortium supports the implementation of the so-called 3Rs principles - replace, reduce and refine - for the ethical use of animals in medicine testing across the European Union (EU).

These principles encourage alternatives to the use of animals in the testing of medicines while safeguarding scientific quality and improving animal welfare where the use of animals cannot be avoided.

The 3Rs principles are set out in the now famous treatise of R. Russell and W. M. S. Burch entitled “The Principles of Humane Experimental Technique” (London, 1959).

- Replacement refers to the preferred use of non-animal methods over animal methods whenever it is possible to achieve the same scientific aim.
- Reduction refers to methods that enable researchers to obtain comparable levels of information from fewer animals or to obtain more information from the same number of animals.
- Refinement is much broader and refers to methods that alleviate or minimize potential pain, suffering, or distress, and enhance animal welfare for the animals still used.

Animal Experimentation

Clinical Animal Ethics Manager will be formally appointed when the project starts and will lead the ethical monitoring. This task will provide a comprehensive analysis on ethical issues in animal experimentation and clinical settings, particularly regarding the treatment of sensitive data. Coordination will lead to the production of all related documents and reports. Potential ethical issues will be monitored and managed, and when required, a close cooperation between partners, with IMI, with the Ethics Helpdesk of the EC will be established. It will ensure that all analysis/experimental work performed within the project comply with national and European ethical guidelines

and ensure that all data collection and experimental work have been approved by relevant local Ethical Committees.

The preclinical assays will require the fulfilment of all the EU regulations regarding experiments on vertebrate animals and all animal studies will be performed in sites with approved animal facilities. The GLP assays to be performed should be in compliance with the requirement of the GLP regulations, the OECD principles of GLP, EU directive 2010/63 on the protection of animals used for scientific purposes and the voluntary AAALAC guidelines. Development of clinical protocols subject to ethical and legal aspects of patients (autonomy, justice, confidentiality, non-maleficence) and their samples to be totally compliant with legislation and in coherence with their needs and clinical needs. This will imply monitoring, surveillance and on-site tutoring towards the proper development of clinical activities.

All partners and CROs agree to abide with the standard conduct and standard manipulations of animals in the respect of ethics principles and in compliance with the applicable international, EU and national law in particular with EU Directive 2010/63/EU on the protection of animals used for scientific purposes. Although the use of animals for experimental medicine is necessary for the development of safe and efficient therapeutics, this does imply strong efforts to guarantee animal welfare and preservation of endangered species. The 3Rs policy of Refinement, Reduction and Replacement endorsed by the European Union (99/167/EC: Council Decision of 25/1/99) is a primary demand of the European citizens to which the consortium will actively contribute.

In the absence of applicable alternative methodologies, such as mathematical or computational models or *in vitro* methodologies, preclinical trials are indispensable to address the rationale of the use of ERA4TB products. At this stage, there are no alternative methods to the use of animals to obtain reliable data. So, the project involves the use of three different animal models: Mice, Marmosets and Macaques. Rigorous statistical modelling of the studies will be performed in order to adjust to a minimum the number of animals per experimental groups while maintaining a statistical power of 80% or higher. In addition, the consortium will foster development of non-invasive methods for monitoring immune responses and infections, particularly *in vivo* imaging, so that the need for tissue samples requiring biopsies or necropsy will be reduced as much as possible.

The requirement pertaining to biosafety procedures will be met in the licenses provided by the partners performing the tasks. Copies of relevant authorizations for animal experiments, as well as copies of training certificates/personal licenses of the staff involved in animal experiments will be kept on file with the coordinator.

Non-Human Primates

Of all the animal models used for TB research (rodents, rabbits, fish, etc.) non-human primates (NHP), especially the rhesus and cynomolgus macaques, share the most extensive anatomical and physiological similarities with humans. NHP can be infected by the natural route with low doses of aerosolized *Mtb* and display the full range of clinical and pathological signs of TB found in humans. These include the presence of caseous granulomas, calcification and pulmonary cavities that are rarely encountered in mice infected with *Mtb*. In recent years, macaques have found extensive use in TB vaccine research as they replicate the immune responses encountered in humans including latent TB. The PK/PD properties of most TB drugs are generally accepted as being closer to those observed in humans than in rodent models of TB although exceptions are to be expected. An additional advantage of the macaque is its natural susceptibility to the simian immunodeficiency virus, SIV, thus allowing studies of TB/HIV interactions in the cognate host. Disease progression can be monitored in NHP using the advanced imaging technologies available to the ERA4TB consortium. For a recent review see Peña and Ho (2016).

While macaque models of TB are available in Europe, where they have been used primarily for TB vaccine studies, the marmoset model has not yet been established. This is one of the objectives of this proposal. A major advantage of the marmoset for drug development work is its small size and low body weight, one tenth of that of a macaque. Consequently, lower amounts of drug substance are required thereby lowering the costs of the investigation and allowing more experimental drugs to be evaluated. Marmosets have been used extensively for TB drug development by investigators at NIH and Rutgers University, who will provide advice and expertise to the ERA4TB consortium to ensure rapid and efficient uptake of the model.

Both, the macaque and marmoset models will be used in ERA4TB accordingly to the development stage of the drug candidates, feasibility of production of drugs in sufficient quantities and previous PK studies validating the use of one model or the other. The use of marmosets will be privileged, and the macaque model will be considered when no other alternative will be identified.

ERA4TB will use non-human primates, more specifically Marmosets (*Callithrix jacchus*) and cynomolgus macaque (*Macaca fascicularis*), for preclinical assessment of safety and efficacy of the most advanced products candidates. Experiments in non-human primates will be performed only when strictly necessary and after previous evaluation in small laboratory animals. NHP will be used only for candidates selected by the steering committee based on strong scientific rationale. Two major reasons justify the choice of NHP in ERA4TB:

(i) The marmoset TB model will allow a first screening in NHP of drug entering late stage preclinical evaluation, after a preselection step in mice models (WP3.1). The advantage of marmosets is 1) the requirement of limited quantities of compounds because of the small animals' size and 2) the rapid progression of disease allowing rapid efficacy estimation.

(ii) The macaques are phylogenetically close to humans and share many similarities in the immune systems. The macaque model will be used when marmosets will not be suitable for assessing of more advanced ERA4TB compounds, where the quantity available is not restricted, and where assessment of specific biomarkers is required. Indeed, the marmoset model may have limitations for exploring immunomodulators, anti-human determinants that rarely cross-react with marmoset target, or combinations of drugs, most notably for long term treatment. In addition, there are limited number of tools for exploring biomarkers in this species. For these reasons, drugs that have passed successfully the evaluation in marmosets or strategies that includes immunological targets, may require additional studies in cynomolgus macaques. The larger size of the subjects in the macaque model allows collection of 1) larger volumes of samples permitting the application of a wider range of evaluations; and 2) more frequent collection of samples during studies enabling enhanced profiling. Reagents for assessment of the immune response are more plentiful for macaques than marmosets, which makes macaques more suitable for studies to identify and validate biomarkers correlating with efficacy. Finally, the cynomolgus macaque model develops a disease recapitulating the human infection and disease with progression compatible with testing long-term treatments efficacy.

Protocols and methodology for studies in NHP will be submitted to careful evaluation, including an internal peer review process, before submission to the national ethical committees. It is of primary importance to avoid the realization of methodologically flawed experiments, which represent unacceptable misuse of NHP. To avoid bias in methodology, we will use external expertise of professional statisticians whenever necessary.

NHP will be used at two animal facilities: IDMIT ("Infectious Disease Models and Innovative Therapies) and PHE (Public Health England, Porton Down, UK). IDMIT is an infrastructure from the Commissariat à l'Énergie Atomique et aux énergies alternatives (CEA) located at Fontenay-aux-Roses Centre under BSL-3 containment (Animal facility authorization #D92-032-02, Prefecture des Hauts de Seine, France). In application of Directive 2010/63/EU, transcribed in France regulation as "Décret 2013/118", protocols will not start before the favourable evaluation by the local ethical committee CEtEA #44 and prior authorization by the "Research and Education Ministry". The ethical

committee is approved by the CNEA (Commission Nationale de l'Experimentation Animale) which is a specialized body composed by experts from the Agriculture and from the Research and Education ministries (Décret 2005-264).

At PHE all procedures will be performed under authorization through the appropriate national laws and regulations, in compliance with European Directive 201/63/EU and its implementations in national legislation. The animals will be housed in compatible social groups and cared for in accordance with the UK Animals (Scientific Procedures) Act 1986. Under this Act, the use of animals at the PHE-PD site is allowed by an Establishment Licence granted by the UK Home Office. The facility is issued with an Establishment Licence by the UK Home Office (Ref 70/1707) and has a US OLAW (Office of Laboratory Animal Welfare) Certificate. The studies are permitted under the current TB NHP Project licence (P219D8D1A) that defines the experimental protocols, the species and number of animals to be used, granting a Project Licence requires clearly defined humane endpoints based on clinical assessment throughout the experimental period. Procedures will be conducted by trained staff holding Home Office Personal Licences defining the permitted procedures and animal species. Work permitted under this licence has been reviewed and approved by the PHE-PD Animal Welfare and Ethical Review Body (AWERB). Under this licence PK studies are categorised as Mild whilst studies involving challenge with *M. tuberculosis* are classified as Moderate. PHE-PD has a commitment to improving the welfare of the animals through an established programme of environmental enrichment. Security is controlled by a series of swipe access doors and only designated personnel are allowed to enter at each security level. As required by the Establishment Licence the facility has a Named Animal Welfare Officer (NACWO) and a Named Veterinary Surgeon (NVS) who are responsible directly to the Certificate Holder (Site Director) for animal welfare. Both the NACWO and NVS attend AWERB meetings at which all aspects of animal welfare and licensing are discussed. The work has been reviewed and approved by the PHE-PD Animal Welfare and Ethical Review Body (AWERB). The Named Veterinary Surgeon provides 24-hour clinical cover to deal with any non-study related injuries or to advise on anaesthesia and analgesia as required.

Statistical power calculations and data from previous studies will be used to determine the minimal group size required to result in an acceptable level of confidence in any read-out or endpoint of the experiment. Only those experiments justifiable on ethical grounds based on well-justified and research-motivated objectives will be conducted. We will reduce the numbers of animals per group as far as possible within the constraint of achieving statistically significant results when comparing groups of animals.

Animals will always be kept in the facility with the lowest level of authorized confinement. Confinement classification is determined accordingly to the OECD classification of pathogens. None of the animals will be housed

in single cages unless required by the protocol or because incompatibility of behaviour with other animals. Most of the animals will be in pairs or groups of four. Groups can be extended up to 12 animals. Cages have transparent separations, so groups that should be separated always remain at least on visual and auditive contact.

There are three veterinarians and a staff of technicians at CEA-IDMIT who are in charge of animal welfare and there is a program for environmental enrichment, training of animals and development of methods for reducing invasive interventions. Different kinds of toys are provided which are regularly changed. With respect to refinement, we will build on our extensive previous experience with NHP to minimize any discomfort. Experiments will be terminated at the earliest possible time.

The procedures adopted will ensure that the amount of suffering to the animals is minimized (sampling, immunization, challenge under anaesthesia) and their welfare is protected as far as possible. In addition, the consortium will foster the development of non-invasive methods for monitoring host responses to infection and treatments. In addition to adhering to general guidelines of 3Rs, by using appropriated methodology and statistics, we will refine the use of NHP by applying whenever feasible low invasive in vivo imaging technology (CT and ET-CT). This will be highly valuable for reducing the need for high invasive approaches like tissue biopsies.

According to directive 2010/63/EU and French regulation (Code Rural art R214-90 and art R214-94), NHP shall be purpose-bred. Cynomolgus macaques will be acquired from AAALAC accredited breeding centres from Mauritius and marmosets will be acquired from AAALAC accredited breeding centres from France. NHP will be purpose bred of first, second or higher generation. All NHP that will be used in ERA4TB program will undergo screening for class I and class II MHC types [Krebs 2005; Blancher 2006]. Randomization for study plans will be performed with respect to the genetic background, group compatibility and body weight. Finally, animals will be screened first for SIV, STLV, SRVD, filovirus, Herpes B, Measles and TB and only those found negative for all pathogens will be included in the study for obvious reasons. A copy of the personal history file for the NHP will be kept on file.

Daily checks of the animals' health status and well-being will be performed. Animal care staff is present 7 days a week, 365 a year. A room book is filled daily and in case of abnormalities, reports are immediately addressed to the veterinarian in charge of the facility. Animals that reach suffering endpoints following infection or for other reasons or manifest untreatable clinical symptoms that may occur associated to treatment or infection will be given a lethal dose of pentobarbital by intravenous route following ketamine anaesthesia to induce humane death of the animal. Humane endpoints will be evaluated by the ethical committee and validated by the Research Ministry (Code Rural

art R214-119). The severity of the experimental procedures will be evaluated and validated by the ethical committee (Code Rural art R214-122). Retrospective assessment will be performed as requested by national regulation (Code Rural art R214-120). None of the procedures that will be used are considered major surgeries and heal rapidly. In case of euthanasia, tissues will be sampled for bio banking and sharing. All metadata and experimental data (raw data and analysed data) from NHP studies will be recorded in a database (BATLab, <http://www.idmitcenter.fr/>) and residual samples will be biobanked to optimize its possible utilization in the future therefore reducing the need for repeating *in vivo* studies.

ERA4TB WP3 partners have proven track records in animal experimentation, all complying with the EU Animal Protection Directive 86/609/EEC. Experimental protocols, species and number of animals used are subject of approval by the local Regulatory and Ethical Committees of the individual partner institutions. In addition, practices in animal experimentation of each partner will be supervised by the ERA4TB Ethics Governance team. Experiments in WP3 by ERA4TB partners will comply with all relevant statutes, legislation, regulations and guidelines for the care, welfare and ethical treatment of animals used in research, applicable in the country where the research is performed.

These main principles include the following points: compliance with the “3R” principles, access to species appropriate food and water, access to species-specific housing, access to humane care and a programme of veterinary care, ability to demonstrate species-specific behaviour, adherence to principles of 3Rs in the design of *in vivo* studies, commitment to minimizing pain and distress during *in vivo* studies, and appropriately trained staff who will perform the work.

The set of experiments performed in WP3 will assess the bioavailability and the anti-TB efficacy of new anti-TB compounds, alone and in combination, in experimental animal models, focusing initially on relevant mouse models and for selected, highly promising compounds, evaluation of anti-TB efficacy in NHP models. The rationale for using NHP models for evaluation of highly advanced anti-TB compounds that are foreseen for the use in humans, is linked to the fact that low dose NHP infection models represent the closest approximation to human naturally acquired infection with *Mtb*, and NHPs are the most relevant species in which human-like PK/PD of drugs and drug combinations can be evaluated. NHP models also offer the advantage over studies in humans that more frequent, longitudinal assessments can be made (using many of the same measures as applied in humans e.g. medical imaging) from the known point of infection, through to a subsequent endpoint.

Mouse models

Partner and Place	IPP,IPL,FZB,SCI,CNR
Design	In vivo efficacy evaluation of new anti-TB compounds will be tested in selected murine models. Here, the example of C3HeB/FeJ mice, which develop caseous necrotic lesions in the lungs, mimicking TB pathogenesis in humans, is shown. The study design for these experiments will be further optimised with the help of partner CNR in close interaction with the Collaborating Partners, as well as with input and guidance from WP5 to ensure appropriate data collection for use in translational modelling.
Study Procedures	Proposed experimental design for one compound and/or combination: Use of 35 mice (6-10 week old), day 1 aerosol infection (low dose ~50-100 cfu) with the selected strain of <i>M. tuberculosis</i> (3 control mice for CFU determination of dose), start of treatment 8 weeks post-infection (8 control mice for CFU determination prior treatment), treatment for 4 weeks, CFU determination 3 days after treatment stop (8 mice per group, a) non-treated, b) INH control, c) compound to be tested). Breeding colonies for C3HeB/FeJ mice are available at partners IPP and FZB.
Animals	C3HeB/FeJ mice
Sample Size (N)	Use of 35 mice (6-10-week-old) for testing 1 compound or drug combination.
Duration	12 weeks

NHP models

Partner and Place	PHE, IDMIT, IPP, CNR
Design	Testing of drug candidates in NHP models will enable evaluation of efficacy against Mtb- induced disease under conditions that correspond to the closest approximation to human naturally acquired infection with Mtb. NHPs are the most relevant species in which human- like PK/PD of drugs and drug combinations can be evaluated and efficacy predicted by mathematical modelling be validated. Advanced strategies for blood sampling and analysis of immunological and PK/PD parameters will be applied to

	<p>evaluate bioavailability and anti- mycobacterial efficacy of advanced-stage drug candidates in the marmoset and macaque models.</p>
<p>Study procedures</p>	<p>12 NHPs (marmosets or cynomolgus macaques) will be used per experiment. Groups of six animals would provide two test groups, which could allow either, assessment of two test compounds if efficacy is determined as a knock down in disease burden between start and end of treatment within an individual, or, a test compound and an untreated control group to enable evaluation of treatment effect by direct comparison with the level of disease that develops in the absence of treatment. Alternatively, compounds could be tested in smaller groups in sequential studies e.g. three in the first assessment then a second group of three added in a second assessment if the treatment looks promising. Similarly, untreated control groups can be included, either as groups of six in single studies, or groups of three and spread across studies.</p> <p>As described in detail in the WP3 description, the NHPs will be infected by controlled exposure to aerosols containing Mtb and monitored for six to eight weeks according the NHP species (six weeks for marmosets and eight weeks for cynomolgus macaques) prior to the start of treatment after which treatment will be initiated and continued for six to eight weeks (six weeks for marmosets and eight weeks for cynomolgus macaques). Animals will be sedated for a clinical examination at two weekly intervals throughout the study period. On each occasion, body weight and core temperature will be measured, a thoracic X-ray taken, and a blood sample for the evaluation of PK will be collected. In addition, a full blood count that includes an assessment of red cell haemoglobin concentration, as an indicator of anaemia, will be performed together with an evaluation of erythrocyte sedimentation rate as a measure of non-specific inflammation. Peripheral blood mononuclear cells (PBMC) and serum will be cryopreserved as a resource for the evaluation of potential biomarkers and the impact of treatment. The mycobacterium-specific Interferon gamma (IFNγ) response will be assessed using assays, such as an ex-vivo IFNγ ELISPOT, which are analogous to those used to diagnose TB in humans, to evaluate the effect of treatment on the immune</p>

	<p>response. Blood samples for PK analysis will be collected for transfer to the site selected to perform the PK analysis.</p> <p>Image collection (in collaboration with WP4) using human medical scanner will be conducted accordingly.</p>
Animals	Marmosets and/or macaques
Sample Size (N)	Use of 12 animals per experiment, up to 2 experiments per year and per site
Duration	16 weeks

4. Clinical trials ethics plan

ERA4TB plans to conduct several Phase-I clinical trials in different sites in accordance with European Union , the respective applicable national laws and the ICH-GCP Guidelines. A description of the clinical trial is presented in the document “Clinical Trials”. The clinical sites involved have experience in performing this type of studies. The description of clinical studies is contained in WP7. WP7 will report to WP9 all ethical information related to the research completed and the research to come. This section summarizes the ethics related actions.

4.1 Recruitment, Informed Consent and data collection procedure

Participants consist of recruited healthy adult volunteers.

Their decision will be taken freely after being duly informed of the nature, significance, implications and risks of the research. All participants will provide full verbal and written informed consent to participate in the studies, which includes the use of personal health information in scientific studies. Information sheet will be approved by the Ethic Committee and investigator will be given a reasonable time to consider the study and to ask any questions they have regarding the study. The written subject information sheet and ICF will be prepared according EU regulation 536/2014, Guideline for good clinical practice (ICH E6(R2)) and other local legislation (if applicable) and will be in a language that the subject can understand.

Prior to signing an informed consent form, participants will be informed of the purpose, duration and possible adverse events of the study in a clear and unambiguous manner and using a language and terms understandable to the participants. Research staff will clearly state to the participants that participation is voluntary, that refusal to participate will involve no penalty and that the participant could discontinue participation at any time without penalty and without having to provide a motivation for the discontinuation.

Only the investigator, a medically qualified sub-investigator or a suitably qualified and trained authorized person may be involved in the informed consent process. The ICF must be signed and dated by the subject before exposure to any study-related procedure, including screening tests for eligibility. The subject will receive copies of the written subject information sheet. If new safety information becomes available and results in significant changes in the risk to benefit assessment, the written subject information sheet will be revised or updated where necessary. Under these circumstances, all subjects (including those already being treated) should be informed of the new

information, given a copy of the revised form and allowed to re-evaluate their consent to continue in the study. According to EU General Data Protection Regulation (GDPR), Data subjects shall have the right to object at any time to the processing of their personal data in various situations unless one of the exceptions in the GDPR applies. For clinical trials, the GDPR provides (article 17) that subjects have the right to object to the processing of their personal data on grounds relating to their particular situation, unless the processing is necessary for performing a task carried out in the public interest or another limitation set forth in member state legislation applies,

Data and Safety Monitoring Board (DSMB)

During each trial, this committee will periodically review and evaluate the accumulated study data for participant safety, study conduct and trial progress. They will also review each protocol for any major concern prior to implementation. As part of their responsibilities, they will verify that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study participants. This committee will be composed by expert in FTIH trials, biostatisticians, clinical pharmacologist and methodologies investigators with expertise in methodology and clinical trials.

4.2 Regulatory in each country with CTU

Investigational Medicinal Product dossier (IMPD), Investigator Brochure (IB), Informed Consent Forms (ICF), protocol and, protocol amendments of each First Time in Human (FTIH) protocol will be evaluated and approved by **local IRB and National Regulatory Authorities** before the study is initiated.

Any amendments to the protocol will require Institutional Review Board/Independent Ethics Committees (IRB/IEC) and National Regulatory Authorities approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Country	Regulatory Agency	Institutional Review Boards (IRB)
Spain	AEMPS(Agencia Española de Medicamentos y Productos Sanitarios)	Ethics Committee of La Paz University Hospital

The Netherlands	CCMO (Central Committee on Research Involving Human Subjects)	Stichting BEBO
Germany	BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte)	Ethics Committee of University of Cologne

Table 1. Local IRB and National Regulatory Authorities (FTIH)

For each molecule entering Phase I, WP7 will conduct a FTIH trials in healthy adult volunteers. The study will evaluate the safety, tolerability and pharmacokinetics (PK) of single ascending (Part A) and multiple oral doses of compounds as monotherapy (Part B). Final design and sampling schedule for PK analysis and safety monitoring will be defined for each molecule depending on their characteristics and previous information.

Blood samples for plasma PK analysis and urine samples will be collected at different time points (depending on the characteristics of each molecule). The PK parameters (clearance, half-life, volume of distribution, systemic exposure (Area Under the Curve, AUC), peak concentration and steady-state concentrations after repeated dosing) will be determined and any indication of adverse effects assessed with special focus on cardiovascular and hepatotoxicity according to European Medicines Agency (EMA) Guidelines. Moreover, an attempt will be made to establish the pro-arrhythmic potential of the compounds by assessing the correlation between drug levels and QT interval prolongation (ICH E14).

Demographic and clinical information will be collected. Physical examination, Haematology, Biochemistry, 12-lead ECG/Holter, Urinalysis, Microbiology, drug screen and pregnancy test (if applicable) will be performed in each healthy adult volunteer.

All information will be recorded pseudonymised in an electronic Case Report Form (eCRF) designed for each FTIH trial.

4.3 Monitoring

An independent CRO or academic institution will be subcontracted in order to assure the quality of the clinical trial data, according to EU legislation. The CRO or academic institution will develop the “Study Monitoring Plan” in collaboration with WP7 and sponsor.

The purpose of monitoring visits is to ensure that Informed consent forms and CRFs are completed correctly, the protocol is adhered to, perform source data verification (some of the documents due to their origin could be in paper but will try to have them included in the eCRF), monitor drug accountability, collect completed CRF pages and ensure data queries are identified and resolved. Queries will be also managed by the data management team of the CRO. In addition, the monitor must ensure that the Trial Master File is up to date for the status of the study and all essential documents collected. As a minimum requirement the following data must be source data verifiable in source documentation other than the CRF:

- Existence of patient
- Confirmation of participation in the trial (patient ID, trial ID, and signed and dated informed consent form)
- Inclusion/Exclusion criteria compliance
- Visit dates
- Data from:
 - AE form
 - Safety information form
 - PK sample tracking
 - Relevant concomitant medication and relevant medical history and/or concomitant illness
 - Reason for exclusion or withdrawal

For all other data in the CRFs, it must be possible to verify these against source documents. For all data recorded, the source document must be defined in a source document agreement at each site. Sample management and tracking/storage logs must be available to demonstrate chain of custody and storage. Shipment logs must be monitored if samples/data are transferred to external vendors. Dispensing and drug storage logs must be monitored, and destruction certificates obtained at study end if necessary.

The investigator and study staff will be responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from sponsor and/or applicable regulatory authorities. Elements should include all essential documents as listed in ICH GCP: Subject files containing completed CRF, informed consent forms, and subject identification list. For each FTIH trial a copy of the Ecrf (WHERE APPLICABLE), this will be provided to sites after database lock as part of the archivable process. At the end of the study, the monitor must complete study close out activities and ensure that all study

documentation is archived in an appropriate file for 25 years after study completion. This would be formally documented within study documentation.

4.4 Adverse events reporting

The investigator and their designees will be responsible for detecting, documenting and reporting events that meet the definition of an Adverse Events (AE) and Serious Adverse Events (SAEs).

AEs and SAEs will be collected from the start of informed consent until the follow-up contact. All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, according EU legislation.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

Appropriate questions will include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

After the initial AE/SAE report, the investigator will be required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (AESI) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

Pregnancy

Women during pregnancy and lactation must not be included in the studies. Female patients capable of bearing children should inform their sexual partner of their participation in the clinical study and use highly effective methods of birth control such as abstinence, sterilization, birth control pills...during treatment and for an additional period that will be defined after the end of treatment.

The protocols will take into account the CLinical Trial Facilitation Group document:

Recommendations related to contraception and pregnancy testing in clinical trials:

https://www.hma.eu/fileadmin/dateien/Human_Medicines/0-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Male patients should inform their sexual partner of their participation in the clinical study and use highly effective methods of birth control such as abstinence, vasectomy, or condom in combination with hormonal birth control or barrier methods used by women during treatment and for an additional period defined on each trial after the end of treatment.

If a subject becomes pregnant or fathers a child during the study, the investigator should report to the sponsor and use the provided pregnancy notification form. The sponsor will inform the BfArM and provide respective initial and follow-up information in cooperation with the investigator.

4.5 Management of biological samples

Ethical Issues	Research Objectives	Research Methodology
Blood and Urine Samples obtained within this project for PK and pharmacogenetic analysis.	Collecting human samples will be decided according to study characteristics and considering legal requirements and guidelines.	Samples will be collected in each healthy adult volunteer at different time points (depending on the characteristics of each molecule). Samples will be stored in each clinical centre developing FTIH trial and shipped to a Central Laboratory for PK analysis. Back-up sample will be stored in each centre, if it is necessary a re-analysis, or for future analysis.

Blood samples for plasma PK analysis of each molecule will be collected at the time points that will be defined in each FTIH (depending of the characteristics of each molecule). The actual date and time of each blood sample collection will be recorded. Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures will be provided in the “Laboratory Manual” (LM).

Urine samples for PK analysis will be collected from each subject prior to dosing and over the details of urine sample collection, processing, storage and shipping procedures will be provided in the LM.

Blood samples for pharmacogenetic analysis will be collected into K3 EDTA tubes and DNA will be extracted in

each healthy adult volunteer. Potential SNPs and other enzymes or transporter mutation involved in disposition and safety of each molecule will be determined.

Ethical Issues	Research Objectives	Research Methodology
Blood and Urine Samples Obtained within this project for safety assessments.	Collecting human samples will be developed in the screening and follow-up visit for safety analysis.	Samples will be collected in each healthy adult volunteer in the screening and follow-up visit. Samples will be shipped to a Local or Central Laboratory for their analysis. Samples will be destroyed after the analysis.

Blood samples for safety assessment will be collected in the screening visit to and haematology, biochemistry and microbiology analysis will be performed.

Urine samples for safety assessment will be collected to perform a urinalysis in the screening and follow-up visit, and urine drug determination in the screening visit.

Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle. The investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate). The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival. Monitoring of study sites, auditing or process checks and contractual requirements of external laboratory providers.

If samples retained for further use will be stored in each clinical centre according to their capabilities (Clinical Trial Unit, Biobank or Central Laboratory).

Biological materials and associated personal data should only be transferred to another state if that state ensures an adequate level of protection.

Withdrawal of Informed Consent for donated biological samples

Research on biological materials should only be undertaken if it is within the scope of the consent given by the person concerned.

When a person has provided consent to storage of identifiable biological materials for research purposes, the person should retain the right to withdraw or alter the scope of that consent. The withdrawal or alteration of consent should not lead to any form of discrimination against the person concerned.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed and the action documented. If samples are already analysed, is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The organization(s) holding the samples will be informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented.

Management of Incidental and Secondary Findings

Analysis of biological specimens such as blood or urine, and ECG or Holter study can be a source of incidental or secondary findings and could require a series of additional diagnostic tests to determine the health implications, if any, of the result.

Investigators will communicate healthy volunteers the possibility of discovering incidental or secondary findings, and this information will be included in the informed consent process, and there should be a specific plan for their disclosure or management. They can also ascertain at the outset what participants prefer to know—and not know—about incidental or secondary findings. However, if the volunteer had indicated his refusal to know about incidental or secondary findings, but according to the criteria of the responsible physician, is necessary to avoid serious damage to his health, a familiar or a representative will be informed, after consulting the Ethics Committee of the centre. The communication of this information will be carried out by professionals who can adequately explain its relevance and the options that may arise.

4.6 Personal Data

The studies to be performed in ERA4TB require the collection of personal data of participants, including sensitive data (e.g. *health, ethnicity*), and personal details. These data will be recorded in the participants' source documents that will be filed and kept at the research site. It is the responsibility of the investigator to maintain the source documents. The investigator has to permit trial related monitoring, audits, Independent Ethics Committee/Institutional Review Board review and regulatory inspections providing authorized persons direct access to source documents.

All participants enrolled onto the trial during the first study visit will be identified by a study generated participant identification code for anonymity (participant number). All site staff, the sponsor, and any sponsor representatives will preserve the confidentiality, and all personally identifiable information (PII) of all participants taking part in the studies, in accordance with EU and applicable local legislation or regulations. Only participant study number and initials will be used on the case report form (CRF) and in all study correspondence, as permitted. For countries such as Germany, Austria, Norway, Finland, Holland, Hungary etc that restrict the data capture of initials. These should not be part of eCRF (assuming EDC being used) or entered into the clinical Data Management System (CDMS), details are only permissible on lab reports or other source related documents at site.

No material bearing a participant's name will be kept on file by the sponsor. The written informed consent document will contain a clause granting permission for review of the participant's source data. Human data from the studies must only be used for purposes that are consistent with the consent obtained and in compliance with relevant laws and regulations.

The personal data and its handling are part of the protocol authorization and when needed will require a revision and specific authorization by the national data protection authority. Subjects of the studies will be informed on the data that will be obtained and its use and will be presented a notification/authorization for processing of sensitive data (included in the informed consent forms, see annexes).

The data obtained will be processed according to national and EU regulations on data protection. When transferred for data processing, this data will be encrypted, and the data will be Pseudoanonymized by the data provider prior to transfer. Keys to identification numbers will be held confidentially by the sponsor and will not be transferred to the organizations performing the curation and integration into the ERA4TB centralized Drug Development

Information Management system (DDIM). Prior to the data being processed within the DDIM platform, it is expected that all monitoring and data management activities (in accordance to CRO SOPs and study Data Management Plan) have been successfully completed and declared as clean. In addition, as data may be transferred between EU and non-EU countries, ERA4TB will include in its Consortium Agreement a data transfer section that ensures compliance with national data protection policies and or regulation(of the sending and receiving States). Only Pseudoanonymized data will be exchanged.

Regarding the processing of personal data, the protection of privacy in electronic communications, as well as the retention of data generated or processed in connection with the provision of publicly available electronic communications services/networks (e.g. cloud, big data, open data, cookies etc.), ERA4TB consortium will comply in its handling of Electronic data, with National applicable legislation and EU Directives 2002/58/EC and 2006/24/EC⁹ and updates if any during the negotiation and implementation of the project, will seek alignment with Pillar A of the IMI2-AMR Accelerator for homogeneous ethics management throughout all the AMR Accelerator Projects.

No personal data collected as part of the ERA4TB project will be used for commercial purposes. However, the therapies, tools and knowledge derived from the research using the personal data may be brought forward to such use as appropriate, and this process will be regulated by the Grant Agreement and the Consortium Agreement, in accordance with any applicable governing legislation and regulations.

The project has a dedicated Ethics and Data Privacy work package (WP9). It is the project intention to make the anonymised results of any clinical trials available as will be described in the relevant Data management section of this proposal, the Data management plan and in the Consortium Agreement. The project will appoint a project Data Protection Officer and will identify the DPO in each institution.

Quality of data collected across the project will be ensured through

- ERA4TB Data Integrity Policies aligned with International Conference on Harmonisation (ICH) Good Clinical Practices GCP R2 regulatory guidance, ensuring Food and Drug Administration FDA (attributable, legible, contemporaneous, original and accurate-ALCOA) and European Medicines Agency EMA (complete, consistent, enduring and available- CCEA) principles on electronic source data in clinical investigations.
- The expertise and track record of participating centres and clinicians collecting the data

- Accuracy of laboratory tests will be guaranteed by centralizing analyses wherever possible in specialized laboratories and using SOPs of validated tests.
- The expertise and track record of participating organizations that will be receiving, curating and integrating data from each of the participating centres into the centralized Drug Development Information Management system (DDIM)
- The implementation of data standards and templates for the collection, transport and storage of data in the DDIM
- Standard Operating Procedures that clearly outline consortium-wide practices and role-specific responsibilities for the collection, transport and storage of data
- Data curation processes and quality control measures to identify potential data quality issues, such as: missing or invalid values, incorrect terminology or units of measure, gaps or other inconsistencies.
- Automated, repeatable processes for the transport, transformation and integration of data into the DDIM
ERA4TB participants will comply with the eight enforceable principles of good practice for personal data management. They will thus make sure that personal data is:
 - Fairly and lawfully processed
 - Processed for limited purposes
 - Adequate, relevant and not excessive
 - Accurate
 - Not kept longer than necessary
 - Processed in accordance with the data subject's rights
 - Secure
 - Not transferred to countries without adequate protection

Study subject confidentiality and welfare will always be maintained as the highest priority. In particular, study participants will be informed of:

- The categories of data concerned and the recipients or categories of recipients to whom the data are disclosed
- How their data will be used and by whom, including information on pharmaceutical entities involved.
- Their total right of access, modification, correction or even suppression to personal information concerning them

- The name and contact information of the DPO to be contacted to exert this right

Collection and/or processing of sensitive personal data

Ethical Issues	Research Objectives	Research Methodology	Potential Impact of the Research
Collection and/or processing of sensitive personal data	Personal and clinical data will be recorded and processed following an Pseudoanonymization process.	The recording data procedure will be developed under the principles of confidentiality and privacy protection	The treatment of information will consider the special ethical issues.

After completion of the project, research material used in this research proposal will be archived, to enable future use of research data. This research data archive is only intended to allow for checks on published data or future follow-up research. If limits to retention of data differ depending on the rule to apply (e.g. between EU and National legislation), the Consortium will request EC/IMI support. Duration of retention will be included in the ICs, as well as means to opt out and request removal of the data from the database. The “right to be forgotten “ requests should first be directed to the data owner with a corrected data transfer delivered for curation and upload into DDIM/Data Archive.

4.7 Processing of genetic Information

Ethical Issues	Research Objectives	Research Methodology	Potential Impact of the Research
Collection and processing of genetic information	Collecting pharmacogenomic data will be decided according to drug characteristics and taking into account regulatory guidelines.	Blood samples will be collected, and DNA extracted in each healthy adult volunteer.	Genetic assessment of SNPs and other enzymes or transporter mutation involved in disposition and safety of each molecule.

Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion; mechanism of action of the drug. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants. We will store the DNA samples in a

secure storage space with adequate measures to protect confidentiality. No genetic resources will be transferred across borders.

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main studies.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers. For example, in the case of a medical emergency, an investigator might know a subject's identity and have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, although the subject's medical information and the genetic files would remain physically separate. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the clinical study report itself or as an addendum, or separately in a scientific report or publication.

4.8 Third Countries

ERA4TB is a consortium integrated by EU and non-EU Partners, and is part of a broader platform, the AMR Accelerator that aims to integrate information from different consortiums. The Consortium Agreement will provide a legal frame and will set the rules to abide under EU legislation. Regarding the transfer to/from third countries, studies will comply with the specific provisions on import/export under Directive 2004/23/EC¹¹, including the rules on data transfer to third countries. No Material transfer of any type is planned from EU to non-EU or vice versa in the project plan. The potential ethics issues focus on the provision of clinical data from previously performed clinical trials. The project will ensure that permission for use of the data from another project was obtained in through proper Informed Consent, and that data is anonymized (EU standards or above) before entering the ERA4TB Data platform and the keys to identification will not be known or held by any consortium member. Furthermore, data from previously performed clinical trials will only be accessible in aggregate to further reduce the risk of identification of any individual patient in any individual trial.

Furthermore, ERA4TB will seek alignment with COMBINE - Pillar A, as overall support of the AMR Accelerator, to ensure GDPR fulfilment, and seeking to implement best practices in Data Integrity, validation, access controls, allowable sites for posting data, protecting individual patient information (including SOPs on individual human data) and overall consortium data security measures. IMI and the EU are presently financing several initiatives in this

area, and ERA4TB will seek to implement advances in this area. Common procedures which will be included in the data transfer agreements between Pillars in the AMR Accelerator will be set, to ensure a lawful basis for data processing from previously collected data and safeguard the rights of the data subjects, through data Pseudoanonymisation. On this, a 2-stage general procedure will be established for incoming data, by 1st, gathering information from the data provider kinds of data, character (personal, or not) and their provenance, and 2nd obtaining explicit confirmation from the data provider that the relevant approvals, authorisations and consents for secondary use are available and can be provided if requested.

5. Legal Framework and Guidelines

Compliance with International, EU and National Legislation

ERA4TB partners guarantee free and informed consent of candidate human volunteers and protection of personal data and bio-samples. Research involving animals will be made in strict compliance with the 3Rs rule as animal welfare will be one of the partner's priorities. The coordinator and project Management Team will ensure that all activities of each Beneficiary in the ERA4TB consortium comply with ethical International and EU Conventions, Declarations and guidelines, as well as with their respective domestic laws. If during the life of the project new guidelines or regulations appear, the protocols developed will be adapted accordingly. The coordinator and project Management Team will ensure that all activities of each Beneficiary in the ERA4TB consortium are in full agreement with the national and international regulations.

A revision on applicable legislation, taking into account EU and national legislation, Good Practices GxPs by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), as well as Standard Operation Policies (SOP) by the Asset Owners (such as Investigator Sponsored studies (ISS) and Supportive collaborative studies (SCS) with Academia or other Institutions Including Consortia SOPs), will be performed before planning the studies, with the outcome of this revision being included in the Study Documents and Reports to the Steering Committee (and IMI). In case of doubt the strictest rule will be applied. The Consortium Agreement will include provisions (additional resources on country compliance experts, external legal advice, etc.) for solving possible regulatory conflicts.

International conventions and declarations

ERA4TB members will comply with the latest amended version of the following international conventions and declarations:

- World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.
- Convention of the Council of Europe on Human Rights and Biomedicine signed (Oviedo 1997) and the Additional Protocol on the Prohibition of Cloning Human Beings (Paris 1998)

- International Ethical Guidelines for Biomedical Research Involving Human Subjects - Council for International Organizations of Medical Sciences (Geneva: CIOMS, 2002)
- The Universal Declaration on the Human Genome and the Rights of Man (UNESCO 1997)
- The Declaration on Human Genetic Data (UNESCO 2003)
- The Universal Declaration on Bioethics and Human Rights (UNESCO 2005).
- UN Convention on the Rights of the Child
- OECD Guidance on the recognition, assessment, and use of clinical signs as humane endpoints for experimental animals used in safety evaluation (ENV/JM/MONO(2000)7)

The ERA4TB participants will comply with the **European Legal Framework** and will apply its ethical standards and guidelines:

EU legislation

ERA4TB partners will conform to the last amended versions of the following EU legislation:

- The Charter of Fundamental Rights of the European Union
- Directive 95/46/EC of 24 October 1995 on the protection of individuals with regards to processing of personal data and the movement of such data
- Directive 2001/20/EC of the European Parliament and of the Council of 4 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.
- Directive 2004/33/EC as regards information to be provided to prospective donors, information required from donors, eligibility of donors; storage, transport and distribution conditions for blood and blood components; quality and safety requirements for blood and blood components.
- Directive 86/609/EEC of 24 Nov. 1986 on the protection of animals used for experimental and other scientific purposes
- Protocol on Protection and welfare of animals (protocol to the Amsterdam Treaty)
- Recommendation of 18 June 2007 on guidelines for the accommodation and care of animals used for experimental and other scientific purposes (2007/526/EC)
- Directive 2004/23/EC of 31 March 2004 on Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

- Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components.
- Directive 2005/28/EC on Good Clinical Practice
- **EU legislations for use of pathogens**
 - EC Directive (93/88/EEC) on Biological Agents
 - Directive 2000/54/EC regulating the protection of workers exposed to pathogens at work
- **EU legislations on Data Protection**
 - EU General *Data Protection Regulation* (GDPR Regulation (EU) 2016/679 12) on data protection.
 - Handling of Electronic data, and EU Directives 2002/58/EC and 2006/24/EC13
- **EU legislations on Third Countries**
 - Directive 2004/23/EC14, including the rules on data transfer to third countries.
- **EU legislations for research on animals**
 - Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes.
 - Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work.
 - Directive EC (92/65/CEE) and derived regulations and national laws for the transport of animals (including transgenic animals) within the European Union.
 - The “3 Rs” policy of Refinement, Reduction and Replacement towards the use of animals for scientific procedures (99/167/EC: Council Decision of 25/01/99).
 - Protocol on Protection and welfare of animals (Protocol to the Amsterdam Treaty, 2/10/1997).
 - The 2000 Report of the AVMA panel on euthanasia; Ethical standards as specified in “Ethics for researchers” and other supporting documents.
 - The Recommendations for euthanasia of experimental animals: Part 2-Working Party Report (Laboratory Animals (1997) 31, 1-32).
 - CoE: European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (2005).

Also, **National Legal and Ethical** requirements will apply:

- **Belgium:** Animal Welfare Act (7 USC 2131) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.
- **France:** Articles R214-87 à R214-137 of French rural code
- **Germany:** German legislation (German Animal Protection Act / "Tierschutz-Gesetz").
- **UK -** Animals Scientific Procedures Act, 1986 (an Act of the Parliament of the United Kingdom 1986 c. 14) (Home Office Project licence Number 70/5933)

EU Legislation on Clinical Trials

The ERA4TB participants will comply with the **European Legal Framework** and will apply its ethical standards and guidelines:

- Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
- Directive 2001/20/EC of the European Parliament and of the Council of 4 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 (the "Clinical Trial Directive").
- Regulation (EU) 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)
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (the "Community Code for medicinal products").
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (the "GMP Directive").
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (the "GCP Directive")

- Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council.).
- Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections EudraLex - Volume 10
- Requirements relating to the quality, safety and efficacy of products, as well as specific types of products. See EudraLex - Volume 3
- Inspection procedures and guidance for GCP inspections conducted in the context of the Centralised Procedure
- Guidelines on clinical trials of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- Council for International Organizations of Medical Science (CIOMS)
- World Medical Association (WMA) Declaration of Helsinki – Ethical Principles For Medical Research Involving Human Subjects (64th WMA General Assembly, Fortaleza, Brazil, October 2013).
- International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO)
- The Guidelines on FAIR Data Management in Horizon 2020
- Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation laid down by law, regulation, or administrative action relating to proprietary medicinal products.
- UNESCO International Declaration on Human Genetic Data, 16 October 2003.
- Recommendation Rec (2006)4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin
- Guide of the Organization for Economic Cooperation and Development (OECD) for biobanks and databases of genetic research in humans, 2007

National Legal and Ethical requirements that apply:

Spain:

- Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry
- Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain
- Memorandum on Collaboration and Exchange of Information between the Spanish Agency of Medicinal Products and Medical Devices and Ethics Committees for investigation with medicinal products
- Royal Decree 1/2015, of July 24, approving the revised text of the Law on guarantees and rational use of medicines and health products.
- The General Health Act (Law 14/1986 of 25 April).
- Law 41/2002 governing patient autonomy and the rights and obligations concerning clinical information and documentation.
- Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights
- Law 14/2007, of July 3, on biomedical research.
- Royal Decree 1716/2011, of November 18, which establishes the basic requirements for authorization and operation of biobanks for the purpose of biomedical research and the treatment of biological samples of human origin and regulates the operation and organization of the National Registry of Biobanks for biomedical research.
- Royal Decree 65/2006, of January 30, which establishes requirements for the import and export of biological samples

France: Jardé law N°2002-300 related to research involving human (March 5, 2012)

The Netherlands:

- WMO (BWBR0009408) Act of February 26, 1998, regulations concerning medical-scientific research with human individuals (Act medical-scientific research with human individuals)

Germany:

- Medicinal Products Act (Arzneimittelgesetz), 12 December 2005 (Federal Law Gazette [BGBl.] Part I p. 3394, last amended by Article 3 of the Law of 4 April 2016 (Federal Law Gazette I p. 569)

- GCP ordinance (GCP-V), of 9 August 2004

First Time in Human (FTIH) trials will be developed according current and future EU and ICH guidelines and regulations, in particular:

- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07 Rev. 1)
- EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. In particular, Annex 13: Manufacture of Investigational Medicinal Products.
- Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMA/CHMP/BWP/398498/2005-corr.).
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008).
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015).
- Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (ICH M3(R2)) and related Q&A document.
- Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (ICH M7).
- Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A) and related Q&A document.
- Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes.
- Pharmacokinetics: Guidance for repeated dose tissue distribution studies (ICH S3B). Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6(R1)).
- Safety pharmacology studies for human pharmaceuticals (ICH S7A).
- Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (ICH S7B).
- Questions and Answers concerning the implementation of Directives 2004/9/EC and 2004/10/EC on Good Laboratory Practice (GLP).
- EudraLex - Volume 10 - Clinical trials guidelines.

- Guideline for good clinical practice (ICH E6(R2)).
- Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH E14) and related Q&A document.
- Guideline on good pharmacogenomic practice (EMA/CHMP/718998/2016)