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PROJECT FINAL REPORT

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4.1 Final publishable summary report

4.1.1 Executive summary

The ESFRI Roadmap of 2008 identified a critical need for an adequate and coordinated European BSL-4 capacity to enable the European Union to address the challenges posed by the emergence or re-emergence of highly pathogenic agents. While seven BSL-4 laboratories are operational in Europe (United Kingdom, Sweden, France, Germany, Italy and Hungary), the current European BSL-4 capacities still lack coordination, coherent and efficient biological resources management as well as training capacities.

ERINHA, the "European Research Infrastructure on Highly Pathogenic Agents" worked to address this need. It aimed to reinforce the European capacities for the diagnosis and the study of Risk Group 4 pathogens, enhance the coordination of BSL-4 activities and give access to BSL-4 facilities to all interested European scientists by establishing ERINHA as a pan-European distributed research infrastructure during the 46-month project period – the Preparatory Phase. ERINHA sought to reach a level of legal, financial and organisational maturity required to continue to construction and operational phases following the project.

The ERINHA Preparatory phase has represented the first step in paving the way towards this final result through the work conducted during this first phase. Significant progress on the legal aspects of the RI has been made: a governance structure has been drafted and an initial legal status for the next phase has been put forward. As it was not possible to formally agree on these aspects during the project, this will be a priority in the interim phase. An inventory of existing BSL-4 laboratories and facilities as well as a list of potential sites for building a new BSL-4 laboratory has been conducted. Contact with funding agencies has been made and lobbying among Member States' representatives is ongoing. Financial and business plans have been developed to provide potential funders with information. Procedures, models and tools for the definition of user requirements for BSL-4 facilities have been developed. An evidence base on BSL-4 facilities highlighting best practices but also knowledge gaps in BSL-4 containment evidence base such as disinfectant validation has also been established. Work has been conducted on harmonizing the main biosafety and personnel selection procedures and training programme and a consensus among the consortium was reached on these issues. In addition, guidelines for the handling and shipping of (potential) high-risk infectious material from BSL4 laboratories have been prepared. An ERINHA research strategy has been established and an analysis of the interest among researchers in conducting research at the BSL3/4 divide and at the BSL-4 level was performed. This enabled the consortium to put forward recommendations for achieving a truly open access infrastructure. Finally, the feasibility of the ERINHA coordination structure was tested through pilot research and diagnostic activities, which gave rise to recommendations which will be adopted in the future phases of the RI.

As ERINHA has not yet obtained official agreement from the Member States and financial commitment, it has been decided that an interim phase (1 September 2014 – 31 December 2015). This will enable the RI to reach the legal maturity level required to move forward to the construction phase (1 January 2016 to 31 December 2016). Should sufficient funding be obtained, it is expected that the operational phase will begin from 1 January 2017. Through its implementation, the ERINHA RI will contribute to the attractiveness of the European Research Area (ERA), to stimulating research and scientific advancement. It will boost European competitiveness, bringing Europe to the forefront of BSL-4 research activities. Faced with major outbreaks of highly pathogenic infectious

diseases, ERINHA RI will ensure that Europe as a whole is capable of offering the best expertise, procedures and facilities.

4.1.2 Summary description of project context and objectives

In the context of the emergence and re-emergence of infectious diseases involving highly pathogenic microorganisms, there is a crucial need for Europe to be well prepared to face any pandemic threat. It is thus necessary for European countries to have sufficient BSL4 laboratories at their disposal to fully manage diagnosis and development of prophylactic and therapeutics means against these types of pathogens.

In this context, the ERINHA project therefore aimed to create a top world-class research infrastructure that will address the BSL4 capacity sparseness in Europe and offer a word-level service in response to needs of users from the research community. As ERINHA will be a civil purpose infrastructure, all BSL4 facilities under military governance will be excluded. All European and International scientists that need access to a BSL4 structure and to BSL4 classified biological resources will have open access to ERINHA provided that they meet ethics, biosecurity and biosafety requirements specifically set up in ERINHA. The ERINHA infrastructure will operate as one coordination entity that will centralise all access and training request at the European or international level, and dispatch the request on the relevant BSL4 laboratory, depending on the pool of BSL4 capacities and expertise. In this organisation, each BSL4 laboratory keeps its own autonomy regarding the orientation of its activities. The efficient exploitation of the ERINHA infrastructure together with the increase of BSL4 capacities, will allow growth of the activities in the field of highly pathogenic agents in Europe. The infrastructure will give rise to: (i) strong development of therapeutics means and diagnosis tools, (ii) harmonised biosafety and biosecurity procedures, (iii) efficient management of biological resources, (iv) substantial training capacities, and (v) establishing global coordination capacities. These are all crucial activities to efficiently fight highly pathogenic agents. In line with the Lisbon strategy of establishing Europe as the world's most competitive knowledge based economy, the ERINHA infrastructure aims at improving European competitiveness in the field of infectious diseases involving L4 pathogens, and in particular compared to the United States where an important capacity in terms of BSL4 facilities exists. Strengthening European BSL4 capacities and the establishment of a pan-European coordination, through the implementation of the ERINHA infrastructure, will significantly increase the scientific excellence and efficacy of European research in the field of infectious diseases.

To achieve its ambitious objectives, the ERINHA project planned to conduct five main actions: (i) increasing or upgrading the existing BSL4 capacities, (ii) Building new BSL4 laboratories in EU countries where no BSL4 facilities exist, (iii) Building support infrastructures mainly dedicated to host scientific visitors and staff, (iv) Organising the users access to the infrastructure, (v) developing a European BSL4-coordination body for optimal collaborations and exchange. To ensure an optimal and secure sharing of information within the consortium, an e-infrastructure, with different levels of security, will be created.
The ERINHA infrastructure started with a preparatory phase of 46 months – the ERINHA project, of which main purpose was to implement the infrastructure to the level of legal, financial and organisational maturity required for future construction and operational phases.

The operational steps the consortium set out to achieve during the preparatory phase are as follows:

1. Identifying and evaluating relevant sites in Europe for new BSL4 construction or major upgrades;

2. Acquiring political and financial commitments from National, European or International concerned entities to support construction;
3. Establishing a secured and validated financial plan for the construction phase taking into account the operational phase. The establishment of financial plans will rely on (i) the estimation of construction costs from design studies and (ii) the identification of sustainable funding and financing solutions for construction and operation phases;
4. Defining and implementing an appropriate governance and legal framework following EC recommendations and partners' requirements, to allow the infrastructure to act as a legal entity;
5. Harmonizing, standardizing and disseminating SOPs related to L4 biological resources management, biosafety and biosecurity issues;
6. Defining and implementing standardized training programs for operating in BSL4 facilities.
7. Identifying ERINHA users and organizing user access rules, ensuring that the infrastructure is most efficiently exploited by the European scientific community;
8. Defining the organisation between academic and industry activities within ERINHA;
9. Assessment of the whole ERINHA organisation by performing research and diagnosis pilot projects.

To achieve these nine objectives, the project consortium gathered relevant and complementary expertise of key partners and associated partners from 14 countries across Europe, including research institutions and national ministries as well as key personnel/organisations from other relevant European Research Infrastructures.

The project was organized into 7 WPs, each with specific objectives as described below: WP1 was dedicated to the management of the consortium.

WP1: Management of the project

This WP consisted of managing the consortium activities. It involved contractual follow-up of the consortium and grant agreements and the overall legal, financial and administrative management of the consortium. It also included coordinating and completing project reporting.

WP2: Strategy and commitments (Leader: INSERM, France)

The ultimate goal of the ERINHA preparatory phase was to establish the European entity. The aim of WP2 was focused on establishing the European infrastructure with the support of the Member States. The objectives of the WP2 were:

- to reach agreements of principle from representatives of relevant ministries and funding agencies of the Member States on the concept of ERINHA operating as one European integrated structure;
- to reach an agreement between the Member States on the financial support and the construction sites;
- to obtain financial commitments for construction of ERINHA.

WP3: Governing structure and legal status

This WP sought to define and implement a governing structure for its efficient operation of the ERINHA infrastructure and its strategic development in coordination with other EU BMS research infrastructure such as BBMRI, OPENSCREEN, INSTRUCT, ELIXIR and others. The WP3 also aimed to define and implement a legal framework enabling the ERINHA infrastructure to act and manage contracts as one legal entity. As the infrastructure will participate in public-private partnership projects, the management of intellectual property rights was considered in both the legal status and the governance structure.

WP4: Technical work: Design considerations and estimating construction costs for new BSL4 areas (Leader: DH, UK)

Based on the stakeholders commitments obtained in WP2, WP4 aimed atdrafting engineering plans for the construction of the new BSL4 areas (additional BSL4 areas on existing sites and new BSL4 structures) on the most relevant sites identified in WP2. WP4 also aimed to provide cost estimations for these new infrastructures.

WP5: Definition, harmonisation, standardisation and dissemination of best practices in the management of biosafety and biosecurity issues in BSL4 laboratories and for associated biological resources centres

This WP set out to define, harmonize and standardize SOPs in the management of mutualised and shared biological resources centres related to L4 agents, as well as in biosafety and biosecurity issues. It also examined ways to efficiently disseminate and ensure implementation of harmonised and standardised good practices among users. In addition, WP5 aimed to develop standard training programmes.

WP6: Access to BSL4 infrastructure for academic research, industrial research, and diagnosis activities (Co-Leaders: RKI, Germany/DH, UK)

This WP‘s objective was to organize the user access to the ERINHA infrastructure and define the organisation of BSL4 access for partners and external users, by elaborating access rules based on an evaluation of the partners’ and external users' needs. Drafts of agreement related to access rules between countries will be elaborated. This WP has also defined the research strategy for ERINHA, both internal and external, and how academic and industrial research and diagnostic development activities should be facilitated and organised within the BSL4 laboratory infrastructure.

WP7: Research and diagnosis pilot activities

This WP focused on validating the operability of the ERINHA infrastructure through pilot RTD activities on research and diagnosis that will form proof of concept. It will allow testing of the overall organisation of the ERINHA infrastructure and prove it to be efficient and sufficiently mature at the end of the preparatory phase.

4.1.3 A description of the main S&T results/foregrounds

The main results for each WP and individual tasks are described in this section.

WP1 Management of the project

The main objective of WP1 was to set up an effective management framework for the ERINHA project consortium.
It aimed to ensure the progress of the project towards its planned objectives e.g. to make sure the deliverables were released in due time, the milestones reached, all budgetary actions performed correctly within EC rules, and to coordinate the different workpackage activities. It ensured contractual and legal management within the consortium.

The ERINHA management WP involved the contractual administrative tasks (financial, reporting, organization of consortium meetings, management of Intellectual Property, etc.). The project management team was also very much involved in overseeing the results emanating from all WPs and ensured the work was conducted according to the DoW. The management team acted as the interface between the partners and the European Commission and was in regular contact with EC Scientific Officer, relaying problems and questions as soon as they occurred. The team was

involved in the organization of main project meetings (General Meetings, Executive Board), promotional materials (leaflet, poster, newsletter, etc.), and the maintenance of the project's website.

WP2 Strategy and national commitments

The ultimate goal of the ERINHA preparatory phase was to establish the European entity. WP2 focused on establishing the European infrastructure with the support of the Member States.
The objectives of the WP2 were:
- to reach agreements of principle from representatives of relevant ministries and funding agencies of the Member States on the concept of ERINHA operating as one European integrated structure;
- to reach an agreement between the Member States on the financial support and the construction sites;
- to obtain financial commitments for construction of ERINHA.

WP2 was organised into **8 tasks**:

Task 2.1 Making contacts and obtaining and agreement in principle from the relevant ministries and agencies of the Member States.

Task 2.2 Listing of the existing BSL4 facilities

Task 2.3 Identifying collection centres

Task 2.4 Analysing the socio-economic impact of the new infrastructures

Task 2.5 Identifying the gaps and the best sites to set-up new BSL4 labs or major upgrades

Task 2.6 Conducing interactive dialogue between relevant inter governmental and decision-makers to reach an agreement on the financial support and the construction sites

Task 2.7 Establishment of the financial plan for the construction and operation phase

Task 2.8 Final financial commitments obtainment

The **S&T results of the WP2** are as follows:

Task 2.1 Making contacts and obtaining and agreement in principle from the relevant ministries and agencies of the Member States.

The main aim of Task 2.1 was to obtain an agreement in principle from representatives of the Member States on the concept of ERINHA operating as one European integrated structure.

From start of the project, all project partners contributed to identifying the key representatives from their governments to contact for ERINHA. Government's representatives have been identified in the 15 countries taking part in the project via the partner's organization (France, Austria, Belgium, Germany, Greece, Italy, Romania, Slovakia, Sweden, UK, Portugal, Spain, Hungary, Turkey, and Denmark). Formal letters introducing ERINHA have been sent to the identified contacts and meetings have been held with government representatives with the aim of introducing ERINHA concept and providing details on what is expected from them.

A concept paper was finalised and distributed to each partner to brief its National authorities on ERINHA. Considering its high added value, it has been agreed amongst all partners to replace the initially planned Memorandum of Understanding (D2.1) by the Concept Paper.

Lobbying activities have been conducted at the European Parliament for the sustainability of the research infrastructures of the ESFRI roadmap in the frame of horizon 2020 in collaboration with other BMS RIs (Biological and Medical Science Research Infrastructures of the ESFRI roadmap).

Task 2.2 Listing of the existing BSL4 facilities

The main objective of Task 2.2 was to provide an inventory of all existing BSL4 facilities. The capacities/capabilities of the BSL-4 laboratories partners of ERINHA preparatory phase have been listed and analysed. Ten high containment facilities, including current and pending areas, have been included in the report and specific capacities (cell culture capacities, animal handling capacities as well as equipment) have been detailed. The position of ERINHA RI at the world level has been analysed.

Task 2.3 Identifying collection centres

The goal of this task was to evaluate the 33 biobank centres associated with BBMRI and put forward a plan for required upgrades and/or inclusion of additional centres.

Surveys were distributed to key institutions, networks and societies have been analysed to identify collection centers to be associated with ERINHA. Of the 49 institutions that returned the questionnaire, 35 reported that their collections include RG3 pathogens, of which 21 having these samples available to external research groups. Seven institutions reported having RG4 pathogen-containing material, five of which indicated willingness to share with external research groups. 24 of the 35 centers have the collection within a biobank. Equipment of centers holding samples containing high-risk pathogens were also investigated (D2.3). The assessment of the current situation was used as a basis for the BBMRI/ERINHA strategy paper (D5.1).

Task 2.4 Analysing the socio-economic impact of the new infrastructures

This task aimed to assess the impact of the BSL4 laboratory and their networking on healthcare and economic issues. This task was deleted because no new potential laboratory has been identified.

Task 2.5 Identifying the gaps and the best sites to set-up new BSL4 labs or major upgrades

By comparing the status of BSL4 capacities with the L4 epidemiological threats issues, this task aimed to highlight the needs and gaps of BSL4 structures. While the analysis of existing BSL4 capacities in Europe did not enable the consortium to identify an immediate need for a new BSL4 laboratory, a study has been conducted in order to define strategic region for potential new building. A list of the most relevant countries from Eastern Europe has been established (D2.5) on the basis of specific science-based and social-economic indicators (population size, gross domestic product, sector of performance, number of doctorate students etc.)

Task 2.6 Conducing interactive dialogue between relevant inter governmental and decision-makers to reach an agreement on the financial support and the construction sites

This task aimed to nurture a dialogue with relevant decision-makers to pave the way towards a decision on which country would host the coordination structure and how it would be funded.

During the first period of the project, an expert from the ECDC has been designated as the ECDC contact point for ERINHA (Dr. Amanda Ozin) and nominated as a member of the ERINHA Scientific Advisory Board. Moreover, expert from WHO (Pierre Formenty) was invited to participate in the Lisbon meeting on users' access (26th April 2012, WP6). Contacts have also been established with decision makers from Member states.

Contact with the ECDC and WHO were reinforced during the second phase of the project namely. A listing report of the most relevant site to build new BSL4 facilities has been established. This report has been submitted to ECDC to obtain their agreement in principle on the best choice of site for potential new BSL4 laboratory construction.

Task 2.7 Establishment of the financial plan for the construction and operation phase

Task 2.7 involved preparing the financial plans for future ERINHA phase's to ensure the infrastructure's feasibility and viability. Major components of the financial needs for the different following phases of the project (Interim phase Construction phase and operational phase) as well as the type of funding have been defined and described in D2.8 (ERINHA Financial plan).

Task 2.8 Final financial commitments obtainment

This task sought to obtain the final political and financial commitments for construction of the new facilities and of ERINHA.

Due to the specific sensitivity associated with high containment facilities, more time will be required before moving to the formal construction phase. Therefore the ERINHA consortium decided to move to an "interim phase" to avoid losing the benefit of the unique work done to design the future pan-European BSL-4 laboratory. This phase will mostly focus on obtaining the final and formal financial commitment and signature from member states, associated countries and national institutions that will support ERINHA RI.

However, it should be noted that commitment to participate to this interim phase has not yet been obtained from funding parties. Funding is still necessary to cover the salary of the ERINHA Central Coordination Unit (CCU) as well as travel/meeting expenses of the coordinator, the project leader and the representatives of each funding parties. These funding parties will comprise organizations and member states/associated countries bringing resources to the infrastructures (possible in the form of in-kind contributions). Countries and national institutions that should be involved during the interim phase are: France, Italy, Hungary (National Center for epidemiology), Germany, Greece, Belgium (Institute of Tropical Medicine) and possibly (to be confirmed by formal agreement) England, Spain and Sweden (Swedish institute for Communicable Disease control)

WP3 Governing structure and legal status

The objective of WP3 was to define and establish a legal status and governing structure for the ERINHA infrastructure towards the implementation of a sustainable research infrastructure. The legal status will allow the infrastructure to act as a legal entity enabling financial and contract management with parties. The governance structure will relate to consistent coordination of efforts, cohesive policies, decision-making processes within the infrastructure, steering extension to other networks and coordination with other EU research infrastructures (BBMRI, ELIXIR & others).

WP3 was divided into 2 tasks:
Task 3.1 Setting up a governing structure
Task 3.2 Setting up the infrastructure legal status

The S&T results for each task were as follows:

Task 3.1 Setting up a governing structure

This task set out to establish an appropriate governing structure for ERINHA.

A draft of the ERINHA Governance structure was prepared and described in D3.1. The structure includes:
- At the decision-making level:
    - An assembly of members in charge of the overall management and strategic decisions with regard to ERINHA;
    - A governing board to monitor the execution of the Central Coordinating Unit;
    - Advisory boards: Scientific Advisory Board, Ethical Advisory Board, Regulatory Advisory Board, Final Advisory Board, Users Advisory Board
- At the executive level:
    Central Coordinating Unit (CCU): under the responsibility of the Director General, the CCU will provide a common access portal to the available BSL-4 capacities and capabilities of ERINHA.

The governance structure was agreed on by all partners.

Task 3.2 Setting up the infrastructure legal status

This task aimed to set up and obtain the Member states' agreement on the ERINHA legal status.

The results of this task were as follows:

Throughout the project, there was much discussion on the status of the ERINHA infrastructure and the country that would host the coordination structure, the two aspects being interlinked. A tender process was launched to contract a legal firm to conduct analysis of potential legal statuses for the ERINHA infrastructure and draft a status based on the outcome. Ernest and Young was selected to perform the analysis.

In the context of the ERINHA project, discussions were led on a possible location for the ERINHA BSL-4 laboratory and six potential host countries are currently targeted: Germany, Belgium, Greece, Hungary, Italy and France. At the proposal stage of the project, it was envisaged that two statuses would be explored: European Research Infrastructure Consortium (ERIC) and a European company. While the ERIC structure is well adapted to ERINHA's activity, according to Ernest & Young's initial analysis, this status was considered difficult and time-consuming to set up. In addition, VAT exemption is one of the main advantages of ERIC but ERINHA is not planning to have large investments. As for the possibility of a European company, as ERINHA will be involved in commercial activity this status was deemed unsuitable.

As described in D3.2, E&Y analysed 10 different statuses, namely different national versions of associations and partners were asked to vote. As not all partners were able to vote at this stage, 10 partners voted to obtain a better idea of the ERINHA partner countries' position on the various legal statuses to prepare for the Interim Phase. The partners voted on the status of an association and two partners specified preference for a 1901 Act Association under French law and 1 partner preferred and AISBL under Belgian law.

This vote is not yet official but will be formalised during the ERINHA interim phase to conclude on a legal status and host country for the structure.

WP4 Technical work: Design considerations and estimating construction costs for new BSL4 areas

The objectives of WP4 were:
1. To produce a set of procedures, models and tools to help scientists and engineers in defining user requirements for BSL4 laboratory construction (including the supporting infrastructure to accommodate the host unit's scientists and visiting users of the facility).
2. To make recommendations on design and construction philosophy for BSL4 labs based on scientific evidence and ergonomic considerations (including the supporting infrastructure to accommodate the host unit's scientists and visiting users of the facility).
3. To estimate the likely construction and operational costs of the new facilities and major upgrades identified in WP2 by reference to the construction and operational costs of existing BSL4 labs and cost prediction models used by the construction industry.
4. To provide construction plans and estimates of building costs for the new BSL4 facilities (up to 3) and the major upgrades (up to 2) identified in WP2.

To achieve **WP4 objectives** a number of workshops were held, information gathered and reports were provided to the consortium partners and some made freely available on the website. It became clear early into the project that WP2 would be unable to identify any new facilities and major upgrades to help meet objectives 3 and 4. Therefore a more generic approach was taken, in which flexible designs and costing for standard BSL-4 facilities were provided.

Activities in Work Package 4 were divided into five tasks:

Task 4.1: Definition of User Requirements (lead: DH)

Task 4.2: Evidence-based rationale and ergonomics for safe building design (lead: DH)

Task 4.3: Storage, archiving and access to samples (lead: MUG)

Task 4.4: Estimating construction and operational costs (lead: AGES)

Task 4.5: Commissioning designs for new BSL-4 labs (lead: INSERM)

The main S&T results for work package 4 have been **the provision of procedures, models and tools for the definition of user requirements for BSL-4 facilities**. These tools were used in the training of members of the consortium without (and with no plans to build) BSL-4 facilities, where it became apparent that these tools could also be utilised for partners planning 'enhanced BSL3' (BSL3e, BSL3+) facilities to handle high consequence pathogens such as MDR-TB and highly pathogenic agents. An international workshop and an in-depth literature review have produced a report detailing the evidence base behind BSL-4 facilities. This has highlighted best practices but also knowledge gaps in the BSL-4 containment evidence base such as disinfectant validation. This has influenced the planned ERINHA research strategy. Other workshops gathered information on biobanking requirements at BSL-4 and tools for estimating the costs for construction and operation of BSL4 facilities. Finally, designs for three generic BSL-4 facilities were produced along with cost estimations by contracted architects. These designs along with the other reports delivered in Work Package 4 will greatly aid ERINHA members without high containment facilities in any future planning and construction activities.

Task 4.1 Defining User Requirements for BSL-4 facilities

At the outset of a project to design a new BSL-4 facility (or any other high containment facility), close consultation is required between scientists and engineers to capture the user requirements and translate these into a building design. There will be many conflicting drivers in this process and care needs to be taken to ensure that the requirements of the facility are captured before room plans and designs are defined.

In September 2011, an ERINHA workshop was held to discuss the URS process with various stakeholders involved in the design, building and operation of new high containment laboratories. Representatives of the ERINHA Consortium gathered in Lyon, France alongside invited expert researchers, regulators, designers, and architects. Each speaker presented their own perspective of the key factors to consider when designing a new BSL-4 facility, along with lessons learned from past design and construction projects. Consideration was also given to how new advances in technology might be incorporated into future high containment facilities. A report of this consultation exercise was produced (D4.1) with examples of model facilities.

The outputs from the Lyon workshop were combined with the experiences of PHE, specialist architects and designers in URS development to develop a range of tools (flow diagrams, models and check lists) and guidelines to facilitate the provision of a URS. A report was produced detailing the resulting draft tools and guidelines designed to help engineers capture the needs of users and translate them into a building project that is feasible, economic and achievable, whilst meeting the requirements of its scientific staff. These tools included:

- A flow diagram to allow the basic facility requirements to be identified and defined as one of four model BSL-4 facilities;
- The provision of four model process flows to define sample flow through these facilities.
- Provision of checklists for each of the facility types in order to define the major functional, equipment and spatial requirements;
- Reference tables for spatial requirements for different activities: e.g. viral culture, animal work for different species including legislative requirements for cage sizes, and specialist tasks including post-mortems.

The URS process was intended to facilitate understanding between architects, engineers, designers and scientists so that preliminary designs capture the scientists' needs. The process also draws on examples of bad practice so that lessons can be learnt and errors avoided in future facilities at the design stage. While the document is mainly focussed on BSL-4 human infectious disease facilities the principles developed are relevant to the construction of other high containment facilities

The tools provided were trialled in a practical workshop (D4.6) by an invited group of engineers and lab users from ERINHA partner organisations.

Task 4.2 Evidence base for design, construction and ergonomics

A review of the evidence base for the **design** of BSL-4 facilities was undertaken examining scientific literature, outputs from expert workshops and other technical literature. The review considered the extent to which current design of BSL-4 laboratories is based on scientific evidence and how much

is done by habit or tradition alone. The scientific literature was reviewed to search for the evidence base that underpins the design and operating limits of key protective laboratory controls, including; air handling systems, effluent treatment, personal protective equipment and specification of building materials.

The main S&T results of task were as follows:

- The EU regulations which govern the standard of design and build of a BSL-4 facility are limited, yet the solutions used to meet them are becoming increasingly complex and expensive to build and maintain.

- Consensus reached amongst the international experts present at the workshop organised for this task that that current BSL-4 laboratories are over-complex, due to national regulatory frameworks governing BSL-4 and also from facility design based on the performance of pre-existing facilities (plus 10%).

- The rates of laboratory-acquired infection at BSL-4 are very low, and there is a reluctance to deviate from current design and construction practices as they are known to work. However, there is little empirical evidence for many of the engineering controls employed at BSL-4; without validation data it is difficult to objectively assess whether particular engineering controls are sufficient or even excessive as protective containment measures.

- There is no centralised repository of data on laboratory accidents, near-misses and laboratory-acquired infections at BSL-4. It is therefore difficult to judge which of the many safety precautions present at BSL-4 are actually the most critical in protecting workers and the surrounding environment.

To avoid increasingly prohibitive levels of regulatory control over the design and operation of BSL-4 labs, existing facilities need to work together to collate, and where possible, publish the validation data they have, identifying knowledge gaps and then generating further data in order to satisfy regulators. The BSL-4s of the future may need to give greater consideration to sustainability, so it will become important to know which systems are most critical for maintaining containment and what parameters they should operate within. Such knowledge will inform the development of intelligent, risk-based designs for new BSL-4 labs specific to the activities needed to counter emerging health threats.

The two most common designs of BSL-4 facilities, the cabinet line and suited laboratory, both place physical constraints on the laboratory workers which may cause fatigue and loss of dexterity, increasing the potential for accidents or near-misses. The number, variety and complexity of engineering controls and other protective measures present in modern BSL-4 facilities with which the human operator must interact, further exacerbate the challenges for the BSL-4 user. Concerning the ergonomics of BSL-4 facilities, a questionnaire was distributed to 11 BSL-4 labs in Europe. The findings that emerged from this study included awkward or difficult interactions with equipment in both facility types, and various complaints about reduced sensation and range of movement when wearing positive pressure suits. A number of different sources of ergonomics guidance and expertise were identified by survey respondents. This indicates that ergonomic information is available for those designing a new containment facility and in fact architecture firms with experience in biocontainment should be able to access relevant guidance. Some labs have also

developed bespoke solutions to their particular ergonomic challenges, experimenting using full scale mock-ups where required.

Overall, this study demonstrated that there is a great deal of user expertise in the ergonomic challenges of working in a modern BSL-4 facility within the ERINHA project consortium and the wider European BSL-4 community. The ERINHA infrastructure will be able to utilise this combined knowledge in the future development of the BSL-4 research capability in Europe.

Task 4.3 Proposed strategy for storage and biobanking at BSL-4

A workshop was held in Spiez, Switzerland in March 2013 in order to discuss how BSL-4 laboratories have implemented specific procedures for sample management and biobanking. The main S&T results of this task were as follows:

- There has been limited exchange of information on this issue between BSL-4 laboratories and the general biobanking community, resulting in different procedures and lack of interoperability.
- Several issues were identified where no clear recommendation for a best practice can be provided (e.g., type of sample tubes, labelling of tubes, appropriate information on tubes). There is great interest in collaboration to agree and implement common best practice protocols. Because of the recently started initiative of CEN TC 140 to develop technical specifications to the ISO 15189:2012 for molecular in–vitro diagnostics, which are also relevant to quality of sample management in BSL-4 laboratories it is recommended to follow this process, and that SOPs for sample management in BSL-4 laboratories should comply with these specifications. These specifications focus on quality-related issues that impact on reliability of molecular analyses but do not address biosafety and biosecurity issues, which therefore have to be addressed in addition. In this context the overlapping nature of biosafety and biosecurity issues as well as the limited open exchange of information in the scientific community because of biosecurity concerns is a specific challenge.

Task 4.4 Estimation of construction and operating costs

Data collected on technical specifications, costs and cost estimation tools provided the basis for a workshop involving major European and U.S. construction groups. This "BSL-4 construction workshop" was held in Spiez, Switzerland in March 2013, organised by AGES. The main S&T results of this task were as follows:

- Total construction costs for a BSL-4 facility can vary from €2 million to €5 million for the building shell, from €1.5 million to €3 million for the electricity-infrastructure, and from €1 million to €3 million for the laboratory equipment. The materials used for construction of the containment areas in present European BSL-4-facilties varied widely, but consensus was gained on recommending mixed construction systems, using concrete and steel-panels as preferred choice.
- Yearly operational costs usually amount to 10% up to 15% of the total construction costs; this can be reduced by limiting costs such as time-periods (e.g. shutting down the

containment area during night hours). Operational cost savings of up to 15% were documented for some of the participating BSL-4 facilities.

- The restriction of the number of back-up systems (redundancy concerning actual number of HEPA-filters, disinfection systems, UPS, etc.) during planning and construction of a new BSL-4-facility can drastically influence future costs for operational activities and maintenance.
- Maintenance costs are another main cost contributor, which can be influenced by minimizing the number of back-up systems, a decision which inevitably affects risk management.
- The legal requirements for maintenance intervals and other standards regulating maintenance differ widely between the participating ERINHA countries.
- The right choice of materials, which were found to vary in prices depending on the location and topography of the BSL-4 facility (e.g. earthquake-prone area), can significantly influence the total construction costs.
- Detailed pre-planning is essential for future cost efficiency in operating a BSL-4 facility.
- A balance between risk reduction and cost reduction, although difficult, should be achieved, requires consensus among the future users, clients, government agencies, and technical specialists.

This task connected experts from European and international countries and allowed exchange of data (like constructions details and costs) and experiences relevant for construction and operation of high level containment laboratories. It revealed the considerable variation in approaches chosen for operation of today's BSL-4 facilities and showed significant differences between national legal regulations, consensus was reached concerning a need for European standardization of construction and operation of BSL-4 facilities. **To our knowledge, the WP4 task 4.4.-report is the first document summarizing national data, making them available to ERINHA-partners and thereby providing guidance for further BSL-4 laboratory planning activities.**

Task 4.5 Construction plans and building costs

Due to the lack of new BSL-4 facilities being planned in WP2, a different approach was adopted for the provision of construction plans and building costs. It was decided to limit the task to the provision of generic plans and costs for three different types of BSL-4 facilities identified from the tools for developing User Requirements for BSL-4 facilities (Task 4.1). These facilities were:

- A small diagnostic facility based on the use of a cabinet line;

- An *in vitro* research facility;

- A research facility incorporating an animal room.

A tendering process was launched and ClimaPlus with Tourret Jonery Architects and Altergis engineers were selected. Initial designs were prepared for comment and then final designs were

provided along with three documents detailing the design features of each facility and giving cost information for their construction. These costs are detailed in D4.4.

The designs and reports now form resources open to use by members of the ERINHA consortium that can be used to inform their future designs for the construction (or upgrade) of high containment facilities.

As described above, the work carried out in Work Package 4 has met its objectives. The work undertaken has shown that there is not a one-size-fits-all 'best' design for a BSL-4 lab. Rather, best practice is to engage lab users at a very early stage of planning to determine the types of infectious material to be handled, the likely throughput and the typical processes that the material will undergo in the laboratory from how it is brought in to the facility to whether it is archived, disposed of or inactivated for processing outside containment. The process flows should inform the size and layout of the facility.

The evidence base for the level of engineering controls implemented for biosafety purposes is not extensive and the low numbers of laboratory-acquired infections at BSL-4 are regularly used as justification for what in fact could be an excessive level of biocontainment engineering. ERINHA should build up a repository of performance data for engineering systems including failures, as well as a database of laboratory accidents/near misses at BSL-4. Only if this knowledge is recorded systematically will it be possible to see whether BSL-4 containment is sufficient, or indeed excessive protection for operator and environment.

Greater inter-operability between Europe's BSL-4s is key to making them competitive in global high containment research. In order to facilitate this, it is important to identify areas where policies and procedures can be harmonised. One area where there is a great deal of potential to create a harmonised best practice is in the archiving/biobanking of RG-4 material and samples. The European research infrastructure for biobanking, BBMRI-ERIC, already has good links with ERINHA and these should be further strengthened in order to develop harmonised storage and transfer protocols.

During the ERINHA Preparatory Phase there have been no requests madeto ERINHA from the European Member states for help in the planning of any new BSL-4s. Therefore the focus of ERINHA WP4 became the production of some generic tools and guidance that could be used in the future if economic conditions improve or the threat from RG4 agents becomes such that building new BSL-4s become financially viable. Task 4.1 produced sample process flows and a general structure for generating a User Requirements Specification for a new lab, an essential prerequisite for the facility design process. Task 4.4 explored the processes necessary to calculate the cost of a new BSL-4 facility, noting that there will be significant cost variation due to local availability of labour and construction materials. Task 4.5 produced sample building designs and costs for three different types of generic BSL-4 facility, providing a starting point which could be adapted by an organisation looking to build a facility in the future.

These resources have been produced in consultation with world experts in biocontainment design and engineering, and as such represent a valuable information resource held by ERINHA. Access to this information represents significant added value to membership of the ERINHA infrastructure for European member states who perhaps do not have extensive national biosafety networks or experienced architects of their own.

BSL3+ facilities

There were numerous discussions throughout the course of the project about the potential future requirement for the use of multi-drug resistant bacterial pathogens such as MDR-TB at BSL-4. However, it became apparent that in fact what was required by many partners was not a BSL-4 facility as presently understood but a type of high level BSL3 facility often referred to as BSL3+. This type of facility would use a high level primary containment using Class III microbiological safety cabinets as the main mode of containment. Many of the partners with no BSL-4 facilities and no intentions of building one have expressed interest in having this type of facility. As ERINHA evolves these facilities should be included within the infrastructure's total capability.

WP5 Definition/harmonisation/dissemination of best practices in management ofbiosafety/biosecurity/BRCs

The **objectives of WP5** were:

1. To produce a set of procedures, models and tools to help scientists and engineers in defining user requirements for BSL4 laboratory construction (including the supporting infrastructure to accommodate the host unit's scientists and visiting users of the facility);
2. To make recommendations on design and construction philosophy for BSL4 labs based on scientific evidence and ergonomic considerations (including the supporting infrastructure to accommodate the host unit's scientists and visiting users of the facility);
3. To estimate the likely construction and operational costs of the new facilities and major upgrades identified in WP2 by reference to the construction and operational costs of existing BSL4 labs and cost prediction models used by the construction industry;
4. To provide construction plans and estimates of building costs for the new BSL4 facilities (up to 3) and the major upgrades (up to 2) identified in WP2.

WP5 was organised into 4 tasks:

Task 5.1 Training and best practices in BSL4 labs
Task 5.2 Establishing or preparing a network of sample collection centres and biorepositories associated with ERINHA
Task 5.3 Preparing best practices and common standards for material handling and exchange within collection and repository centres
Task 5.4 Reviewing the borderline between BSL3 an BSL4

The S&T results are described below for each task:

Task 5.1 Training and best practices in BSL4 labs

The aim of Task 5.1 was to harmonise training and best practices in BSL4 labs. To this end, the following work was undertaken:

- a space in the existing ETIDE website (*www.etide.eu*) has been created. This site was also linked with the ERINHA website.

- a training questionnaire was developed to study the training requirements of all the participating Institutions and sent to all partners of ERINHA project (MS15). The results obtained from the training questionnaire were illustrated during the workshop held in Lisbon (Lisbon, 26th-27th April 2012 Workshop on "training and biosafety in BSL4 laboratories").

- a training workshop was held in Spiez, Switzerland in March 2013.

The main S&T result of this task was the consensus statement that was obtained on training activity and the “ERINHA code of conduct”, a code which represents a minimum set of biosafety principles that are binding on partners of ERINHA project (D5.7).

Task 5.2 Establishing or preparing a network of sample collection centres and biorepositories associated with ERINHA

The aim of Task 5.2 was to engage in dialogue with the BBMRI to review and develop a common vision on the future and strategies regarding the collection, research and diagnostics with high-risk infectious material in Europe.

The main results of this task were as follows:

A joint ERINHA/BBMRI strategy paper in which INSERM, as ERINHA coordinator and MUG, as BBMRI coordinator agreed on the terms of their collaboration from the 1 November 2010 until the end of the operational phase of both infrastructures.

The borderline between BSL3 and BSL4 was explored using several approaches. The deliverable 5.2 (Analysis of BSL3/4 risks in associated centres) and D5.3 (List of pathogens and risks on BSL3/4 divide) provided response from ERINHA partners on questions related to the demands and practices for diagnostic and/or research work requiring BSL-3 or BSL-4 containment facilities. This deliverable highlighted that all laboratories of RG4 pathogens have certain measures in place, such as SOPs on sample receipt, EQA for the differential diagnosis of RG4 pathogens, and are involved in diagnostics for bioterrorism. Concerning risk assessment for research experiments, several criteria were broadly applied while others were considered important by few participants. It was found that the approach to different case scenarios was diverse and that a consensus may fave to be found on minimal requirements for BSL4 and non-BSL4 laboratories. It was concluded that BSL4 and BSL3 laboratories have appropriate procedures regarding biosafety and the handling of samples. However, considerable efforts may be needed to achieve a level of harmonization fitting for a joint infrastructure.

Task 5.3 Preparing best practices and common standards for material handling and exchange within collection and repository centres

The aim of this task was to analyse the needs and modality for a pan-European transport system of biological material and corpses requiring BSL-4-type containment measures. Task 5.3 also aimed to prepare draft SOPs for associated collection centres.

The following recommendations emerged from assessment of transport issues:

- Establishment of a process that allows exchange of information between expert groups and facilities;

- Identification of contact persons for transport of patients and corpses;

- Collaboration, interoperability, adjustment of processes and organsation of transnational exchange of information are needed;

- Building of capacities, resources from different countries should be compatible;

- On request, resources of several countries should be able to be summarized (larger outbreak scenarii).

In this task, a template content structure for SOPs for tissue sample management in BSL4 laboratories according to CEN TC 140 WI 00140090 was prepared and took into account the consortium's recommendations of the biobanking workshop in Spiez 2013.

Task 5.4 Reviewing the borderline between BSL3 an BSL4

This task aimed to review the strict divide between BSL3 and BSL4. The report on alternative approaches on BSL3/4 borderline (D5.10) sought to increase the evidence base of biosafety around TB, by optimizing a culture based environmental sampling method to identify M. tuberculosis in- and outside of biosafety cabinets.

This task gave rise to the following main conclusions:

- It was illustrated that the current standard protective measures already provide a high level of protection and that minor improvements in practices may be sufficient.

- Another option of working with an adapted closed front cabinet was further explored, the specifications of which can be used as a guideline for other applications. However, greater dialogue with the authorites is required.

- The biosafety audit and risk analysis highlighted the limited data available on which to base an evidence-based approach.

- The findings of this study identified M. tuberculosis as outside of the biosafety cabinet. Concerns were raised about sustained proper use of masks so it was recommended to enhance containment of M. tuberculoisis 'at the source', which was approved by the authorities.

WP6 Access to BSL4 infrastructure for academic research, industrial research, and diagnosis activities

Academia and industry on occasion require BSL4 expertise and capacity not available in their respective institutions. The main objectives of WP6 were to define the extent and nature of these requirements and determine how these needs could be satisfied by cross-border access to the European BSL4 lresearch infrastructure. This workpackage has produced guideline access procedures, including appropriate biosafety and biosecurity measures, and proposed scientific programmes to encourage external and transnational users to access the ERINHA BSL4 infrastructure. The access procedures were tested in year 3 of the Preparatory Phase of ERINHA, in conjunction with WP7.

Activities in WP6 have been divided into 5 tasks:
Task 6.1: Analysing the capacity of existing and newly built laboratories (lead: RKI)
Task 6.2: Defining the need and customer base (lead: DH)
Task 6.3: Defining Access Procedures (lead: RKI)
Task 6.4: Funding Facilities and Programmes (lead: DH)
Task 6.5: Stakeholder liaison (DH and RKI)

Task 6.1 Analysing current BSL-4 capacity in Europe

An analysis of the capacity of existing and newly built BSL-4 laboratories belonging to ERINHA partners was performed by questionnaire (MS18). The analysis focused on the following parameters:

- capacity of the laboratory (size of labs, no. of labs, lab units, location etc.)

- capacity of the personnel
- technical equipment (tables, centrifuges, microscopes etc.)
- animal facilities (size, no. of animal species etc.)
- storage capacity for samples (-20°C, -80°C, liquid nitrogen)
- main focus of research
- existing BSL-4 pathogens
- experience with hosting visiting scientists
- biosafety and security measures

Data was collected from all ERINHA partners (22 at that time) of which 7 had operational BSL-4 facilities in 6 European countries. All operating BSL-4 labs worked in public health carrying out diagnosis and / or research.

The **main S&T findings** of this task were as follows:

- All the operational ERINHA partner BSL-4 labs have some spare capacity that could, in principle, be made available to ERINHA for cross-border access. It also identified that some functions and capabilities were duplicated at several partner sites whereas other functions could only be performed at a single partner site or were not available at all.

- Redundancies and gaps were identified in the capabilities available across the putative distributed ERINHA infrastructure. It will be a challenge for ERINHA to balance the capacities and capabilities contributed by each partner BSL-4 facility to the operational infrastructure. This is an inevitable drawback of building an infrastructure from existing national assets rather than being able to design and provision a new purpose-built infrastructure.

Task 6.2 Defining the need and customer base

An operational ERINHA infrastructure will offer access to external scientists from academia and industry who do not have access to BSL-4 facilities in their own institutions or nations. Task 6.2 aimed to identify potential academic and industrial users and determine the functions and capacities they would need.

The main output of this task was a database (D6.2) of potential external users of a European BSL-4 infrastructure drawn from academia, industry and the public health sector, using information provided by 10 of the ERINHA partners. The database is divided into 4 categories: academia & government, biotechnology SMEs, multinational pharmaceutical R&D and miscellaneous customers (NGOs, charities) from which 53, 23, 20 and 5 named contacts are listed, respectively.

All named contacts in the database, together with ERINHA partners and member states representatives, took part in a held in Lisbon, Portugal on 25th and 26th April 2012. The access needs of different users were discussed, gaps in the current provision of capabilities at BSL-4 were identified and dialogue with the agencies that fund European BSL-4 research was initiated.

11 out of the 96 contacts identified participated in the workshop. DH therefore carried out further work to determine the size and needs of the potential customer base for a European BSL-4 infrastructure. A questionnaire developed for the MS19 workshop was adapted for use as a web survey and the link distributed widely through professional infectious disease, microbiology and virology networks. Only 14 individuals filled in the entire survey; of those respondents who chose to

be identified, all but two were already known to the ERINHA project. Through the questionnaire, workshop participation and work on Task 4.2, the main S&T results for this task as a whole can be summarized as follows:

- Interest in BSL-4 research is currently low and perhaps hindered by lack of ready access to BSL-4 facilities (namely due to funding);
- There is a current unmet need to undertake research at enhanced BSL-3 containment.
- ERINHA will need to work to raise the profile of, and funding opportunities for, BSL-4 work and thus generate more interest and demand for research at BSL.

Task 6.3 Defining Access Procedures

The aims of this task were to:

- produce guideline access procedures, including appropriate biosafety and biosecurity measures to allow external and transnational users to access the ERINHA BSL-4 infrastructure.
- test these procedures as part of the pilot training and diagnostic / research activities in Work Package 7.

Guideline access procedures need to consider the existing regulations under which the ERINHA partner BSL-4 facilities operate. Therefore, further information was requested from ERINHA partners with a BSL-4 lab to identify the local requirements for access to work in national BSL-4 facilities and to determine if local rules depart from or supplement EU legislation. The findings can be summarized as follows:

- Several differences in national legislations for different BSL-4 laboratories were identified, particularly concerning the stringency of background security checks and the agencies that are responsible for carrying these out e.g. local checks or screening by national security authorities.
- All facilities require a period of training to be undertaken before access to the BSL-4 lab will be granted and further training and supervision, of variable duration, in the BSL-4 environment. Typically, prior experience of working at BSL-3 or BSL-4 is required and the duration of BSL-4 training depends on the level of prior experience.

Based on the information collected in tasks 6.1 and 6.2 (questionnaire, workshop), a first iteration of general access procedures for the ERINHA infrastructure were produced (D6.4 report). These access procedures consider the steps required to grant experienced external or transnational users access to ERINHA partner BSL-4 laboratories and considering the following:

- Security clearance and background check
- Medical surveillance
- Skills
- Training
- Justification of the need for access

The access procedures were tested in the pilot projects run by WP7.

The main S&T results from this task were as follows:

- Most of the general access procedures identified can be harmonized across the European BSL-4 laboratories taking part in ERINHA although there may be variations in the duration of training required.

- The security clearance and background checks follow national legislation and therefore differ across Europe; these might be difficult to harmonize. One approach may be to set up transnational agreements to simplify the access for transnational users.

Task 6.4 Funding Facilities and Programmes

Task 6.4 in WP6 has focused on ways in which research can be carried out in the infrastructure and how access to the infrastructure will be financed. Task 6.4 has developed the **research strategy** for ERINHA which was a requirement identified by the Expert Assessment Panel during the review of the ERINHA project in March 2013. Therefore, in a departure from the stated deliverables for task 6.4, D6.5 comprises minutes from meetings with 3 funding agencies AND the ERINHA research strategy document.

During the task 6.2 workshop in Lisbon, it was explored how access to the ERINHA infrastructure might be achieved for scientists who do not have access to their own national BSL-4 facility. Two options emerged:

- *Contract research:* carried out by ERINHA staff on behalf of an external organization. This is the most likely access mode required by industry. They would expect to pay full economic cost and, in return, to own all the data, intellectual property etc.
- *Collaborative research:* carried out jointly by ERINHA staff and the external organization with the option for the external staff to be trained and work at BSL-4 depending on the duration of the project and their preference. Outputs including data, publications and intellectual property would be shared. This is the most likely access mode required by academia. Typically, academic projects do not receive funding at full economic cost.

For ERINHA partners without a national BSL-4 facility, the option for 'fast track' access was proposed. This could be achieved by carrying out security clearances, basic training etc in advance of need. However, ERINHA should take care not divide European member states into "haves" and "have-nots".

Through **contact with research funders** (EC, the Wellcome Trust (WT) and the UK Biotechnology and Biosciences Research Council ((BBSRC) in this task, **the following results/observations emerged**:

- Projects involving Risk Group 4 agents are not excluded from receiving EC funding; the low number of such projects that receive EC funding at present may in part be due to a lack of recognition within the Commission of the added value of these high-cost projects.

- All 3 funding agencies would, in principle, consider funding research projects requiring access to BSL-4 facilities, providing the science was competitive and a good fit with their funding priorities. In the case of BBSRC, cross-border access projects would be studied on a case-by-case basis. WT is already accustomed to such projects.

- A funding model that allows entry that is free at the point of access, thus avoiding transferring money across borders would be preferable.

- ERINHA needs to identify how it will enable transformative science to be carried out that addresses critical questions for Europe and can only be achieved through a coordinated infrastructure, which could not be achieved if the infrastructure did not exist.

This message was reinforced during the Expert Assessment Panel interview in March 2014 when ERINHA was advised to develop and carry out its own programme of research (Research Strategy D6.5), which was then discussed at a Grand Workshop.

This task therefore produced a research strategy that:

- sets out the ways in which research will be carried out in the ERINHA infrastructure, through internal, external and hosted projects.
- identifies a series of possible internal research projects that build the capabilities, workforce and practice of cross-border working so that ERINHA is prepared to respond to the next unknown infectious disease threat that emerges in Euro.

Task 6.5 Stakeholder liaison

The aim of task 6.5 was to work with the different stakeholder groups to capture information and maintain an interactive dialogue between laboratory owners, potential users and regulators. While no formal milestones or deliverables were attached to this task, the main S&T results of this task were as follows:

- information collection about potential academic and industrial users and other stakeholders such as funding agencies (see D6.2).
- 3 issues of a bulletin were produced to inform potential stakeholders about the aims of ERINHA and progress during the Preparatory Phase and distributed these to all ERINHA stakeholders and partners
- a web-based survey to capture information about additional potential users was developed
- two external workshops were held (MS19 and MS21)

WP7 Research and diagnosis pilot activities

The objective of this WP was to challenge and validate the operability of the ERINHA infrastructure via pilot RTD activities on research, diagnosis, dissemination and training that will form proof of concept. These pilot activities, relying on the existing European BSL4 laboratories framework aimed to allow to test and demonstrate that the overall organisation of the ERINHA infrastructure – in terms of infrastructure's governance and legal organisation, harmonisation of SOPs, training, access to the resources for external scientists and companies – is efficient and mature at the end of the preparatory phase. Pilot activities also allowed evaluation and refinement of the set of SOP's, as well as training programs.

WP7 was divided into 5 tasks, the results of which are presented below:

Task 7.1: Performing a pilot training activity;

Task 7.2: Testing dissemination;

Task 7.3: Defining and performing a research pilot project;

Task 7.4: Defining and performing a diagnosis pilot project;

Task 7.5: Retrospective analysis of the efficiency of the infrastructure.

Task 7.1 Performing a pilot training activity

The aim of this task was to test the efficiency of the training program defined in WP5 and put forward suggestions to improve training course guidelines.

In order to simulate and test the operational feasibility of the ERINHA infrastructure, three institutions (INMI, BNI, FoHMI) organized “pilot training and research/diagnostic activity” at their BSL4 facilities. The research and diagnostic pilot projects were open to partners in the ERINHA consortium that were all experienced laboratory scientists, some with and some without prior BSL4 experience.

The participants were selected on the basis of a shared core curriculum for BSL4 workers as previously defined in WP5 (task 5.1). The training session combined theoretical and practical courses: each participant was asked to perform procedures according to SOPs of the institute and the training session was centered around biological activity of type III Interferon on CCHFV.

At the end of the BSL4 biosafety training, participants were asked to complete a questionnaire in order to collect comments on the organizational aspects of the event and their opinions on the content of the course. The questions were related to the objectives of the training course, relevance of the included topics and modules for the trainees, asking also for spontaneous comments on strengths and weaknesses of the course. The aim was to check the suitability and applicability of the training program both with those who have or do not have experience in BSL4. This task enabled the consortium to put forward recommendations to fine-tune future training activities. The same structure has been used in the other two Institutes and the full results are presented in D7.6.

Task 7.2 Testing dissemination

This task aimed to verify the efficiency of dissemination and the efficacy of SOPs, based on the results of WP5.

A workshop was organised in Lisbon in April 2012 on “training and biosafety in BSL-4 laboratories” where most of the BSL4 labs presented their biosafety procedure, and an outline of six procedures was decided on.

In September 2012 (Hamburg, workshop on “pending biosafety issue for Erinha project”), all Erinha partners agreed not to duplicate BSL4 labs biosafety manuals (WHO, CEN, BMBL), that provide sufficient information, but rather to take into account the same aspects (i.e. emergency procedures, clothing protocol, storage material system, security check ...), describe minimal requirements without many details. The SOPs list was circulated among all the partners, (ERINHA general meeting in Vienna October 2012) and submitted to Scientific Advisory Board. These procedures are intended to constitute a common platform that will be integrated by the local SOPs and are included in an “ERINHA code of conduct”.

During the training activity, there were constructive discussions among participants which contributed to the review of existing regulations and procedures used in the laboratories of origin, as well as implementation of new or more adapted products and equipment. Other key points raised were the resource-intensive nature of the training, the costs related to staff which can be a major expense.

Task 7.3: Defining and performing a research pilot project

The aim of this task was to establish the study programme for one research pilot project.

The Central Coordination Unit (CCU) developed a protocol for collecting ideas for research pilot projects. The protocols were distributed to all partners within WP7. The collected proposals were discussed internally within the CCU and then presented to the Steering Committee at a meeting in Berlin in December 2011. The selected projects were discussed and validated. These projects were then presented to all the partners within the ERINHA to collect the names of scientists interested in being part of this action. The candidate list was submitted and approved by the Steering Committee.

The scientists approved to participate in the pilot project were informed by each NODE. Each NODE took responsibility for performing the pilot project. Training and education were performed separately in these different NODEs, based on internal biosafety training.

The projects selected for the pilot research activity were as follows:

NODE 1, INMI: Title: Biological activity of Type III Interferons on CCHF virus. Within this project we sought to study: i) The effect of Type III IFNs (IFN-λ) on CCHFV replication cycle and ii) Whether the activity of IFN-λ can enhance the antiviral activity of Type I IFNs against CCHFV. Host: INMI, No of participants: 3 Scientist (from AGES, ITM and NCE); Schedule: 4-11 February 2013 (training and project)

NODE 2: FoHM: Title: Production of Antibodies against CCHFv.Isolation of a new CCHF virus strain and production of antibodies against recombinant nucleocapsid proteins (NP). A European CCHFV strain has been isolated and cultured. The harvested virus were inactivated by Trizol. The RNA used to clone CCHFV NP in prokaryotic expression systems. The expressed NP purified and would be used for production of monoclonal antibodies. Host: FoHM: No. of participants: Two scientists (from INSERM and PHE) Schedule: 13-17 May- 2013 (Training), 20-24 May-2013 (project).

The results produced included a manuscript from the pilot project at NODE 1 and laboratory reagents (vRNA) to prepare a recombinant proteint from a Turkish CCHF virus strain at node 2.

Task 7.4 Defining and performing a diagnosis pilot project

The aim of this task was to define and prepare the study programme for one diagnosis pilot project with advice from the Scientific Advisory Board.

The Central Coordinating Unit developed a protocol for collecting ideas for research pilot projects. The protocols were distributed to all partners within WP7. The collected proposals were discussed internally within the CCU and then presented to the Steering Committee at a meeting in Berlin December 2011. The selected projects were discussed and validated. These projects were then presented to all the partners within the ERINHA consortium to collect the names of scientists

interested in being part of this action. The candidates list was submitted and approved by the Steering Committee.

The scientists approved to participate in the pilot project were informed by BNI. BNI took responsibility for performing the pilot project. Training and education were performed separately in these different NODEs, based on internal biosafety training.

The following project was selected:

NODE 3, BNI: Title: Diagnostic tools for CCHF; preparation of molecular and serological tools for diagnostic. Host: BNI, No. of participants: 6 Scientist (from HPI, HU-Ank, FLI, RKI and NCE); Schedule: 16-19 December 2014 (training and project)

Task 7.5 Retrospective analysis of the efficiency of the infrastructure

The aim of this task was to analyse the efficiency of the infrastructure based on the four pilot studies.

WP7 developed an artificial structure which could correspond to the governance structure of ERINHA (see D7.4). The operability of the ERINHA infrastructure was analysed through pilot RTD activities. These pilot projects sought to ensure that i) the infrastructure governance, ii) training and iii) access to resources for external scientists – are efficient and mature at the end of the preparatory phase. As described in D.7.6 and D.6.3 we have identified several common and differences in training program and open access for external scientist- however, these pilot projects demonstrated that several of these moment could be harmonized (D.7.6). As described in D7.4 and D7-8, we have experienced that the overall governance of the ERINHA and the selected process works. However, we have to mention that the complexity and extent of the pilot projects, which is the basis for this analysis, has been very limited due to time and budget constraints. As a conclusion, the tests done in the framework of this WP have demonstrated that the overall concept and organization of the infrastructure indeed work. The few gaps that have been identified will be taken into account and included in the management process the CCU will adopt.

In this context, the main lessons learnt from this WP can be summarized as follows:

- Organization of the project (including access to the host laboratory; the start date of the project and training of new staff) is essential and needs to be started long before the project should be launched (see D. 7.6 and D. 6.3).
- The timeline of the project (the duration and the period of project) should be calculated and communicated very carefully with the host laboratory. The duration and period depend on several elements such as access to the internal staff for training and daily supervision, yearly validation and etc.
- The project description/plan should be carefully detailed and there should even strategies for handling unexpected outcomes.
- The budget of the project should be clearly described.
- IPR should be discussed with the host Laboratory and an agreement should be written.

- Issues related to the publication of the data; such the authorship and other matters should be clarified with the host Laboratory.

4.1.4 Potential impact

The ERINHA research infrastructure is in line with the European Strategic Forum on Research which has recognised the importance and benefits of Pan-European research infrastructures. The considerable work carried out in the ERINHA project (preparatory phase) has paved the way for the creation of the ERINHA research infrastructure which was based on the following actions:

- Major upgrading of existing BSL4 laboratories;
- Building of new BSL4 structures;
- Building support infrastructures;
- Organising user access to the infrastructure;
- Creating pan-European coordination capacities.

As implementation of a new research infrastructure needs to solve critical questions which mainly concern reaching the legal, financial, political, technical, and coordination maturity. The Preparatory Phase of the ERINHA project represented the first step in this process, making significant and major progress on each of these levels:

- *Reaching the financial and political maturity*

The Preparatory Phase sought to define the strategy for BSL4 upgrades and new BSL4 laboratories construction. Specific tasks aimed at identifying the best relevant sites to build BLS4 upgrades and new BSL4 laboratories in view of socio-economic impacts, integration of the new BSL4 areas in the fabric of the existing BSL4 laboratories, localisation of pandemic threats in Europe, and national entities financial/political support from these entities identified that would be willing to support construction and operation phases of BSL4 areas.
The preparatory phase of ERINHA RI did not highlight an immediate need for building new BSL4 laboratories. However, considering the analysis of the geographical repartition of existing European BSL4 capacities, combined with a potential endemic issue of the Crimee-Congo hemorrhagic fever (only RG4 pathogen identified as a public health challenge in Europe), Eastern Europe has been identified as a pertinent candidate for potential new BSL4 capacities building. A list of the most relevant Eastern European countries has then been established on the basis of specific science-based and social-economic indicators (population size, gross domestic product, sector of performance, number of doctorate students etc..)

The preparatory phase also aimed to obtain political and financial commitments signed by national and European decision-making entities for supporting financial construction and operation is of main strategic importance for the project, as implementation and long-term sustainability of the infrastructure is almost impossible without these support. While contacts with decision-making entities have been established and a business plan as well as financial plan have been produced. However, due to the Due to the specific sensitivity associated with high containment facilities, official commitment was not yet obtained during the Preparatory Phase and will therefore become a main objective of the Interim Phase.

- *Reaching the technical maturity*

The Preparatory Phase was also dedicated to the elaboration of study design for the new BSL4 areas or laboratories during Preparatory Phase. During the ERINHA Preparatory Phase there have been no requests made to ERINHA from the European Member states for help in the planning of any new BSL-4s. Therefore one focus of ERINHA preparatory phase became the production of generic tools and guidance that could be used in the future. User Requirements Specification for a new lab, cost of a new BSL-4 facility, Sample building designs and costs for three different types of generic BSL-4 facility, have been produced in consultation with world experts in bio-containment design and engineering. These resources represent a valuable information resource held by ERINHA and a significant added value to membership of the ERINHA infrastructure for European member states who perhaps do not have extensive national biosafety networks or experienced architects of their own.

- *Reaching the legal maturity*

At the beginning of ERINHA preparatory phase all participants owning a national facility were convinced that there was a real need but most of them were not so familiar with the concept of "open access" and did not clearly perceived what would be for them the added value. These issues made difficult progress in governance structure, legal status and financial model definition even if it did not block those on other tasks.

In this context and to make progress, it was unavoidable to take time discussing and clarifying these issues and to find a consensus on the concept.
This major work was completed by March 2013 and led to the definition of a strong concept for the Pan-European BSL-4 laboratory agreed by all. This work has even gone beyond being simply a concept since it has created a community at the European level, where all BSL-4 owners are on board alongside other partners. This situation created a unique opportunity to build the expected Pan-European BSL-4 laboratory. As a demonstration of this commitment, since March 2013, the consortium has agreed on the governance, legal status and financial models for which final drafts just need to be refine before moving to the next phases.

The issue of the legal status was therefore one of the most complex aspects of the ERINHA project. A study was completed on potential legal statuses based on those existing in the 7 countries that could potentially host the ERINHA coordination structure. An unofficial vote was held to gain partners' opinion on which status they favoured. The partners voted in favour of the status of an association and the status was drafted in light of this. However, as all partners could not take part in the vote, it remains unofficial. The legal status will therefore be agreed on and formalised in the interim phase. It is noteworthy that the status of an ERIC remains a feasible and open possibility for the RI in the future.

- *Reaching the coordination maturity of the infrastructure activities*

The Preparatory Phase produced a feasible and suitable governance structure to coordinate activities at the European Level (described in WP3 results). **The governance structure has been established to ensure efficient coordination of ERINHA activities at the European level. This**

will allow the beneficiary scientific communities to exploit the new facility with the highest efficiency and in the most optimised way, to efficiently and resourcefully coordinate research and diagnosis activities within the infrastructure.
Moreover, in case of a pandemic outbreak, effective coordination will lead to an efficient control and dispatching of all activities required to face such situation.

The work carried out in the Preparatory Phase produced valuable information and recommendations for reaching standards biosecurity and biosafety management including biological resources centres, as well as training standards for operators in BSL4 areas, and to disseminate good practices within the infrastructure:
- a consensus was reached regarding training and biosafety;
- a joint ERINHA/BBMRI strategy paper on collaboration of the two infrastructures;
- all laboratories of RG4 pathogens have measures in place, such as SOPs on sample receipt, EQA for the differential diagnosis of RG4 pathogens, and are involved in diagnostics for bioterrorism. Concerning risk assessment for research experiments, several criteria were broadly applied while others were considered important by few participants. It was found that the approach to different case scenarios was diverse and that a consensus may have to be found on minimal requirements for BSL4 and non-BSL4 laboratories. It was concluded that BSL4 and BSL3 laboratories have appropriate procedures regarding biosafety and the handling of samples. However, considerable efforts may be needed to achieve a level of harmonization fitting for a joint infrastructure.
- recommendations to develop common standards on transport of samples
- an increased evidence base on biosafety using the case of TB

- *Assessing the overall organisation maturity of the ERINHA*

Finally, pilot research and diagnosis projects were performed during the last period of the Preparatory Phase (WP7). These pilot activities illustrated that the overall concept and organisation of the infrastructure are functional. The few gaps identified will be taken into account and adopted by the CCU in the next phases of ERINHA.

Beyond the direct impact the ERINHA project will achieve through the future implementation of the ERINHA infrastructure, the Preparatory Phase contributed to achieve the following potential impact:

Contribution of ERINHA to the attractiveness of the ERA

The Preparatory Phase and the following implementation of the proposed ERINHA infrastructure will certainly contribute to the European Research Area (ERA) and has actively contributed to overcoming the three main weaknesses of the concept:
- i*nsufficient funding*: The ERINHA consortium liaised with funding agencies to identify potential gaps and issues regarding access to funding. The results produced from the project will provide **policy-makers and funding agencies with valuable information to take into account the needs regarding L4-related infectious diseases and a potentially significant response in the form of a pan-European infrastructure. This is especially relevant in present context of the Ebola outbreak in which the partners have been very much involved.**

In order to continue funding the subsequent phases of ERINHA and to respond to such current needs, the ERINHA partners will submit a proposal to the current open Infrastructures call in April 2015.
- *lack of an environment to stimulate research and exploit results*: The ERINHA project has put forward a governance structure which was tested through two pilot projects. This structure has proved to be feasible. Work on access was also undertaken: for ERINHA partners without a national BSL-4 facility, the option for 'fast track' access was proposed. This could be achieved by carrying out security clearances, basic training in advance of need. Recommendations will be taken into account in the next phase to further improve the environment and exploitation of results.
- *fragmented nature of activities including dispersal of resources*: The ERINHA preparatory phase was successful in reaching consensus to harmonise procedures and identifying where such procedures still diverge. Work to further overcome this issue will continue in the Interim phase.

Boosting European competitiveness

By integrating complementary capacities within the European BSL-4 infrastructure, ERINHA will facilitate complex and comprehensive research programs able to compete with those conducted outside the EU, thus boosting European Research competitiveness. In addition, the integration of multiple BSL-4 capacities within one structure will enable to respond more effectively and efficiently to the partnership needs of Academia and Industry. Thus, a huge scientific and economic potential could be more fruitfully exploited, ranging from basic research over proof-of-concept to supporting marketing authorisations.

Contribution of ERINHA to socio-economic impacts and to Community objective of balanced territorial development

As the difficulties faced in tackling the current Ebola outbreak have illustrated, infectious disease control is one of the main challenges requiring the development of new drugs, new vaccines, and diagnostic tools. **By implementing the ERINHA infrastructure, European academics and industries will be able to meet this challenge more efficiently and more rapidly.** At the request of national authorities, ECDC, WHO and existing relevant laboratory networks, ERINHA will coordinate Europe's high containment assets to provide access to and mobilisation of services needed for a comprehensive and timely response to new and emerging health threats at both the MS and EU levels in close contact with national authorities, ECDC, WHO and existing relevant networks. Support could include investigation of pathogenic mechanisms, virus isolation and development of diagnostic tools, back-up of epidemiological and clinical surveillance and containment. This should impact the health sector in a commercial and industrial perspective (e.g. development of new drugs, finding innovating diagnosis tools), but also in the perspective of Public Health and socioeconomics (e.g. preserving human health which is an engine of the economy). Therefore, the **ERINHA project will examine opportunities during the interim Phase to exploit the potential for scientific excellence of most regions in Europe. The following infrastructure implementation, with potential building of new BSL4 laboratories in Eastern countries, will contribute to establishing a balanced territorial development.**

Scientific advancement

ERINHA will impact on scientific advancement within the EU, since the infrastructure will create a comprehensive expert environment that allows and stimulates cutting-edge research, attracts talented scientists and enables leadership in world-wide networks.

The Added Value of the Community financial support

Implementing the ERINHA infrastructure will be achieved over the coming years. After this Preparatory Phase, the interim phase will to aim to obtain agreement on the both the legal status and the host country for the coordination structure, as well as financial commitment from the member states participating in the future phases. By submitting a proposal in the upcoming Infrastructures call in April 2015, **ERINHA hopes to continue to involve of the EC, which will have a catalytic and leveraging effect on the infrastructure implementation, as during the Preparatory phase. The continued involvement of the EC will ensure the EU is at the forefront of BSL-4 infrastructure development and research activities.**

Strengthening the EU position in Global Health

The ERINHA transnational infrastructure will strengthen European capacity and visibility in the field of Global Health, in a competitive research and development environment but also in view of international responses to old and new infectious diseases, pandemic outbreaks, extreme drug resistance and other consequences of globalisation.

4.1.5 Main dissemination activities and exploitation of results

Dissemination of foreground outside the consortium was done externally using various means:

1. A specific logo and graphical chart;
2. A brochure presenting the partners and the project's goals, actions and expected results will be issued to support the dissemination activities to a wider public and policy-makers;
3. The project website displays general project information in English. All communication supports are downloadable from the site (brochures, press releases, publications, etc);
4. Participants presented the project and related results at conferences and workshops on infectious diseases in and out of Europe. Attendance to these meetings will give them the opportunity to present the consortium’s work and develop the interest of other field experts. Please see table B1 below;
5. Bulletins to inform potential stakeholders about the aim of ERINHA and progress.

Concerning management of intellectual property, the partners have respected and will continue to respect the consortium agreement. In particular, conditions for the access and use of knowledge as well as for the management of intellectual property are specified in the Consortium Agreement signed by all the partners. Concerning the use of foreground, The ERINHA participants will continue to use the results they own and ensure their use either in further research activities or for economic exploitation in accordance with their interests.

The consortium has planned to exploit the foreground in the following ways in the post-project period:

- During the Interim phase, ERINHA will continue to build on the results of the preparatory phase and pursue financial commitment from Member States and funding agencies. The results produced during the preparatory phase will indeed pave the way for an operational ERIHA research infrastructure by the 1st of January 2017. Faced with future outbreaks such as the current Ebola crisis, a pan-European research infrastructure bringing together the expertise, capacities and facilities of the entire EU in the field of highly pathogenic, would be an ideal and powerful mechanism.
- To secure additional funding, the ERINHA partners will submit a proposal in the framework of the 2015 Infrastructures call, building on the partnership formed in the framework of the preparatory phase.
- Significant information regarding the progress of the interim phase will be updated on the website.

4.1.6 Address of project public website and relevant contact details

A full list of the beneficiaries and main contacts is presented below:

INSERM	Dr. Hervé Raoul
INSERM	Dr. Caroline Carbonnelle
AGES	Prof. Dr. Franz Allerberger
MUG	Prof. Dr. Kurt Zatloukal
ITM	Bruno Gryseels
FLI	Prof. Dr. Martin H. Groschup
PUM	Prof. Dr. Stephan Becker
BNI	Prof. Dr. Stephan Günther
RKI	Dr. Andreas Kurth
HPI	Dr Dionyssios Sgouras
INMI	Giuseppe Ippolito
INMI	Antonino Di Caro
SVB	Dr Maria Nica
SMURB	Eva Mitrová
FoHmi	Ali Mirazimi
UK	Dr Tim Brooks
UK	Dr Amanda Semper
INSA	Dra. Sofia Núncio
HU	Koray Ergunay
IT	Florence Chung/Sinéad Quigley
ISCIII	Dr. Rafael De Andres-Medina
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