PROJECT FINAL REPORT

Biobanking and Biomolecular Resources Research Infrastructure

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Project acronym: BBMRI

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Name of the scientific representative of the project's co-ordinator[1], Title and Organization:

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EXECUTIVE SUMMARY
Grant Agreement: 212111
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Human biological samples, such as blood, tissue or DNA, plus associated clinical and research data, as well as biomolecular research tools are key resources in unravelling genetic and environmental factors underlying diseases and influencing their outcome. Biological samples are used in high-throughput techniques which allow examination of changes in the genome, transcriptome, proteome, or metabolome. Insights derived from these are expected to assist with the development of new diagnostic, prognostic, and therapeutic tools. Consequently, biological resources are considered as the essential raw material for the advancement of biotechnology, human health and research and development in life sciences. This was the landscape where the pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) prepared to integrate the existing quality controlled biobanks, biomolecular resources, and enabling technologies into a novel pan-European biomedical Research Infrastructure, and guided the way towards establishment of high quality *de novo* European biobanks adhering to the recommendations drafted by BBMRI.

The European Commission (EC) has granted 5 Mio € funding (2008-2011) to the Preparatory Phase of BBMRI (www.bbmri.eu) to conceptualise and secure funding for the construction of the European Research Infrastructure for biobanking and biomolecular resources. Management of BBMRI during the Preparatory Phase was divided between the Medical University of Graz (AT) and the University of Turku (FI). This has been a sizeable task as BBMRI comprised 54 Participants and 224 Associated Organizations (as of 17/02/2011) from 33 countries.

The objectives addressed by the BBMRI consortium during the Preparatory Phase were to develop a plan to integrate existing quality controlled biobanks, biomolecular resources and enabling technologies into a novel pan-European biomedical Research Infrastructure (BBMRI-ERIC). BBMRI not only provided a comprehensive source of information about existing biological sample collections and biomolecular resources, but also created an operational concept for a sustainable infrastructure, delivered standard operational procedures (SOPs) for future biobanking and codes of conduct for European biobanks. A particular challenge in the future BBMRI-ERIC is the generation of an IT-infrastructure capable of linking the existing biobank-derived genetic and molecular phenotyping data with data from clinical phenotyping and health-related registries.

BBMRI is in the process of submitting its application to the European Commission for a legal status under the ERIC regulation, with an expected start date at the end of 2011. BBMRI-ERIC foresees headquarters (central coordination) in Graz, Austria, responsible for coordination of the activities of National Nodes/Hubs established in participating countries. The Headquarter will provide a common access portal to resources available in Member States as well as appropriate facilities, support and expertise. The National Hubs (see http://www.bbmri.eu/index.php/national-hubs) are also established under the ERIC legal entity and will link the national scientific community (e.g., universities, hospitals, research institutions, and resource centres) to BBMRI-ERIC.

A SUMMARY DESCRIPTION OF PROJECT CONTEXT AND OBJECTIVES (not exceeding 4 pages).

The project content and the action plan of the Preparatory Phase (PP) of BBMRI were defined in the Grant Agreement with the EC. The seven Work Packages (WP) of BBMRI were responsible for the specific deliverables aimed at integrating the existing quality controlled biobanks, biomolecular resources and enabling technologies into a novel pan-European biomedical research infrastructure. The operational concept of BBMRI (Business Plan) for the next stage has been developed based on the experience gained during the preparatory phase. From the beginning it was decided that the national nature of biobanks and related databases requires a distributed structure for BBMRI. The hub and spoke structure adopted has been the basis for cataloguing European population and clinical biobanks, and for generating technological platforms for biological resources, high-throughput techniques, bioinformatics and other IT tools for data analysis. Such platforms also provided a model ("Expert Centres") for collaboration between academia and industry.

The key objectives during the Preparatory Phase of BBMRI were:

1. To provide the scientific, technical, ethical and legal basis for the construction and operation of BBMRI

2. To define the interaction and terms and conditions of members and Participants with BBMRI and securing compliance with sample and data sources

3. To negotiate contracts between BBMRI and Member States as well as funding organizations to solidify the long-term funding for this European infrastructure

4. To agree on IP and data-sharing policies for users and Associated Organizations

5. To incorporate an appropriate legal structure (BBMRI-ERIC)

Biobanks form a foundation to modern biomedical research, better understanding of disease mechanisms and development of novel therapies and diagnostic tools for common diseases. This is particularly important for the grand societal challenges regarding the health of the ageing population, but also to better understanding the role of environment and nutrition to human health. It must be emphasized that in global context, the long tradition of collecting and storing human biospecimens and associated data (i.e. biobanking) is an unquestionable European strength. If biobanks receive adequate support and are able to solve the technical issues and maintain societal acceptance, a pan-European biobanking and biomolecular resouces Research Infrastructure (BBMRI established under ERIC regulation) will become a major asset in the global competition in addressing the heath-related grand challenges.

Obviously, biobanks and related molecular and clinical data form the basis for drug development in the future. It is well known that currently used disease entities are heterogeneous in their molecular etiology. Under the new concept "personalized medicine" biobank-derived material will be used to develop new diagnostic tools to identify disease subgroups and new therapeutic agents will be developed to specifically target such disease subgroups. Both SME's and big pharma are currently very interested in the new analytical and diagnostic technologies in various "-omics" fields, identification of new drug targets and development of new therapeutic approaches. This will require efficient collaboration between biobanks, academia, and industry. BBMRI is developing the innovative concept of "Expert Centres" which provide a novel solution to such public private partnerships. Concrete examples of targeted personalized medicine already exist e.g. in the field of selecting anticancer therapies through molecular phenotyping of the tumours for their receptor profile.

This was the scientific background where this very large project of 54 partners and – in the end – more than 220 Associated Organizations prepared to finalize its Preparatory Phase. This put a lot of strain to management and governance. The WP structure of BBMRI (Table 1.) has clearly helped to structure the different key issues seeking solutions. The success is demonstrated by the fact that most national BBMRI Nodes (BBMRI.nl, BBMRI.se, BBMRI.fi, BBMRI.no, BBMRI.it, BBMRI.at) seem to have adopted similar WP-based organizations than BBMRI. Different WP's have been coordinated and directed by an Executive Management (Steering Committee, Coordinator and Executive Manager), which has received support from a Governance Council and a Scientific and Ethical Advisory Board (SEAB), and received input from the Stakeholder Forum.

Table 1. BBMRI Work Packages (WP's) and governance structure and leaders/chairs

Work Packages (WP)	**Leader(s)**
WP1: Management and Coordination	K. Zatloukal (AT), E. Vuorio (FI)
WP2: Population-based Biobanks	L. Peltonen / M. Perola (FI/UK), A. Metspalu (EE)
WP3: Disease-orientated Biobanks	E. Wichmann, (DE), T. Meitinger (DE)
WP4: Biomolecular Resources and Molecular Tools	U. Landegren (SE), M. Taussig (UK)
WP5: Database harmonisation and IT-infrastructure	J-E. Litton (SE), M. Fransson (SE)
WP6: Ethical, Legal and Societal Issues	A. Chambon-Thomsen (FR)
WP7: Funding and Financing	G. Dagher (FR), J. Ridder (NL) C. Brechot (FR)
Governance Council Chair	L. Peltonen (FI/UK) / E. Vuorio (FI) / G-J. van Ommen (NL)
Scientific and Ethical Advisory Board Chair	G-J. van Ommen (NL)
Coordination Board Chair	K. Zatloukal (AT)
Stakeholder Forum Chair	M. Griffith (IR)

The major technical achievements of BBMRI-PP are summarized in the 78-page draft Business Plan, which is currently being discussed by representatives of Ministries from more than 20 Member States and associated states. Among the major achievements is a catalogue of existing major population-based and clinical (or disease-orientated) biobanks in Europe. Based on questionnaires designed in collaboration with the Public Population Project in Genomics (P3G) a

wealth of information has been gathered on the type and quality of already collected samples and data, standardisation of procedures, IT solutions as well as governance structure, funding, and legal and ethical issues. Furthermore, a review has been performed on existing resources for affinity reagents and other biomolecular resources as analytical tools applicable to biobanking.

Another great technical advantage of the PP scheme was the concept towards a common IT-infrastructure of BBMRI-ERIC, which will consist of a network using the hub and spoke topology to connect the different National Nodes, which are geographically spread through Europe. The planned IT-infrastructure employing a federated database architecture will integrate the complex network of hubs, members and associated partners in the Implementation Phase of the BBMRI.

During the operation of BBMRI-PP various types of analyses on the ethical, legal and societal issues (ELSI) of the infrastructure have resulted in the design of 1) a coordinated ethical review process, 2) a data protection policy for the cross border data transfer issues, both central to the governance of the infrastructure, and 3) in the development of original tools that will facilitate harmonization. The tools designed consist of a legal WIKI+ platform for disseminating validated existing legal documents in use in EU countries, a web based information tool on legal requirements for exchanging biological samples, indicators to promote transparent sharing of bioresources and an ELSI transversal platform. This work will be of great value to future BBMRI operations under ERIC legislation.

The strategic work of BBMRI-PP had several dimensions and can be looked upon from very different perspectives. On one hand, BBMRI will operate as a bridge between sample donors (either patients or healthy individuals) and scientists performing biomedical research in academic or pharmaceutical settings. It will also operate as a firewall preventing certain types of sensitive information from flowing inappropriately between donors and researchers. BBMRI has and will be responsibilities toward patients and toward researchers. In addition, it will be responsible towards researchers to provide the highest possible quality of biospecimens and data to support research excellence.

Concerning the strengths during the BBMRI-PP, the scheme has clearly been beneficial to bringing unforeseen cohesion to the European biobanking scene: an increasing number of biobanks from an increasing number of EU Member States and associated states have applied for associate member status in BBMRI-PP (and most have received it, too). The WP structure of BBMRI has also helped to establish national biobanking networks and to structure their activities. Also governments and Ministries have recognized the importance of this process and several European countries have made huge financial commitments towards national biobanking activities.

Another major advantage of the PP scheme has been that it has brought the different (and partly overlapping) infrastructure communities into better contact with each other which has turned out to be very beneficial.

The main weakness of the PP scheme in BBMRI perspective was overly optimistic estimation (originally two years) of the timeline to organize and connect biobanks across the national borders and committed Members States towards the Construction Phase. This resulted in extension of BBMRI-PP (through two amendments) by a total of 9 months.

The main bottlenecks identified in the transition from BBMRI-PP to the Implementation Phase (BBMRI-ERIC) are:

(1) Divergent views of participating scientists Member State representatives on the determination of joint budget, contribution of funds towards joint budget, and voting rights.

(2) The heterogeneity of the status of current European biobanks. Biobanks are typically linked to hospitals, universities, different research performing institutions, and national health institutes. The ownership of the biobanked samples is sometimes unclear and their use for biomedical research is governed by consent forms, national ethical review systems, and national legislation, which differ from one country to another.

(3) Also the molecular, clinical and life-style data attached to biobanked samples are in heterogenous formats, usually gathered in the respective national languages. Therefore, interoperability of the current data is a major challenge.

(4) The ERIC instrument itself may not be the best possible tool for infrastructure containing sensitive human derived biological samples and data because of the requirement for open access policy that must be balanced with data protection, consent and national legislation.

Not only are the basic principles of BBMRI-ERIC largely agreed upon, but an increasing number of current BBMRI members have contributed to the establishment of a National Node for biobanking and biomolecular resource structures in their countries as defined in the BBMRI-ERIC statutes and described in the BBMRI-ERIC Business Plan. Material to the existing biobanks comes not only from nationally funded projects but also from the several new collaborative projects funded under FP6 and FP7. Many Member States have also granted substantial funding to national biobank activities as summarized in the Business Plan.

Currently, BBMRI is in the process of submitting its application to the European Commission for a legal status under the ERIC regulation with an expected start date at the end of 2011. When the Preparatory Phase of BBMRI came to its end on January 31, 2011, also the Governance and Management Structures which were based on the Grant Agreement came to end. In order to guarantee a smooth transition towards BBMRI-ERIC, the Steering Committee of BBMRI continues to support the further implementation of BBMRI-ERIC on a voluntary basis until the Memorandum of Understanding (MoU) for the BBMRI-ERIC application is signed by the interested Member States. Furthermore, an interim Assembly of Members will be established by those countries that have signed a MoU in order to respond to possible requests of the Commission in the context of the evaluation of the BBMRI-ERIC application and to support the implementation of BBMRI-ERIC until the final governance structure is established. The BBMRI website will remain active informing about the latest developments.

A DESCRIPTION OF THE MAIN S&T RESULTS/FOREGROUNDS

(not exceeding 25 pages)#

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The following section presents a summary of the main results and progress towards objectives of the Work Packages (2-7) during the operation of the preparatory phase of BBMRI. More detailed description of the deliverables is available in Deliverable reports in the attached BBMRI Periodic Report.

BBMRI-PP has focused on technical, legal, governance, and financial issues that have to be solved to construct the necessary infrastructure from existing biobanks, resources and technologies, complemented with innovative components and properly embedded into European scientific, ethical, legal, and societal frameworks. One activity of the BBMRI-PP has been to develop the plan to integrate existing quality controlled biobanks, biomolecular resources, and enabling technologies into a pan-European biomedical Research Infrastructure. This plan will then be implemented by the Biobanking and BioMolecular Research Infrastructure, European Research Infrastructure Consortium (BBMRI-ERIC) in the next phase.

BBMRI-PP focused on existing sample collections, resources, technologies, and expertise, which have been specifically complemented with innovative components. In particular, BBMRI comprised

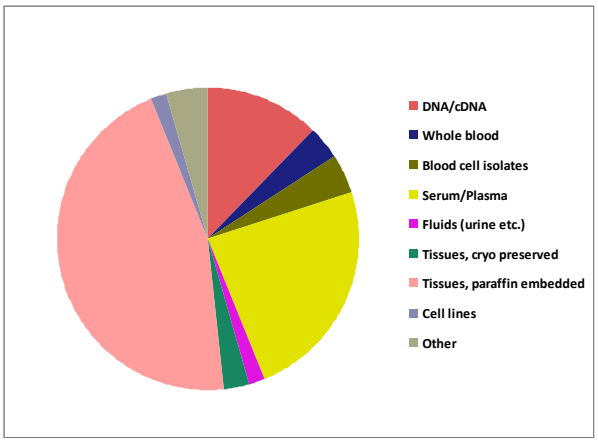
i) all major population-based and clinical biobanks,
ii) biomolecular resources, such as collections of antibodies and other affinity binders and a variety of molecular tools to decipher protein interactions and function,
iii) bio-computing and sample storage infrastructure,
iv) scientific, technical as well as ethical and legal expertise.

All resources are integrated into a pan-European distributed hub and spoke structure and are properly embedded into European scientific, ethical, legal, and societal frameworks. Specific tasks during the BBMRI-PP comprised the preparation of an inventory of existing resources, achieving interoperability by implementation of common standards and access rules, establishment of incentives for resource providers, and to develop solutions for international exchange of biological samples and data which properly consider the heterogeneity of pertinent national legislation and ethical principles.

Catalogues of the European biobanks

An inventory has been prepared of existing major population-based and clinical (or disease-orientated) biobanks in Europe (Figure 1). Based on questionnaires designed in collaboration with the Public Population Project in Genomics (P^3G) information has been collected on type and quality of collected samples and data, standardisation of procedures, IT solutions as well as governance structure, funding, and legal and ethical issues. Detailed data obtained from the survey can be accessed through a searchable catalogue at the BBMRI website (www.bbmri.eu/index.php/catalog-of-european-biobanks).

Figure 1: Summary of the nature of the 20 million human biological samples in Europe catalogued by WP2 and WP3



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Standard Operation Procedures (SOPs) that have been used in biobanks and related research projects have been evaluated in close collaboration of WP2 (population-based biobanks) and WP3 (clinical and disease-oriented biobanks). The review showed that existing biobanks involved in BBMRI-PP have been using several different standards, SOPs, and internal guidelines. Recently, several official guidelines (NCI, OECD, ISBER, IARC, etc.) with quality criteria for storage, retrieval, and transfer of biological samples have become available. WP2 and WP3 have worked towards establishment of common detailed SOPs essential for the future operation of the BBMRI. These are based on the OECD and IARC guidelines and the work carried out by Molecular Medicine Ireland. BBMRI has accepted this as a first version of the BBMRI Laboratory Manual (E. Wichmann 2010; Need for Guidelines – Editorial).

In addition, together with the BBMRI management team (WP1), WP2 and WP3 had created the first version of the step by step access policy to human biological samples and associated data to be implemented in the future BBMRI-ERIC. It will provide access to the collections of BBMRI-ERIC Partner Biobanks and Biomolecular Resources, their expertise and services by providing:

- *Free access to documents, Standard Operating Procedures (SOP's) and best practices developed by BBMRI-ERIC,*
- *Open access to published results and data published in coordination with partners of BBMRI-ERIC, in accordance with the Berlin Declaration (2003).*
- *Fair access to samples and related clinical data. Fair access is primarily based on international scientific peer review and ethical review of the research project proposal.*

Access to human biological samples and identifiable medical data is, however, governed by other restrictions; the proposed research has to be compliant with a variety of ethical and legal requirements, such as the Oviedo Convention (ETS 164), the Helsinki Declaration, the OECD Guidelines for Human Biobanks and Genetic Research Databases (HBGRD) (OECD, 2009) or the Directive 95/46/EC on the Protection of Personal Data. Internationally agreed key principles relevant to the operation of BBMRI-ERIC are that research on human biological samples and identifiable medical data require informed consent from the sample and data donor, and approval

by an ethical review board. Both HBGRD and the Helsinki Declaration foresee that in case informed consent cannot be obtained for practical or scientific reasons, ethical review boards can provide a waiver for informed consent. Alternatively, anonymization would also waive the requirement for informed consent. Therefore, access procedures of BBMRI-ERIC to human biological samples and medical data have to consider the following principles:

- No information related to individuals and their samples can be made accessible by internet; only access to coded and aggregated data can be provided through the BBMRI-ERIC web-portal,
- Access to samples and medical data can only be provided in the context of a specific research project in accordance with the terms of the consent given by the donor,
- The research project has to meet the criteria of scientific excellence (based on scientific review) and has be approved by a ethical review board, and
- All procedure has to protect the privacy of sample donors.

The first step in the access procedure is to register at the BBMRI-ERIC website (Figure 2). A web-based query tool will allow obtaining an overview on available samples and associated medical data. The information provided relates to aggregated data that are sufficiently specific to define a research project. In case required samples, data, or resources could be identified, an access fee will be charged for further steps supported by a project manager at the Executive Management Office and the National Coordinators. In coordination with BBMRI-ERIC partner biobanks a research proposal will be drafted for scientific and ethical review. The ethical review by BBMRI-ERIC Ethical Review Board (ERB) is obligatory for all projects to obtain access to human biological samples or medical data through BBMRI-ERIC. It does not replace the requirement for ethical review at biobank institutions but should support the local ethical approval committees in their decision making process and contribute to the harmonisation of ethical requirements throughout Europe, thereby substantially improving efficacy of national/local review processes, particularly in the context of multinational studies. Scientific review by the BBMRI-ERIC Scientific Review Board (SRB) is not required for projects that have already undergone a qualified peer review process (e.g., EU-funded projects or projects funded by national funding agencies). After positive review a Material Transfer Agreement (MTA), specifying the terms of access (e.g., scientific collaboration, cost recovery for local biobanks, intellectual property rights, reporting requirements, and confidentiality) has to be signed between requestor and local biobanks. Optional BBMRI research services, such as ethical, regulatory, and legal advice, data collection and transportation, sample processing, data analysis, and planning of prospective cohorts can be utilized and specified on a project by project basis. Noteworthy, the establishment of high quality research collaboration is the preferred format for access. There is no obligation for BBMRI-ERIC Partner biobanks to provide access to a specific research project if the terms are not acceptable.

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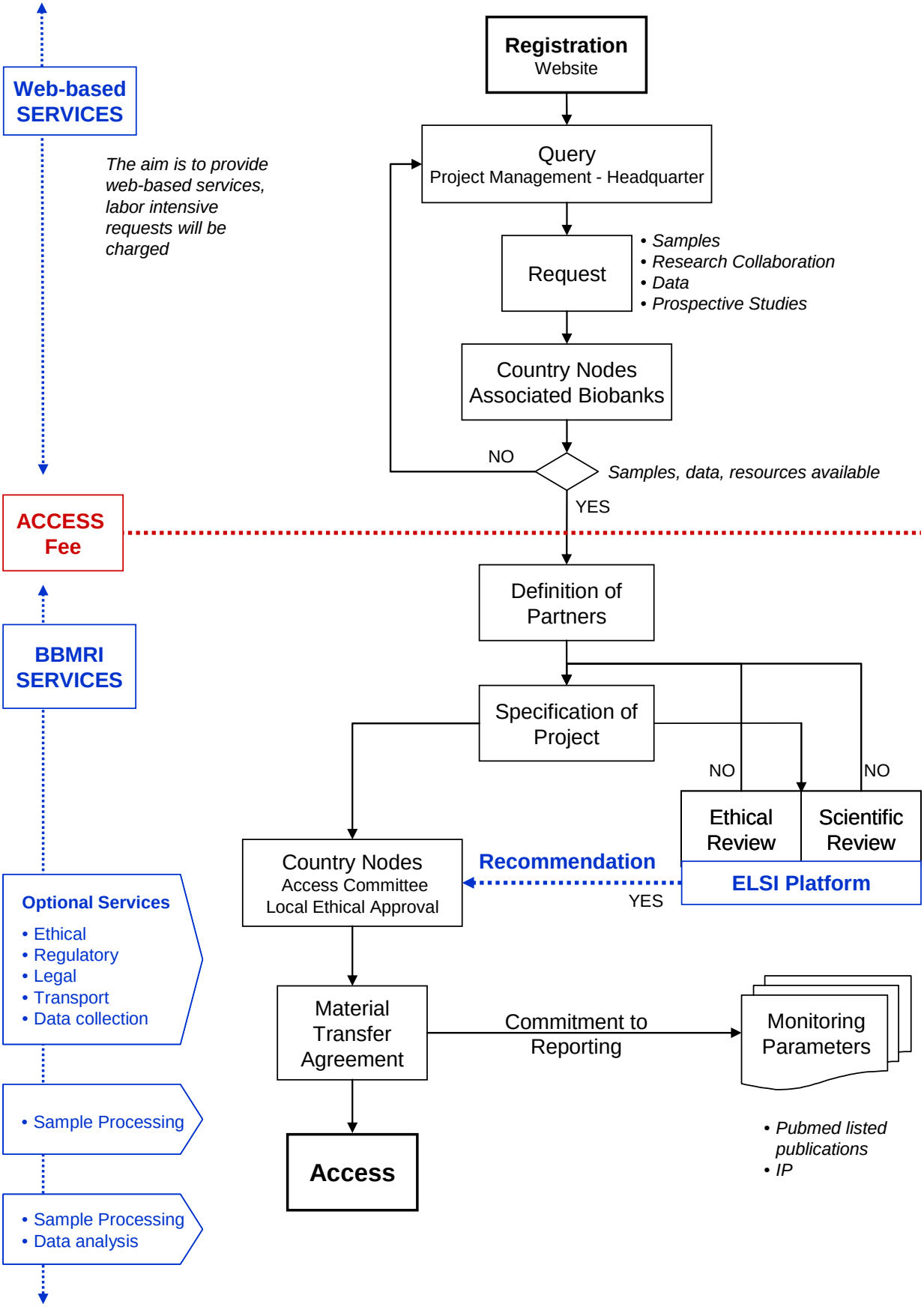
Figure 2. Access to human biological samples and associated data



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Biomolecular Tools and Resources

Biobanks, molecular technologies, and reagents for molecular analyses represent a trinity. For optimal function it is necessary to promote and coordinate excellence in all these areas in order to take full advantage of opportunities for studies of patient sample collections. An overriding aim for BBMRI is therefore to combine high-quality samples, technologies, reagents and advanced expertise, and to coordinate these resources for successful research that can be promptly translated to clinical and industrial utility. At the heart of all these efforts are the ambitions to (i) improve mechanistic understanding of diseases, (ii) define and validate diagnostic markers, and (iii) identify new drug targets.

BBMRI WP4 had as a main purpose to ensure that technologies and reagents are available to make optimal use of patient sample collections. The scope of this aim is larger than that, however, in that an even broader range of biomolecular resources, also ones not directly applicable for biobank-related research, are being considered. These include collections of antibodies and other affinity binders, Open Reading Frame clone collections, siRNA libraries, proteins, cellular resources, etc. as well as the enabling technologies and high-throughput analysis platforms and molecular tools to decipher gene, protein and metabolite functions and their interactions. In the BBMRI hub and spoke structure, BBMRI members represent the key providers of resources and technologies, to each other and to the academic and industrial community. The associated partners and subcontractors provide resources such as services, data, samples, and materials.

The first step to review existing European technology resources for advanced molecular procedures for detection of nucleic acids, protein and metabolites in large series of biobanked samples was to make an inventory. In collaboration with the P3G consortia, WP4 has created a questionnaire to gather information about resources for affinity binding reagents (antibodies and others) for detection of human proteins and plans for implementation of these resources in the construction of BBMRI-ERIC. The questionnaire has been distributed among BBMRI Participants and Associated Organizations. The questionnaire also included questions about additional biomolecular resources and enabling technologies for detection of nucleic acids, protein and metabolites in large series of biobanked samples. Envisaged biomolecular resources included those for the routine analysis of DNA, RNA, protein, metabolites, antibodies, and infectious agents in biobanked samples. Participants were asked to indicate which methods and techniques were used for each type of sample and whether the analysis was available as a service. The results of the questionnaire are available from the Catalogue of European Biobanks (www.bbmri.eu/index.php/catalog-of-european-biobanks).

During the PP, WP4 has produced several other reports or websites, which cover different aspects of resources and technologies available for biobanking. One of the tasks for WP4 was to review existing European resources of affinity binding reagents - mainly antibodies but also other molecular binders - by identifying centres willing to place reagents in the public domain, inventorying those reagents available and assessing the level of coverage of the relevant proteome (e.g. plasma, cancer) for application in biobanked samples. The reagents under review

are primarily monoclonal and polyclonal antibodies, which constitute the majority, together with a more limited but rapidly growing repertoire of recombinant antibody fragments (scFv), single domain binders derived from camelids, and some "alternative" non-antibody related molecules engineered on different scaffolds. Information on current resources was obtained largely through the ProteomeBinders consortium (www.proteomebinders.org), representing the leading academic centres of binder production in Europe. Where appropriate the report also draws attention to the suitability of the reagents for biobank sample analysis in high throughput, e.g. using array based systems for biomarker analysis in plasma samples and tissue extracts

A review has been performed on existing resources for affinity reagents and other biomolecular resources as analytical tools applicable to biobanking and biomedical research. This has led to a new community standard of affinity reagents (MIAPAR), designed to tackle the problems of scattered information and imprecise descriptions and to facilitate database implementation. The idea was to link European sources of antibodies and other relevant molecules into a database and ensure adoption of a common standard ontology and controlled vocabulary for description of binders and binding events. A rationale for cataloguing information on binding reagents is that the current sources are highly scattered and the description of reagent properties and applications is often imprecise and uneven. This documentation issue has led to a corresponding need for the unambiguous description of affinity reagents. As part of this work, WP4 are therefore defining minimum standards for description of affinity reagents, applicable both to publications as well as databases. Databases, standards and ontologies provide key tools for facilitating European cooperation in the area of affinity reagents.

In addition, a new database for molecular methods - The Molecular Methods Database (MolMeth) (www.molmeth.org) - has been established, providing best practice based protocols for molecular analyses of different types of samples. The original aim was to create a publicly accessible database for technologies and methods, including standard methods and data storage, for analysis of DNA, proteins and metabolites, applicable to biobanked samples. The collection and storage of biological samples should be informed by qualified insights into the methods that will be used to investigate the samples. In general, samples are collected with the intention of being used over many years, whereas technologies for analysis can be expected to improve rapidly and radically. It is therefore of great importance that users of biobanked material can promptly and continuously access new, promising techniques and connect older biobank material to the techniques used at the time the samples were collected. Such methods should be standardised, in order to permit coordination of separate research efforts and meta-studies involving distinct investigations involving different sample collections.

The MolMeth has been open to the research community since 2009 and is public, but an individual supplying a protocol can choose to limit access to defined groups of users as needed. All public entries in the database are subject to manual curation by members of WP4. Submitted protocols consist of a number of resources linked together rather than a flat file with all information. New protocols can be created by combining existing and new parts, rather than writing from scratch. This ensures consistency and saves time when making changes to a resource as all protocols become updated automatically. MolMeth also includes resources such as information about materials, contact data and literature references, which are always defined as

their own objects before being incorporated into a protocol. The database has 'help' and 'advanced search' functions. All components in MolMeth are based on Open Source projects ensuring the sustainability of the database. As of January 2011, MolMeth contains over 200 stand alone protocols, with more in the pipeline (under manual curation). It has being selected as the SOP and protocol repository by several EU funded projects (including EuroKup, Affinomics, BILS, and Emerald).

Even though MolMeth is functional and open to the public, it is still under active development to add new functionalities requested by the user community including converting MolMeth into a journal and incorporation of user community feedback online forms. Another further development is of cross-links to other relevant databases e.g. ProteinBinders, IntAct, and also to scientific publications. During the BBMRI Implementation Phase, stronger connections to ISO- and GxP-standards will be created to add extra confidence in the protocols in the database.

An important effort of WP4 has been to establish a publicly accessible, common web-based portal as a centralised information site for European technology resources and platforms serving the major biobanks. The portal is functional and available at BBMRI website (www.bbmri-wp4.eu/resources). It includes links to inventories of available binder reagent resources and molecular technologies for interrogating biobank samples at the DNA, protein and metabolite levels. The infrastructure of the portal is built entirely with open source components, thus securing a sustainable future development. The whole system is driven by a Content Management System (CMS), i.e. the collection of procedures used to manage workflow in a collaborative environment. These procedures can be manual or computer-based. They are designed to allow for a large number of people to "contribute to and share stored data, aid in easy storage and retrieval of data, improve the ease of report writing and improve communication between users" (definition from Wikipedia). Employing a system with a large community of developers and users also makes it easy to recruit personnel for the future maintenance and continuous updates of the portal.

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Database management, biocomputing and IT interoperability

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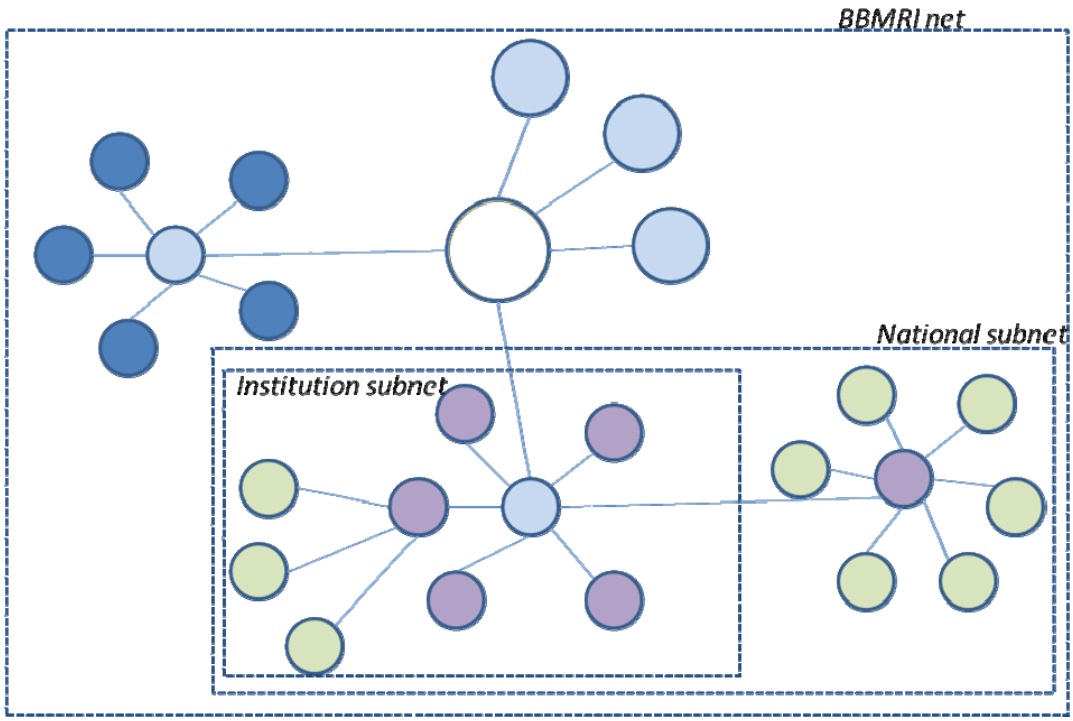
During the BBMRI-PP, the WP5 planned and coordinated the interoperability of the existing biological databases of biobanks. Based on the planning work done during the PP, the IT-infrastructure of BBMRI-ERIC will be created and will consist of a network using the hub-and-spoke topology to connect the different nodes, which are geographically spread through Europe. Major nodes act as hubs, and may for instance comprise a specific region or an entire nation. Local biobanks constituting the end-nodes will be connected via the national or regional nodes. Information harmonization will primarily be utilized by a minimum set of data attributes, which are assumed to be achievable from all biobank collections. Use of the system for data discovery will be the first step towards complete data federation. Initially, exchange of source data may be possible by providing appropriate contact information to responsible authorities.

WP5 has created the necessary IT-concepts, architectural components, and prototypical solutions for an adequate and effective support of this network. The optimal solution will be a federated network of centres established in most, if not all, European Member States, and the topology of

BBMRI will be a distributed hub structure in which the hubs coordinate activities, including collection, exchange and analysis of samples and data for the major domains (Figure 3).

Figure 3. The distributed hub structure of the IT solution for BBMRI. Biobanks, biomolecular re-sources and technology centres are members of BBMRI and connected to their specific hub.



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Use cases and key requirements have been collected and are available as a result of BBMRI-PP. Furthermore, minimal data sets, service concepts and the schema architecture have been defined. The federated database system will enable searching for interesting and comparable material across European Biobanks. Considering the multilingualism of Europe, an online multilingual Biobank terminology system and management environment are being developed to be eventually transferred to a ConceptWiki platform. This will be a major step towards true end-user interoperability, for the first time systematically lowering the language barrier between descriptions of cross-European biobanks.

Based on the results of BBMRI-PP, the IT structure for the Implementation Phase of BBMRI can be developed including:

- Assure confidentiality of donors
- Use state-of-the art open-source frameworks and web technologies
- Use state-of-the art concepts for semantic integration, integrating the terminologies/ ontologies to be further developed by the ConceptWiki project
- Use an agile and user-centred development process, providing maximum support for researchers
- Grant flexibility in terms of biobank content and schema handling

- Grant extensibility in terms of additional participants and new data and information
- Grant efficiency in terms of a priori and a posteriori data harmonization and query processing
- Keep efforts low for biobanks willing to participate in the federation

BBMRI has collaborated and will continue to collaborate closely with other biobanking/health infrastructure initiatives (such as IMI, epSOS and HEALTH.2010.1.1-1: Harmonisation of phenotyping and biosampling for human large-scale research biobanks), the Gen2Phen EU-project and the DataShaper project to reach interoperability of biobanks, both at the concept- and at the sample character (comparability) level.

The most significant outcome of the BBMRI-PP WP5 has been the development and deployment of a portal system and the development of an integration prototype. The portal system already comprises services for authentication and management of user accounts for identification of biobanks, and for the management of metadata. The integration prototype is already connected to test-instances of existing biobank management systems and provides a service interface for the creation, update, and querying of a materialized view. These developments can be used as a nucleus for a service-oriented integration architecture, which is supporting high adaptability and agile development of components. Core services have been designed and implemented and can be further elaborated into a comprehensive integration architecture. Additional services will comprise connection and registration services for the component systems, services for schema integration and terminology mapping, integration services for virtual and secure access of component systems in order to build and query materialized views with regard to semantic integration, as well as services for caching and indexing. The topology of the solution is hub and spokes. Hubs collect and integrate data, but can also provide a data connection service. This results in cascading hubs and spokes, connecting biobanks to regional networks, further to national hubs, and finally to a pan-European BBMRI hub. Thus, key requirements and key concepts together with a successful prototypical solution are available as a starting point for implementing BBMRI-ERIC's IT-infrastructure.
#
E-Health Portal structures and IT-based strategies are currently established to directly integrate biobanking into local and regional healthcare. There are intensive ongoing activities implementing health cards, E-health portals and biobanking into practical medicine. E-health portals will provide access to health information for patients, clinical assistants like nurses, and physicians in clinics and general practitioners, or specialists. Web-based patient health record study support systems can be implemented. Biobanking as an integral part of the workflow of the healthcare process is considered as key element to generate qualified long-term patient databases and health records.

Building on existing knowledge on both the legal and IT aspects, the BBMRI has identified cross-border data protection issues and priorities, mapped existing parallel projects and seeked to apply and customize the existing knowledge to a specific architecture for connecting biobanks. Providing access to human materials and data has to be compatible with the heterogeneous legal, ethical and societal (ELSI) landscape which have to be considered carefully in this process, and has to comply with the European Directive on Protection of Personal Data (Directive 95/46/EC).

Achieving a pan-European solution for said cross-border Data Protection (DP) issues is a prerequisite for the realization of the goal of BBMRI-PP. To address the issues in more detail, a joint working group with representatives of WP5 and WP6 was set up (the DP Group), with the remit to explore pan-European solutions for the cross-border data protection issues associated with BBMRI-EU.

Building on existing knowledge on both the legal and the IT aspects, the DP group reviewed the European legal framework for data protection in relation to (biomedical) research and scrutinized the issues triggered by the transposition of the Directive into the national laws of the Member States, mapped existing parallel projects as well as applied and customized existing knowledge to the specific architecture of BBMRI, and proposed solutions. In view of the cross border nature of the data flows within BBMRI, the proposed solutions on the common standards set by the European Union for "the protection of individuals with regard to the processing of personal data and on the free movement of such data." The proposed BBMRI Data Protection standard was then presented to expert and stakeholder audiences within and without BBMRI and subjected to public scrutiny by posting on the BBMRI-EU WIKI Legal Platform. To further test the proposed standard, the DP group identified cross-border data protection issues associated with the deliverables of the relevant WP's of BBMRI and applied the standard to the design of the data flow within the BBMRI as proposed by WP5.

Harmonising Ethical, legal and Societal issues

During the BBMRI-PP, analyses on the ethical, social and legal issues (ELSI) related to the infrastructure have resulted in the design of i) a coordinated ethical review process ii) a data protection policy for the cross border data transfer issues, both central to the governance of the infrastructure, and iii) in the development of original tools that will facilitate harmonization. This strategy was based on a conceptual analysis on ethics related policies for biobanks and biomolecular resources, an analysis of national ethics committees opinions in this domain, and a pilot study (based on research with focus-groups and in cooperation with the 2010 Eurobarometer) on the public perception of biobanks in Europe (Gaskell and Gottweis, 2011).

The tools designed under ELSI work package (WP6) consist of a legal WIKI+ platform (www.bbmri.eu/index.php/wiki-legal-platform) for disseminating validated existing legal documents in use in different EU countries, a web based information tool on legal requirements for exchanging biological samples (hSERN; human sample exchange regulation navigator, www.hsern.eu), indicators to promote transparent sharing of bioresources and an ELSI transversal platform.

Given the new methodologies used in genetic research, researchers face the increase of the human samples' use as well as questions posed by their exchanges cross-borders. Currently most of the projects involve teams from various countries (within and from outside of Europe) and the exchange of samples is encouraged as an added-value for knowledge. But, most of the time, researchers face troubles in their practices of exchange as regards to legal requirements to be fulfilled. As the law cannot be seen as an obstacle to the development of sharing samples, WP6 constructed in collaboration with computer scientists and lawyers, a web-based tool to deliver

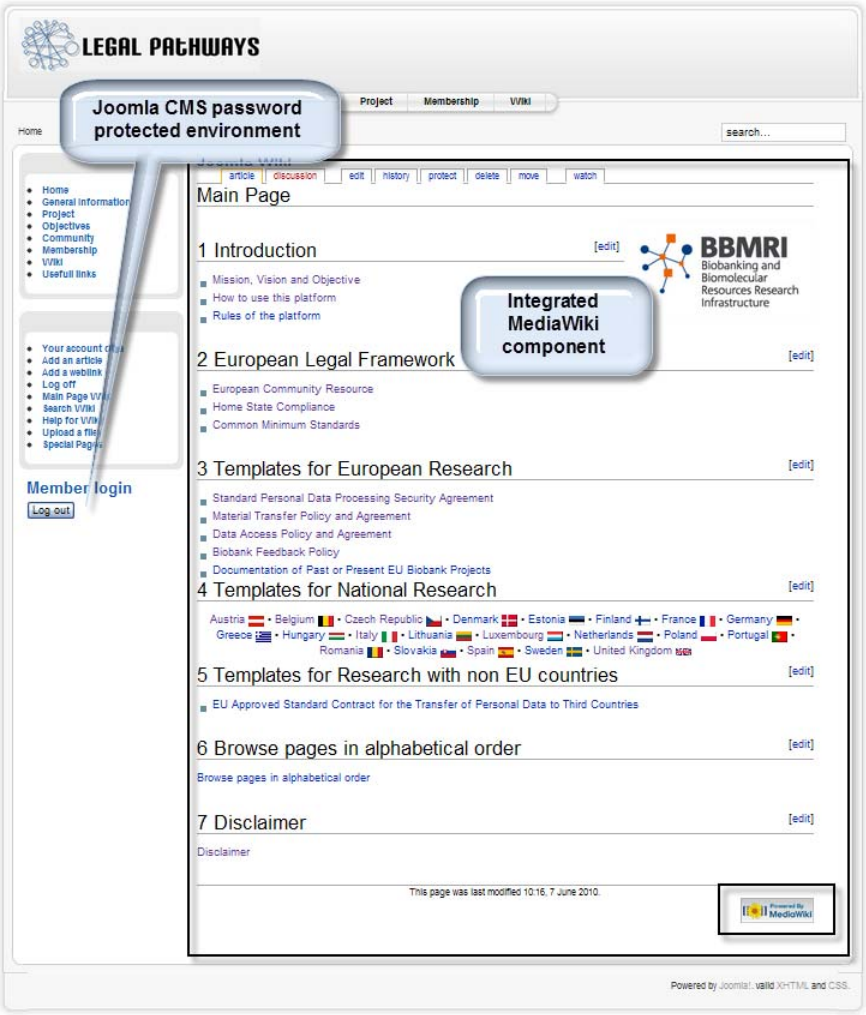
valid administrative information to researchers who aimed at exchanging human samples cross-borders. In that sense hSERN allows addressing practically a series of relevant requests, for different countries, on the issue of regulatory aspects of exchanging human biological samples across borders. This tool permits any user to get information on theoretical as well practical legal aspects, for exchanges of human biological samples for research purposes.

Open source content management system Joomla (www.joomla.org) with an integrated Media-WIKI component (www.mediawiki.org) have been used in development of the WIKI platform at www.legalpathways.eu. The rationale behind using the above-mentioned software was two-fold:

1. The content management system provides for password-secured environment for the Wiki content, by which the content is protected from undesirable editing and deletion.

2. The Media-Wiki software has been chosen for its familiarity to the potential users, as the same software is used by the Wikipedia - the largest Internet Encyclopaedia. The MediaWiki's wikitext format allows users without knowledge of XHTML or CSS to create and edit pages easily and quickly. Furthermore MediaWiki offers extensive tools to keep track of what is going on in the wiki (revision history of one specific article, discussion pages and addition of new articles).

Print screen of the Wiki platform is presented below:



The main exercise published of the public perception perspective, the new 2010 Eurobarometer Life Sciences and Biotechnology contained eight questions on biobanks. The results were released in November 2010 and have recently been published in Nature by George Gaskell and Herbert Gottweis (2011). A report from the European Commission summarized the results as follows: "While approximately one in three Europeans have heard about biobanks before, nearly one in two Europeans say they would definitely or probably participate in one, with Scandinavian countries showing the most enthusiasm. And people do not seem to have particular worries about providing certain types of information to biobanks: blood samples, tissue samples, genetic profile, medical records and lifestyle data elicit similar levels of concern. However, amongst those similar levels there are some nuances. In twelve countries, providing one's medical records provokes the most worry, and in ten countries it is the genetic profile that is most worrying. Asked about who should be responsible for protecting the public interest with regard to biobanks, we find a split between those countries opting for self-regulation (by medical doctors; researchers; public institutions such as universities or hospitals) and those opting for external regulation (ethics committees; national governments; international organizations and national data protection authorities). Broadly speaking, respondents in those countries which show higher levels of support for biobanks tend to favour external regulation more than self-regulation. In those countries where biobanks are unfamiliar, self regulation is a more popular way of guarding the public interest. On the issue of consent, almost seven in ten Europeans opt for specific – permission sought for every new piece of research; one in five for broad consent, and one in sixteen for unrestricted permission. But of those more likely to participate in the biobank, some four in ten opt for either unrestricted or broad consent."

Moving towards the BBMRI Implementation Phase, guidance and a platform on ethical and legal issues will help in reducing obstacles to cooperation and facilitate transnational transfer of resources and data, guaranteeing the patient's privacy and will as well as the quality of resources. An ELSI Representative might be set up in each National Hub to interface both with National Institutions, Biobanks and BBMRI-ERIC. The network of the representatives represents the ELSI Common Service Hub.

Funding and financing

In BBMRI-PP, 23 major European Ministries of Health or Research and representatives of Research Infrastructures or funding organizations were involved in WP7. The implication of these key players in medical research represented a unique opportunity to assess the current needs of biobanks, the existing funding schemes and to define and propose harmonized funding policies for biobanks.

As a first step, WP7 attempted to explore and summarize the current structural and operational funding of biobanks and biomolecular resources in different European countries. As human biological samples have been collected in very different settings (ranging from routine health care to specifically designed cohort studies) such information turned out to be very difficult to obtain in a comparable format. Furthermore, WP7 has collected information on the current and prospective financial needs of case-based and population-driven biobanks. WP7 had also collated pre-existing thinking, proposals and strategic programs at the level of Ministries, research institutions, patient organizations and charities in this area. In order to develop a funding concept

the impact of harmonised organization of biobanks and improved coordination of existing funding schemes has been evaluated. It is anticipated that as a consequence of better coordination of funding, a significant contribution for the construction phase can be demonstrated even without any major need for increasing the overall research expenditures. The reason for this is that current biobank projects often have to waste resources due to duplicated efforts, e.g., by independent development of IT-solutions or by independent implementation of, and therefore often different, standards and quality assurance measures. On the other hand, for full implementation of BBMRI-ERIC and for securing long-term operation, increased investments into these key resources have to be made:

- To justify this increased funding, expert opinions and reports will be produced by independent professional organizations. Specific aspects to be elaborated in these documents are the impact of BBMRI on Health and R&D,
- To improve efficacy and quality of research in the field of life sciences,
- To improve efficacy in drug discovery and development,
- For the advancement of personalized medicine,
- Economic issues, and
- Regional development.

The information collected has been used as the starting point for the development of BBMRI-ERIC long-term funding concepts, which consider the whole spectrum of funding schemes including national, European and private funding organizations as well as financing solutions provided by the EIB. BBMRI-ERIC funding concept is summarized in the BBMRI Business Plan.

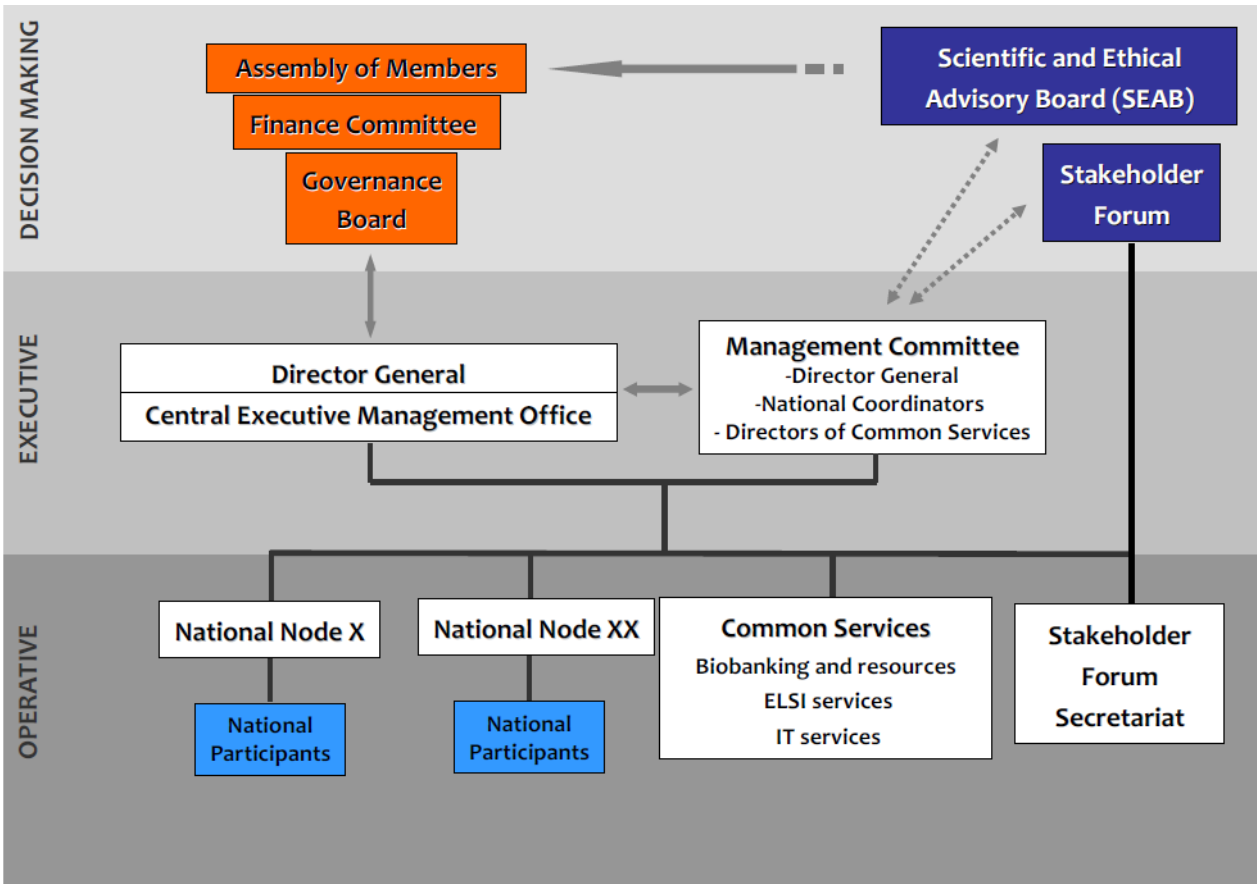
Legal Entity and Governance

A key task and challenge during the BBMRI-PP was to find most appropriate legal entity to support the distributed operation of the construction phase of the BBMRI to provide access to biological samples and data that properly represent the diversity of European populations and diseases. This can only be achieved by a distributed Research Infrastructure with operational units in most, if not all, European Member States. The European Research Infrastructure Consortium (ERIC) legal entity has been identified as the most appropriate legal entity to support the distributed operation of the BBMRI.

BBMRI-ERIC will be established for an unlimited period under the Council Regulation (EC) No 723/2009 of 25 June 2009 on the Community legal framework for an ERIC. The ERIC is set up to sustainably establish and operate, on a non-economic basis, the distributed pan-European Research infrastructure “Biobanking and Biomolecular Research Infrastructure, European Research Infrastructure Consortium” (BBMRI-ERIC).

BBMRI-ERIC foresees a Central Executive Management Office in one Member State that coordinates the interaction of National Nodes established in several Member States. The Central Executive Management Office (CEMO) provides a common access portal to resources available in Member States as well as appropriate facilities and expertise. The National Nodes are also established under the ERIC legal entity and link the national scientific community (e.g., universities, hospitals, research institutions, and resource centres) to BBMRI-ERIC (Figure 4). More detailed description about the governance structure of BBMRI-ERIC is described in the BBMRI Business Plan. BBMRI-ERIC will operate under Statutes approved by the Member States and the EC as well as under Rules of Procedure approved by the Assembly of Members.

Figure 4: BBMRI-ERIC governance structure



Others services to scientific users and interaction with different stakeholders

Education and training

BBMRI has participated in the EMTRAIN training program of the IMI (Innovative Medicines Initiative). The aim has been to coordinate the different training activities at masters' and doctoral levels in the different Member States. The EMTRAIN aims to establish a training syllabus for professional scientists in the different aspects of drug development and BBMRI-ERIC will be an important contributor to such training program.

BBMRI-ERIC will also continue to coordinate national providers of education and training in biological resource management and plans to establish a European Masters' Program in biobanking. State of the art seminars and colloquia will contribute to the global dissemination of knowledge and sustain intellectual stimulation on forefront topics among the biobanking community.

Stakeholder Forum

Close interaction with the European public(s) is essential for the success and acceptability of BBMRI-ERIC. Therefore BBMRI launched already during the Preparatory Phase a comprehensive consultation and engagement process with its broad stakeholder community, comprising patients, clinicians, funding organizations, associated project partners, industry, users, but also the general public. Within BBMRI-ERIC the Stakeholder's Forum (SF) will continue to play an important role in stimulating discussion and keeping the European public(s) informed about the intentions and the progress of BBMRI-ERIC.

The SF operation has included organization of international meetings and workshops, participation in multiple BBMRI work packages (WP1, WP6, and WP7) as well as giving input to BBMRI-ERIC Statutes and Business Plan drafting committees, report and press release writing, media liaison as well as creation of online content for www.bbmri.eu. Significant progress has been made during the BBMRI-PP in identifying unmet needs, developing working relationships, and creating a community of international stakeholders. Some of the key achievements of SF are described below:

Database of participating stakeholders: A stratified database containing the contact details of over 500 participants from SF activities has been assembled over the course of the BBMRI preparatory phase.

International Forum meetings and workshops: SF meetings were designed to provide mechanisms for participants, practitioners and other stakeholders to ask questions, discuss their concerns, and provide feedback. Information was provided on the use of the BBMRI resource and on the value derived from participation, thus enabling stakeholders to formulate informed viewpoints on the BBMRI process as whole and encouraging stakeholders towards active participation in this process. Meeting reports are available at www.bbmri.eu/index.php/publications-a-reports

Patient Consultation Document: The consultation document arising from the patient working group workshop of the BBMRI Stakeholder's Forum was designed as a guideline for basic principles reflecting patient participation in both new and existing biobanks within BBMRI-ERIC. A draft document was distributed for consultation to European patient organizations as a mechanism by which they could indicate their general support for the BBMRI initiative and for appropriate patient representation in the infrastructure. The resultant document entitled "Basic Principles for Patient Participation in BBMRI" has been officially endorsed by the European and Member State patient organizations listed below. The document was presented to the Steering Committee of the BBMRI-PP at the BBMRI Stakeholders' Forum meeting on June 9th, 2010 to assist in the drafting of policies and procedures for the implementation of the research infrastructure. www.bbmri.eu/index.php/stakeholders-forum/events-and-consultations

Supporting Patient Organizations:
- European Organization for Rare Diseases (EURORDIS)
- International Alliance of Patient Organizations (IAPO)
- European Genetic Alliance Network (EGAN)
- European Federation of Neurological (EFNA)
- Europa Donna – The European Breast Cancer Coaltion
- European Network for Research on Alternating Hemiplegia (ENRAH)
- Dutch Genetic Alliance (VSOP)
- Genetic Alliance UK

Content generated for BBMRI Website: As part of a comprehensive consultation and engagement process with the public, an online presence is an important element for providing up-to-date information and user-friendly content. Content generated by the SF has included webcasts of video interviews with relevant stakeholders, blog creation and maintenance, uploading of reports, presentations, photos from SF meetings, press releases, and media coverage. The resultant online traffic to the BBMRI website has led to the SF becoming the most visited section of the website.

Recommendation from the SEAB

The BBMRI Scientific and Ethical Advisory Board (SEAB) consisted of global leaders of the scientific community, industry and the fields of ethical, legal and societal issues. The SEAB (see Table 1) was established to give guidance to BBMRI-PP included production of advisory statements that contained both public and confidential evaluations of scientific, ethical, legal and societal issues related to the activities of BBMRI. It thus assisted BBMRI in achieving scientific excellence as well as compliance with the needs of industry and society. Since SEAB members mainly came from non-European countries, the board was also in a good position to guided BBMRI towards proper global integration.

Based on the advisory statement reports, the SEAB summarized that given the limited financial resources available and the short time span the BBMRI project has performed much more successfully than might have been expected and concluded the following:

1. It is advisable to concentrate, wherever possible, on the key, strategic issues, avoiding getting mired in practical differences which not always need rapid resolution, and may slow down progress;
2. More attention should be given to the inclusion of diagnostic and treatment outcomes

3. The focus should be extended from retrospective to prospective, to reach a better quality of biobanks and better defined objectives of biobank-based research.

General recommendations and advisory statements are published on the public website at www.bbmri.eu under section named "Documents" and subtitled "Final Reporting".

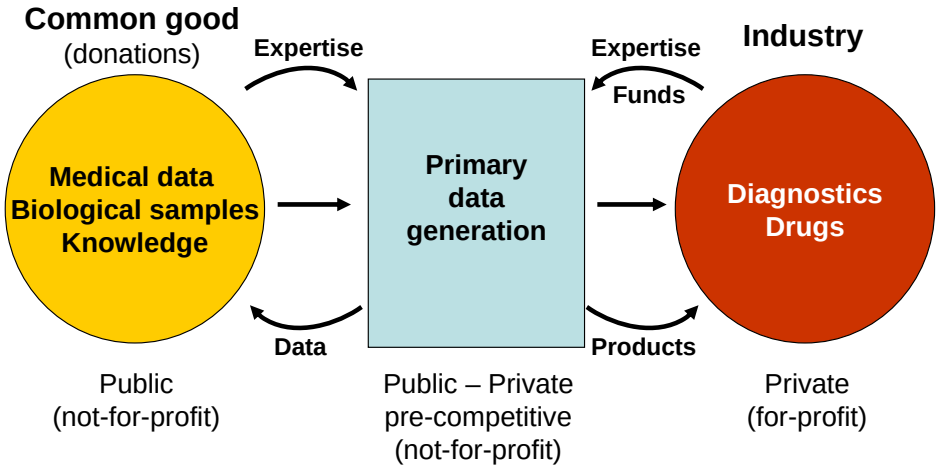
Table 2. BBMRI SEAB Members

Chair: Gert-Jan van Ommen - LUMC, NL
Secretary: Heli Salminen - UTU, FI
Members:
- Karima Boubekeur – Hoffmann-La Roche Ltd, CH
- Jean-Jacques Cassiman – Eurogentest, BE
- David R. Cox – Pfizer, USA
- Mark J. Daly – Broad Institute, Harvard, MIT, USA
- Bartha M. Knoppers – Université de Montréal, Centre for Public Law, CA
- Klaus Lindpaintner – SDI, USA
- Bela Melegh – University of Pecs, HU
- Lyle J Palmer – University of Western Australia, AU
- Howard Cann - The Centre d'Etude du Polymorphisme Humain (CEPH)
- Yusuke Nakamura - The University of Tokyo; JP

Collaboration with industry

Cutting edge research as well as further innovations in the life science industry will strongly depend on transnational access to high quality human biological samples and associated medical information for academia and industry in an efficient and secure manner. Furthermore human biological samples are a finite key resource underlying a series of ethical and legal restrictions thus requiring innovative solutions for efficient usage. By performing the primary analysis of biological samples under internationally standardized conditions in a pre-competitive environment, two major goals are addressed: 1) to provide access to primary data that can easily be shared in contrast to biological samples and 2) to provide high quality information from biological samples to industry for further product development. This should be achieved by so called “BBMRI Expert Centres” (Figure 5).

Figure 5: Expert Centres: Collaborative Research of Public and Private Sectors



BBMRI Expert Centres will be non-profit organizations that represent a novel Public-Private Partnership model. They will be responsible for the analysis of samples in the country of origin under internationally standardised conditions and the generation of primary data. BBMRI Expert Centres integrate pre-competitive public and private research and development activities by providing not only access to biological samples and medical data but also to the broad spectrum of medical and scientific expertise related to the samples and data. Thus a win-win situation is created for both parties by

- enhancing collaborative research,
- using limited resources efficiently,
- sharing data, technology, knowledge and expertise,
- facilitating innovation, and
- increasing competitiveness in academic science as well as on the marketplace through product innovation.

BBMRI Expert Centres will function as a focal point of contact between the public and the private sector. Human biological samples and medical data are provided as donations and are considered as common goods. The private industry sector needs access to biospecimen and data to develop innovative products to keep or gain market leadership. Since commercialization of human bodily materials is forbidden according to the European Oviedo Convention (ETS 164) and by national legislation in most Member States, and even financial compensation on a cost-recovery basis is generally not accepted by the public, only research collaboration provided a sound basis for accessing human biological samples and associated medical data. This situation is a source of conflict that makes the access for industry difficult or even impossible in many cases. Expert Centres that operate on a not-for–profit basis offer an efficient solution for this problem (Nature, Sept 24; 461: 448).

Several countries like China, Russia, Brazil, and India have legal restrictions on export of biological samples that make transnational research collaboration difficult. The establishment of partner Expert Centres in Europe and non-European countries that operate under same standards and quality

management schemes could generate “highways” for future transnational research collaborations since samples will be analysed in the country of origin and only research data are shared. The establishment of a world-wide network of Expert Centres in the context of biobanks and biological resource centres supports the OECD goal to establish a global biological resources centres network (GBRCN) in order to provide efficient and secure access to biological samples as key resources for the advancement of biotechnology and medicine. Expert Centres can in addition to public-private-partnerships also be established as public entities.

Ethical and regulatory issues are often major road blocks to the access to samples and related data. Expert Centres will provide the institutional framework as well as appropriate counselling and services to facilitate ethically and legally compliant access to biological resources for academia and industry within Europe and globally.

The set-up of BBMRI Expert Centres will be decided on the level of the member countries. The implementation plan foresees to demonstrate the feasibility in pilot studies before major financial commitments can be expected. Some pilot studies are already ongoing. Full implementation should be co-financed from the public and private sectors, and by using funding instruments provided by the European Investment Bank (EIB). Major companies have already expressed their interest in BBMRI Expert Centres through their participation in BBMRI Stakeholder Forum and other activities.

Synergies with other ESFRI Biological and Medical Sciences Research Infrastructures

There are currently 13 different Biological and Medical Sciences (BMS) Research Rnfrastructures prioritized in the 2nd update of the ESFRI Roadmap in 2010. Most of these infrastructures either require access to human biological samples or rely on biobanking expertise developed within BBMRI. Consequently, in the future BBMRI-ERIC will provide direct support of biobanking-related activities for all BMS Research Infrastructures. At the same time BBMRI-ERIC will benefit from technologies, know-how, and services developed by other infrastructures. For example, BBMRI-ERIC will not establish high-capacity computing and data storage solutions required for dealing with massive genomics, transcriptomics, metabolomics and imaging data derived from human biological samples but collaborate with ELIXIR and the e-Infrastructures on this topic. Furthermore joint grant applications for improving interoperability of data management between BMS Research Infrastructures has been approved. The development of coordinated strategies for education and training in the life sciences (EMTRAIN) is already a joint activity of all BMS research infrastructure that is funded by the Innovative Medicines Initiatives (IMI).

Table 3: Synergies of BBMRI with other ESFRI Infrastructure

BMS RIs	Fields of collaboration
EATRIS	Target identification and biomarkers
ECRIN	Biobanking of clinical samples, ethical and legal issues
ELIXIR	Management of genetic data
EMBRC	Banking of organisms and libraries, molecular tools
EU-OPENSCREEN	Target identification and validation
EuroBioImaging	Identification of imaging biomarkers, diseases phenotype characterization based on imaging data
ERINHA	Establishment of sample collection centres within health care
Infrafrontier	Banking of biological samples, disease phenotype characterization
INSTRUCT	Banking of proteins and gene constructs, NMR-based metabolomics
MIRRI	Biobanking of pathogens
ISBE	Generation of high quality data for computational modeling; correlation with disease phenotype and outcome
Other ESFRI RIs	
ENV	Investigation of gene-environment interactions, documentation of environmental exposure
PSE	Innovative analytical technologies (structural biology)
SSH	Impact of life style and social factors on health; assessment of life style and social factors, data management, privacy
e-Infrastructure	Distributed high capacity data storage and computing

THE POTENTIAL IMPACT

(including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results (not exceeding 10 pages).

Health has been considered one of the most fundamental resources for social and economic prosperity. While the goal to improve the levels of population health is important for any government, there has been an increasing trend in socio-economic differences in health, health behaviour and access to health care within European Countries. However, access to good quality health services is an important determinant of socioeconomic inequalities in health. EU member states have identified the need to ensure equal access for all as a priority. This goal can only be achieved by targeted investments into health care to address the key factors contributing to inequalities. BBMRI-ERIC will provide the infrastructure for investigation of these key factors by providing solutions for transnational comparative analysis of epidemiology and etiology of diseases, disease outcomes, and the impact of lifestyle and environmental factors.

BBMRI involved in its Preparatory Phase more than 274 Participants and Associated Organizations from more than 30 countries (www.bbmri.eu/index.php/partners-a-membership) which underlines its pan-European scope. Nevertheless, among the institutions involved there is a significant dominance of Western European Member States. In the context of implementing the European Research Area and European Cohesion Policy BBMRI-ERIC further promotes participation of new Member States with its distributed architecture, by the adoption of the ERIC legal framework, and a series of specific stimulation programmes. This process will be officially supported by the Czech Republic. Furthermore, Estonia, Greece, and Malta have expressed their interest in acting as regional hubs for the Baltic, South-Eastern and Southern European regions, respectively, in order to stimulate cooperation within these regions.

The EU’s ageing population is resulting in increased incidence of a number of common diseases and consequently in increased health care expenditure for people in old age. This will put a lot of pressure on the sustainability and viability of the EU’s healthcare systems. The ability to better diagnose, treat, and ultimately cure diseases in the 21st century will depend on two things: understanding the genetic and environmental causes of disease, and the ability to translate this information into new innovative diagnostic tests, therapeutics, and preventive measures. Furthermore, future research strategies will place more emphasis on investigation of factors that protect people from developing diseases. Such studies will lay the foundation for science-based approaches towards healthy ageing, and critically rely on biobanks that enable such research.

Furthermore, clinical practice is shifting from treatment based on symptoms to treatment based on each person's unique genetic make-up and affected biological mechanisms - in other words, personalised medicine. BBMRI will provide access to high quality human biological samples related to a broad spectrum of disease as well as medical data, lifestyle and environmental exposure information thereby enabling systematic research as the foundation of future healthcare.

Investigation of human biological samples has been the central source of our current knowledge on diseases, and laid the foundation for most diagnostic as well as therapeutic opportunities. Modern technologies for the analysis of human biological samples critically rely on defined sample quality. Therefore, standards defining sample quality are directly related to the quality of a diagnostic test (biomarker assays) performed on these samples. Any modification in the regulation related to the quality of human biological samples and consequently also on biomarkers will have an immediate economic and political impact at the international level.

BBMRI-PP provided essential resources and technologies of any research-led response to several of Europe's grand societal challenges, and consequently, will be a fundamental component in addressing the ongoing and future requirements particularly of the EU's health services framework including competitiveness and innovativeness of health-related industries. Exploring new models for public-private partnerships will become a cornerstone for implementing the goals of the European Strategy 2020, in particular the "Innovation Union". BBMRI developed the concept of "Expert Centres" which can be established as public-private partnerships with industry. These centres should provide a framework where public resources as well as expertise and technologies from academia and industry can be integrated to speed-up collaborative research and to perform analyses of samples at the country of origin under internationally standardised conditions. A network of Expert Centres that implement common quality assurance schemes, and will be established within BBMRI-ERIC and outside of Europe, will create a framework that particularly facilitates international biomarker validation studies. Furthermore, in the context of Expert Centres the role of intellectual property in pre-competitive research will be newly positioned aiming at generating a win-win situation for the public and private sectors and at the same time improving competitiveness.

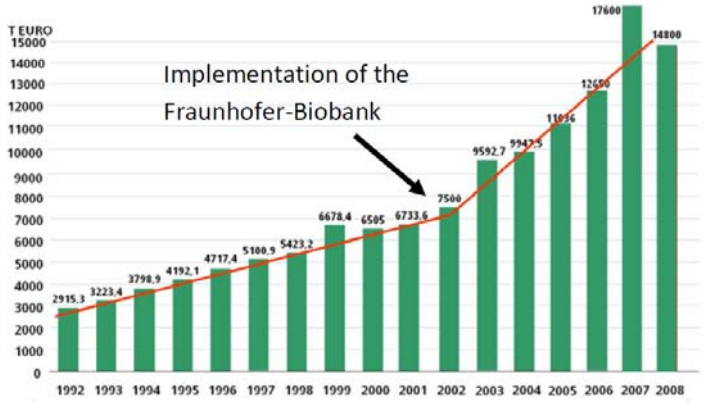
In addition to improving the health, BBMRI-PP contributed to the technological development capacity in ERA by designing an infrastructure with a strong focus on data management and access processes resulting in sustainable operation of the infrastructure. In the existing components of the infrastructure investigations into the biological resources themselves have received most of the attention while the services themselves have received less attention. Development of IT-solutions which would be available for a wider researcher community has proceeded through use case (proof of principle) studies, but need to be tested further. In addition, data management systems have been developed with single locations - rather than interoperability - in mind. The BBMRI-ERIC will further enhance the coordination and develop synergies between these infrastructure components and create a unique body of expertise with the capacity to make such improvements.

Biobanks are emerging as important resources for the progress of science and technology, and have the potential for a substantial impact on the economic growth of the regions in which they are located. However, it is not easy to evaluate the economic and scientific impact of biobanks as there is no standardised tool for this purpose. Large companies increasingly rely on outside sources for Intellectual Property generation. Public funding of research is increasingly linked to technology transfer objectives as the pressure on research public budgets grows because of fiscal deficits. This leads to a fundamental cultural change within research institutes. Exploitation of research results becomes more and more important. These trends represent a great opportunity for BBMRI related

technology transfer. WP7 outsourced three studies on the socioeconomic impact to Technopolis, BETA Group, and Fraunhofer-IBMT (www.bbmri.eu/index.php/publications-a-reports).

Through coordinated collaboration of research institutions, biotechnology companies and the supply of public and private funding sources, geographic concentrations of biobanking related interconnected companies and institutions can be developed. Such clusters foster cooperation and promote competitiveness at the same time. These effects were observed around San Francisco as well as in Cambridge and are exemplified for a BBMRI related region around the biobank activities of the Fraunhofer Institute for Biomedical Engineering (IBMT) within the Saar region. From its beginning, this institute grew continuously in its budget volume and staff. This growth was only possible by discovering and investing in new areas of interest, like the area of cryotechnology in the year 2002 (Figure 6). About 31 % of this budget is generated with industrial project partners.

Figure 6: Development of the IBMT-Budget from 1992 to 2008



In the 'Case Study on the Economic Impact of Biobanks illustrated by EuroCryo Saar' in 2009 shows that a clear impact on the economic development of the Saar region could be assigned to the biobank:

- The existence of the biobank enabled several major R&D projects.
- The operational budget of the division Biophysics and Cryotechnology, one the main users of the Fraunhofer Bioarchive, grew from 200 T € in the year 2001 up to 3.5 million € in the year 2009.
- Biobank activities resulted in job creation within the biobank itself and in connected R&D groups.
- Based on basic research in cryotechnology three science based spin-off companies were recently founded and further concepts for spin-offs are being evaluated.
- So far, more than 20 patents of the Fraunhofer cryotechnology-family are licensed to companies.

Taken together, the observed positive development resulted in additional 12 million € of public funding for further development of the biobank infrastructure (see Figure 6).

An enormous potential exists in Europe for biomedical innovation and knowledge-generation and transfer based on the population base of more than 500 million citizens, a sophisticated medical-

clinical infrastructure, and an advanced biomedical research community that has become highly integrated as a consequence of EC initiatives (e.g. FP, ESFRI programs), as highlighted by the Commission's "European Innovation Union" concept. These resources could be leveraged into an enhanced generation of economical and health-care progress by embedding them into collaborative European networks with a clear orientation towards the value-chain ultimately focused on products and services.

Building on BBMRI-ERIC, it will be important to create a European effort and associated infrastructure to coordinate and foster cooperative efforts that integrate existing biological repository resources (as established by BBMRI) and advanced basic and applied biomedical research resources in both academia and industry, with an clear focus towards novel therapeutics and diagnostics as well as new public health initiatives. It is envisioned that these efforts will specifically include the Eastern and Central European countries which have recognized a clear need in this regard. Moreover, they will be internationally networked beyond the EC (US HHS/NIH, OECD) to leverage the European position in a global context.

In order to refine the concept of this future European infrastructure a BBMRI task group on communication & PR was set up to develop dissemination activities and a public communication strategy. A four step approach was agreed on to address the media/public: 1. high quality journals; 2. international press; 3. television and radio; 4. new media. On the one hand, the communication strategy also addressed the common aspects of all life science (BMS) infrastructures, emphasising the momentum generated by these infrastructures to increase competitiveness of European science and industry. However, the specific assets and features of BBMRI were also emphasized. The solutions developed have been intensively discussed with external experts, users and stakeholders, and has been published, and presented to the public to ensure broad and sustainable acceptance in several meetings and (Table 4).

Table 4: Meetings and public engagement events organised during BBMRI-PP

17 March 2007	Partner and Stakeholder Meeting, Vienna/Austria
10-12 Feb.2008	Kick-Off Meeting, Hinxton/UK
18 April 2008	BBMRI 1st Governance Council Meeting, Florence/Italy
28 May 2008	Seminar at the European Parliament, Brussels/Belgium
17-18 Dec. 2008	Expert meeting on specific requirements for biobanking in Pathology, Laboratory Medicine, and rare diseases
25-27 March 2009	PHOEBE-P3G-BBMRI Joint Conference, Brussels/Belgium
25 March 2009	BBMRI 2nd Governance Council Meeting, Brussels/Belgium
20 March 2009	1st Stakeholder Forum, Brussels/Belgium
16 September 2009	Stakeholder Forum Discussion/Information Meeting, Brussels/Belgium

15 December 2009	Stakeholder's Forum Patient Working Group Meeting, Paris/France
16 December 2009	Expert Centre Meeting, Paris/France
9 April 2010	BBMRI meets Mediterranean Biobanks, Valletta/Malta
9 June 2010	2nd Stakeholder Form, Brussels/Belgium
23-25 Sept. 2010	Biobanking for Science Conference, Amsterdam/The Netherlands
25 October 2010	BMS Strategy Paper Presentation, Brussels/Belgium
26 October 2010	European Parliament Hearing on Health-related Research Infrastructures, Brussels/Belgium

On October 26th, 2010, a public hearing at the European Parliament and joint seminars took place in Brussels. The hearing was entitled “Health-related Research Infrastructures and their Contribution to the EU’s Grand Challenges” and was sponsored by Dr. Paul Rübig MEP, Chairman of STOA and member of the ITRE Committee. The scope of the Hearing was to present specific cases of how Health-related infrastructures contribute to key health-related European strategic priorities, including health challenges in an ageing population, targeted measures to improve health care in Eastern European countries, international standards for sample pre-analytics for biomarkers, sustainable access to biological resources, an infrastructure for rapid evidence-based decision making for new epidemics and preventive measures against bioterrorism and new models for public-private partnerships. Several media representatives reported on the event. Additionally, the Financial Times indicated interest in publishing a special report related to RIs. A comment (Biobanks need publicity) of the results of the "2010 Eurobarometer on Biotechnology" was published in Nature on 2011.

More than 120 press articles, press releases and podcasts related to the BBMRI were published in international journals, national newspapers, magazines, press releases, websites, webstreams, short films, and blog entries during the Preparatory Phase and collected by the Coordination. Although some regional press reports are included in the list below (see Section A2), it's clearly focused on international press coverage and English publications. The distribution of the press reports over the given period shows, for instance, that specific meetings such as the BBMRI Kick-off Meeting in Hinxton/UK on February 10-12th, 2008 or the Hearing at the European Parliament on October 26th, 2009 (alongside with proactive engagement of the media through press releases and press briefings) had generated high media attention. Although the number of publications has decreased from 2008 to 2011, in-depth articles in high quality media have increased. Generally, BBMRI is portrayed as an innovative project for public health. Concerns, if any, were raised in relation to data protection. Lately, reports include discussions about the ERIC legal entity and the need to involve industry and patient advocacy groups for successfully launching BBMRI as a long term tool for the progress in the biomedical sciences and transnational collaboration and cooperation.