Networking Biobanks Throughout Europe: The Development of BBMRI-ERIC

Eero Vuorio

Abstract The purpose of this chapter is to summarize the process towards establishment of the pan-Eurovpean Biobank infrastructure BBMRI (Biobanking and BioMolecular Resources Research Infrastructure) as a legal entity under the ERIC regulation. The chapter gives an overview of the science case for collaboration of biobanks and describes early attempts to bring harmonization, cohesiveness and interoperability to the field, and discusses the possibilities opened up by the ESFRI (European Strategy for Research Infrastructures) process. After inclusion of biobanks on the first ESFRI Roadmap of 2006, BBMRI became one of the first European Research Infrastructure projects to receive funding from the European Commission (EC) from February 2008 onwards. The 3-year EC-funded Preparatory Phase (BBMRI-PP) came to its end in January 2011. During this time BBMRI grew into a 54-partner consortium with 224 associated organizations (largely biobanks) from 33 countries, making it the largest research infrastructure project in Europe. During the Preparatory Phase the concept of a functional pan-European biobank was formulated and was presented to Member States and Associated States of the European Union for approval and funding. The plan was approved by a total of 16 EU Member States and Associated States, which became founding members and observers of BBMRI-ERIC legal entity in late 2013.

Keywords BBMRI • Biobank • Biorepository • Biological sample collection • Research infrastructure

This chapter is dedicated to the memory of Leena Peltonen-Palotie and David Cox, who both made major contributions to the BBMRI concept.

E. Vuorio (retired) (✉)
Chair of International Advisory Committee, ADOPT-BBMRI ERIC,
Hurtinkatu 11 C 18, 20610 Turku, Finland
e-mail: eero.vuorio@helsinki.fi

P. Hainaut et al. (eds.), *Biobanking of Human Biospecimens*,
DOI 10.1007/978-3-319-55120-3_8

1 Origins of European Biobanking

The tradition of sample collection, particularly collection of formalin-fixed paraffin-embedded tissues in pathology departments, within the health care system started in early to mid-1900s. Initially these samples were used for diagnostic purposes, but their storage for extended periods was justified by the need of material for follow-up of disease progression, efficacy of treatment regimens and for quality control. In many countries the requirement for extended sample storage is based on national legislation, which may also set limits for minimum (and maximum) storage of patient-derived samples. Biomedical research on human diseases has also resulted in collections of patient-derived blood and tissue samples, cell lines and other kinds of biological material. Initially such collections have been in the custody of individual principal investigators, but are gradually finding their home in national biobanks. On the other hand, some countries had initiated systematic collection of samples and data from population cohorts already in the 1950s and 1960s particularly in Northern Europe. Although the three types of "historical" collections of human biological samples were not called biobanks at the time of collection, they fulfil most of the criteria of biobanks. One important problem of such early collections is lack of written informed consent, as the concept of informed consent did not exist until much later. Participants were simply informed of the purpose and voluntary nature of the study and if they participated they had given their consent to participate. The different historical backgrounds of the three types of sample collections also contribute to the considerable heterogeneity of early biological sample collections in Europe.

2 Biobanks Become Recognized as Valuable Sources for Genetic Epidemiology and Research on Disease Mechanisms

With the development of molecular genetics and high-throughput tools for analysis of large numbers of human samples, the value of old sample and data collections was discovered in the 1990s. Several projects in Europe and beyond demonstrated that biobanks serve as key resources for epidemiological studies.

Towards the end of Framework Program 5 (FP5) the European Commission tested a new two-stage funding instrument called Integrated Project to support very large research projects. One of the three Integrated Projects that in 2001 was selected for funding in the Health domain was GenomEUTwin (Genome-wide analyses of European twin and population cohorts to identify genes in common diseases) [1] led by Leena Peltonen-Palotie. Supported by a global scientific community participating in the P3G (Public Population Project in Genomics) project, the GenomEUTwin project (2002–2006) was among the first to demonstrate the feasibility of effective cross border collaboration (beyond Europe) on very large numbers of samples from

twin pairs. Development of novel IT solutions made it possible to link federated biobanks and databases in different countries, and prepared the way towards a pan-European biobank [2].

In 2000, the European Commission invited representatives from Member State funding agencies to a Forum of Genomes Research Managers to discuss way of better coordination of national genome research programs. The Commission provided financial support to a follow-up Strategic Accompanying Measure, COGENE (Co-ordination Activity in the field of Genomes Research) in 2002–2004, which marked one of the first pan-European attempts to initiate an inventory of existing sample collections (population cohorts) in Europe, and at the same time encourage new initiatives in population genomics.

By the turn of the millennium the word biobank had been adopted to denote a repository for (human) cells, tissues, blood or DNA, which can be linked to data and information on the respective donors, particularly on their health and life style. Under EU's FP6 and FP7 a number of coordination actions, such as PHOEBE (Promoting Harmonisation of Epidemiological Biobanks in Europe) in 2006–2009 [3], ENGAGE (European Network for Genetic and Genomic Epidemiology) in 2008–2012 [4], GEN2PHEN (Genotype-To-Phenotype project) in 2008–2013 [5] and BioSHaRE-EU in 2011–2016 [6] were funded. These and many other projects worked on development of tools and methods and harmonizing biobanking activities. Under FP7 a novel public-private-partnership IMI (Innovative Medicines Initiative, www.imi-europe.org) also funded several biobank-related projects. The projects listed above occurred in parallel to development of the BBMRI concept during the ESFRI process and subsequently during the Preparatory Phase, and in most cases included partners who were also involved in BBMRI-PP.

Through systematic research on disease mechanisms biobanks were gradually realized as key resources for disease stratification (molecular subtyping of diseases), a cornerstone for personalized medicine. They also play an important role in identification of new targets for therapeutic interventions especially drug development and for companion diagnostics. Large-scale genomics projects aimed at understanding the interactions of genes, environment, nutrition and lifestyle which typically rely on large sample sets and databases present in biobanks.

3 Towards Organizing the Biobanking Community in Europe

By the 1990s the global scientific community had become fully aware of the need to collect very large sample sets from several different biobanks in order to start resolving the genetics of complex common diseases. The different EU-funded projects listed above clearly brought the community together. Also biobanking scientists sought for an organization of their own, which resulted in founding of ISBER (International Society for Biological and Environmental Repositories)

already in 1999. ISBER was not, however, an international biobank, but primarily a professional society of individuals (and organizations) providing an international forum addressing practical issues related to repositories of biological specimens as described Hewitt in Chap. 7 of this volume.

P^{3}G (Public Population Project in Genomics and Society) was founded in Canada in 2003 as a global not-for-profit consortium that provides the international research community with access to the expertise, resources and innovative tools for health and social sciences research. Many European scientists involved in establishing BBMRI had already been active in P^{3}G (Public Population Project in Genomics and Society). An important activity of P^{3}G was cataloguing of human epidemiological sample collections. The P^{3}G questionnaire was later adopted in a slightly modified form by BBMRI Preparatory Phase to develop the first inventory of European population-based and clinical biobanks that may serve as building blocks of BBMRI-ERIC. The large FP7-funded European project ENGAGE also collaborated with P^{3}G, to produce a Consortium Catalogue, a repository of standard information describing ENGAGE cohorts available in the P^{3}G Observatory web site [7].

World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD) also became interested in international cooperation of Biological Resource Centres. OECD drafted its best practice guidelines for biological resource centers [8, 9] with an aim to establish a Global Biological Resource Centre Network (GBRCN).

In Europe, the European Science Foundation (ESF) and its Standing Committee of European Medical Research Councils (EMRC) were actively following the developments in biobanking in their member countries and supported meetings of the biobanking community as described below.

4 The European Strategy for Research Infrastructures (ESFRI) Provides a Potential Instrument to Establish a Pan-European Biobank

Parallel to the self-organization of the European biobanking community through large, often EU-funded projects, another important development started in Europe in 2002: the European Strategy Forum on Research Infrastructures (ESFRI) process. The ESFRI was mandated to “support a coherent and strategy-led approach to policy-making on research infrastructures in Europe, and to facilitate multilateral initiatives leading to a better use and development of research infrastructures”. This process finally brought recognition to key infrastructures in the biological and medical sciences (BMS) domain in par with those in the natural sciences domain, especially physics and astronomy, as well as social sciences and humanities.

ESFRI embarked on a complex methodology to produce the first European Roadmap for Research Infrastructures. One of the three dedicated Roadmap Working Groups (with more than 70 representatives from all EU countries) was the

Working Group on Biological and Medical Sciences (BMS) chaired by Ruth Barrington (IE). Within the remit of the three Roadmap Working Groups, 15 Expert Groups with a total of more than 150 members were created in the summer of 2005 to cover specific areas within the three domains. In the BMS domain three Expert groups were established: (1) Genomics, proteomics, bioinformatics and biology; (2) Clinical and translational research, imaging and radiation; and (3) Biodiversity and environment.

More than 200 proposals were received for the first European Research Infrastructure Roadmap. Each proposal was analyzed for its (pan-European) science case and for concept and maturity, first by an Expert Group, then by the applicable Working Group. For the biobanking field, two different proposals were received, one for basic science domain and another for the clinical/translational research domain. The evaluation of the proposals submitted to ESFRI by the different scientific communities started in August 2005. This involved feedback to the proposing scientists proposing a single biobank infrastructure proposal. The scientists behind the proposal came together and drafted one joint proposal for a Research Infrastructure for Biobanking and BioMolecular Resources, which was subsequently recommended by the two respective Expert Groups to the BMS Working Group for inclusion on the Roadmap. The end result of this long process was the inclusion of BBMRI on the first European Research Infrastructure Roadmap of 2006 [10].

Parallel to the European road mapping process a number of national initiatives to establish research infrastructure roadmaps were started. Soon after the publication of the first ESFRI Roadmap in 2006 biobanks appeared also on national roadmaps in several European countries with long tradition of collecting population cohorts, Finland, Sweden, the Netherlands being among the first. In some countries (e.g. Iceland and Estonia) and regions (e.g. Styria) large biobanking projects had already been established indicating national and regional interest in systematic collection and storage of biological samples and data for research purposes.

5 Building the Concept of a Pan-European Biobank with BBMRI Preparatory Phase Funded by the European Commission

Creation of the 2006 ESFRI Roadmap in 2 years was a major achievement which brought a new kind of momentum to European science policy and scientific community, and brought new concrete meaning to the concept of European Research Area. For the scientific communities a status on ESFRI Roadmap was a major encouragement as it also meant eligibility to apply for a Preparatory Phase (PP) funding from the European Commission under the Seventh Framework Programme. To write such an application the European biobanking community had to organize itself in a more concrete way in order to come up with a work programme towards realizing the

concept of a pan-European biobank. This preparatory work was supported by European Science Foundation (ESF) which sponsored scientific meetings in the area. In a meeting in Amsterdam on December 7–8, 2006, titled Population Surveys and Biobanking, a number of recommendations for European Biobanking and Population Surveying were made, which could be seen as an early version of the work package structure of the future BBMRI-PP work program [11]. Key drivers of the process, professor Leena Peltonen-Palotie from Finland, professor Gert-Jan van Ommen from the Netherlands and professor Kurt Zatloukal from Austria, agreed on the division of tasks. Kurt Zatloukal became the coordinator of the PP application, Leena Peltonen-Palotie the chair of the Steering Committee and Gert-Jan van Ommen the chair of the Governance Board and Scientific and Ethical Advisory Board. The Work Package structure adopted for BBMRI-PP will be discussed below.

Work towards the application also involved contacting EU Member States for their participation in the PP. A meeting of potential partners and stakeholders was organized in Vienna on March 17, 2007. Widespread commitment of Member States and Associated States was remarkable: with 52 partners and some 200 associated partners representing 34 countries (16 partner countries: Austria, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Norway, Spain, Sweden, the Netherlands, United Kingdom; and 18 associated countries: Australia, Belgium, Bulgaria, Canada, Cyprus, Czech Republic, Faroe Islands, Israel, Latvia, Luxembourg, Martinique, Poland, Portugal, Romania, Saudi Arabia, Slovenia, Switzerland, Turkey) BBMRI-PP became one of the largest EU-funded coordination projects. In 2007, the EC granted 5 MEUR to fund the 2-year Preparatory Phase of BBMRI which served as a real trigger towards planning of BBMRI-ERIC as we know it today. Since the beginning of the Preparatory Phase on February 1, 2008, the number of partners grew to 54 and associated organizations to 224 by the end of the Preparatory Phase on January 31, 2011. The associated organizations included biobanks, research institutions as well as several ministries and funding organizations.

6 Activities of BBMRI-PP

In the BBMRI kick-off meeting in Hinxton in February 2008, professor Eero Vuorio was elected as the executive manager of the PP and the tasks of the executive management office were divided between Graz, AT (at Kurt Zatloukal's home university) and Turku, FI with Michaela Mayrhofer and Heli Salminen-Mankonen working as full time project managers. From the beginning it was realized that BBMRI's main task, provision of access to biological samples and data that properly represent the diversity of European populations and diseases, can only be achieved by a distributed research infrastructure with operational units ("National nodes") in most, preferably all European Member States. Considering the national character of both biobanks and the related health and registry data and the heterogeneity of their custodianship a distributed

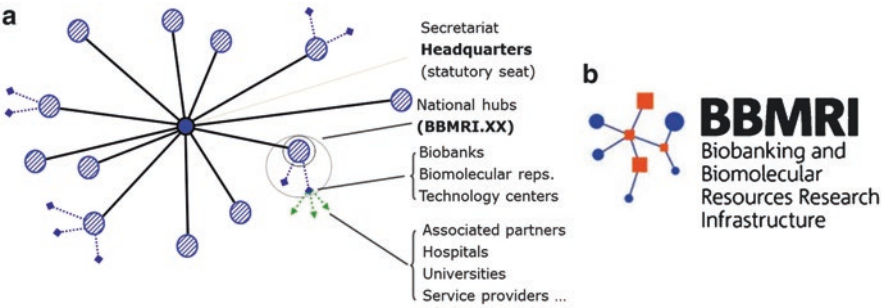

Fig. 1 Schematic presentation of the distributed hub-and-spoke structure of BBMRI (**a**) and BBMRI logo (**b**). A distributed architecture was adopted for BBMRI to accommodate the national character of biobanks and the related health and registry data and the heterogeneity of their custodianship

architecture was adopted as it would allow samples and data to be stored at national level for integration at European level (Fig. 1). The distributed hub-and-spoke architecture had been graphically designed already for the GenomEUtwin project; the same graphic profile was subsequently adopted as the central element for the logo design for BBMRI.

In its application for Preparatory Phase funding BBMRI expressed as its main aim as "to build a coordinated, large-scale European infrastructure of biomedically relevant, quality-assessed sample collections, to enhance therapy and prevention of common and rare diseases, including cancer". Biobanking was considered to represent a unique European strength, although without adequate coordination the valuable and irreplaceable national collections were judged to suffer from underutilization due to fragmentation. To achieve these goals, it became obvious that harmonization, standardization and interoperability became key words during the execution of the work programme of BBMRI-PP. The "pilot" studies conducted by participating scientist summarized above under Sect. 2 had clearly demonstrated the need for synergy to gain statistical power and economy of scale to make it possible to understand the association between subtypes of common diseases and variations in genotype, phenotype, and lifestyle. To reach these goals it was realized from early on that a well-functioning bioinformatics infrastructure must be an integral part of BBMRI.

7 Work Package Structure

In the application for BBMRI-PP funding, a structure of seven work packages reflecting key activities to build a biobanking infrastructure was envisaged (Table 1). This structure has remained essentially unchanged through the interim and the construction phases and now serves as the basis for the Work Program and operations of BBMRI-ERIC. Many national BBMRI nodes have also adhered to the same work package structure, sometimes with minor modifications.

Table 1 Work Package structure of BBMRI-PP

Work packages (WP)	WP leaders
WP1: Management and Coordination	K. Zatloukal (AT) coordinator; M. Yuille (UK) deputy coordinator; E. Vuorio (FI) excutive manager; M. Pasterk (global interactions)
WP2: Population-based Biobanks	L. Peltonen (FI)/M. Perola (FI), 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. Cambon-Thomsen (FR)
WP7: Funding and Financing	G. Dagher (FR), J. Ridder (NL), C. Bréchot (FR)

7.1 Work Package: Governance and Management

The Governance and Management structures adopted for BBMRI-PP were as simple as possible for a project of over 270 partners and associated partners. Due to the very large size of the project, most of the important decisions were mandated to the *Steering Committee* consisting of Work Package leaders and the Chairs of the Governing Council and Scientific and Ethical Advisory Board. The Steering Committee was variably chaired by Eero Vuorio and Kurt Zatloukal from the Coordination office. The Governing council comprising all partners and associated partners only met twice, in Florence, IT on April 18, 2008, and in Brussels on March 25, 2009, to give advice to the Steering Committee and the Coordination Office. Dissemination of information between the Steering Committee and the Governing Council occurred primarily through the BBMRI-PP intranet site.

The *Scientific and Ethical Advisory Board (SEAB)* chaired by Gert-Jan van Ommen comprised ten distinguished scientists, David Cox, Howard Cann, Bela Melegh, Mark Daly, Jean-Jacques Cassiman, Bartha Knoppers, Lyle Palmer, Klaus Lindpaintner, Karima Boubekeur, and Yusuke Nakamura. The SEAB had three meetings where they were presented reports from the Work Packages in Florence (2008), Brussels (2009) and in Amsterdam (2010). In addition to their encouraging support to BBMRI-PP, the SEAB also gave valuable advice, particularly on the scientific focus and the importance of outcomes, interaction with industry and informed consent. The SEAB consistently also expressed their concern about lack of sustainable funding to BBMRI. The SEAB is to be specifically acknowledged for providing ideas for the concept of Expert Centers for industry-academia collaboration.

A separate *Stakeholder Forum* was also set up for BBMRI-PP chaired by Michael Griffith from the Irish Platform for Patients' Organizations, Science

and Industry (IPPOSI). Close interaction with the European publics had been considered essential for the success and acceptability of BBMRI-ERIC. Comprehensive consultation was conducted covering patients, clinicians, funding organizations, associated project partners, industry, users and the general public. The Stakeholder Forum organized meetings and workshops providing information on the use of the BBMRI resources and on the value derived from participation, thus enabling stakeholders to formulate informed viewpoints on biobanking. A Patient Consultation Document "Basic Principles for Patient Participation in BBMRI" was developed and has been officially endorsed by several patient organizations.

An important task of BBMRI-PP was to create a draft governance structure, Statutes and Business Plan for the future BBMRI-ERIC legal entity. Also here the aim was to create a simple, functional governance model which would accommodate for the growing membership and infrastructure activities. The basic idea was to make best use of governance structures of existing intergovernmental organizations rather than starting to reinvent the wheel. The governance of European Molecular Biology Laboratory (EMBL) with its headquarters in Heidelberg, four outstations and a number of partnerships in different Member States was well-known to several partners and served as a model for a well-functioning federated organization. Subsequently the Governance structure and the Statutes of BBMRI-ERIC are based on the ERIC regulation and bear clear resemblance to that of EMBL. As stated earlier, a federated structure was the only possible solution for BBMRI-ERIC since the participating biobanks and registries remain in Member States. The Governance structure of BBMRI-ERIC is illustrated in Fig. 2.

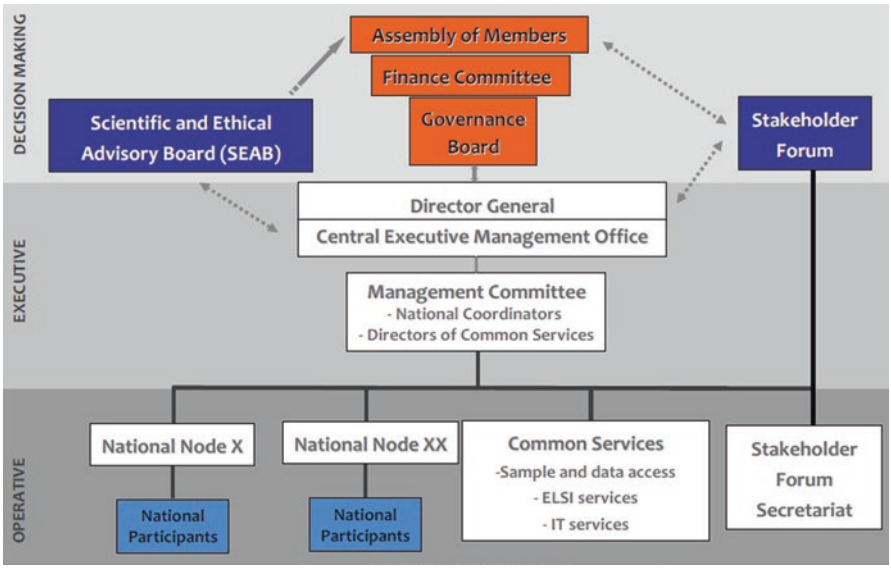

Fig. 2 The proposed governance structure for BBMRI-ERIC

7.2 Work Packages 2 and 3: Catalogues of European Biobanks

From the beginning it was clear that the future BBMRI infrastructure would provide access to the sample and data collections of BBMRI Partner Biobanks, which will physically remain in the Member States. Together with the BBMRI-PP management team, 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. Access to the federated infrastructure was to be based on scientific excellence of the proposed project as determined by an independent peer review and on ethical review of the research project proposal. To achieve this goal, an early task of BBMRI-PP was to produce an inventory of the major existing population-based and clinical or disease-orientated biobanks in Europe. Using questionnaires based on those developed by the international population cohort organization P3G, information was collected on the type and quality of collected samples and data, standardization of procedures, IT solutions as well as governance structure, funding, and legal and ethical issues of catalogued biobanks [12]. Data obtained from the survey can be accessed through a searchable catalogue at the BBMRI-PP/BBMRI-ERIC website.

It was also considered important that BBMRI provides free access to documents, Standard Operating Procedures (SOP's) and best practices developed by BBMRI. Review of SOPs that had been used in biobanks and related research projects showed several different standards, SOPs, and internal guidelines had been in use, although several official guidelines had recently become available from National Cancer Institute, OECD, ISBER and IARC (International Agency for Research on Cancer). WP2 and WP3 worked towards establishment of common detailed SOPs based on the OECD [8, 9] and IARC guidelines [13] and the work carried out by Molecular Medicine Ireland [14]. This led to a useful comparison chart of the various biobanking-related guidelines.

Another important task was to ensure that the source of samples and data are appropriately acknowledged. This turned out to be a long process which finally led to the development of the Bioresource Research Impact Factor (BRIF) concept and publication of a guideline to standardize the citation of bioresources in journal articles [15].

The BBMRI-ERIC Business Plan [16] summarizes much of the work carried out during the Preparatory Phase including the planned access process to human biological samples and identifiable medical data in a way 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) or the Directive 95/46/EC on the Protection of Personal Data. The access procedures of BBMRI-ERIC to human biological samples and medical data were 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 to be approved by an ethical review board, and
- All procedures have to protect the privacy of sample donors.

Optional BBMRI-ERIC research services (Common Services), such as ethical, regulatory, and legal advice, data collection and transportation, sample processing, data analysis, and planning of prospective cohorts could thereafter be utilized and specified on a project by project basis. Noteworthy, the establishment of high quality research collaboration was considered 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.

7.3 Work Packages 4–6: Models for Common Services

During the Preparatory Phase it became obvious that harmonization, standardization and interoperability of European biobanking requires a series of BBMRI-ERIC Common Services to provide the biobanking community and biobank users with top-level expertise, services and tools in specific areas of biobanking. It was envisaged that Common Services are jointly funded by BBMRI-ERIC and the Member State(s) hosting the facility. Decisions on the location of Common Services were to be based on open calls and subsequent decisions by the BBMRI-ERIC Assembly of Members based on scientific excellence and cost efficacy as part of the Work Program jointly funded by the Members. In addition to actual biobanking activities common Services were envisaged for BBMRI-ERIC in the following areas:

Biomolecular tools and resources. During the Preparatory Phase a review was performed on existing resources for affinity reagents and other biomolecular resources as analytical tools applicable to biobanking. This 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 [17]. In addition, a new database for molecular methods (MolMeth) was established, providing best practice based protocols for molecular analyses of different types of samples [18]. The aim is to establish a continuously updated European network of service providers of relevant analytical technologies for measuring and imaging nucleic acids, proteins, metabolites, etc.

Database harmonization and IT-infrastructure. A key to the huge amount of biological, clinical, epidemiological and behavioural data is a well-functioning and reliable information management system to maintain unique and secure coding systems for specimens, subjects and biobanks. Subsequently, coordination and implementation of the interoperability of the existing and new biological databases of biobanks was seen as a key role of BBMRI-ERIC Common IT Service. Such an IT-infrastructure was to consist of a network based on the hub-and-spoke topology

to connect the different nodes, which are geographically spread through Europe, connected via the national or regional hubs. Common IT Services were to connect the entire network of National Nodes, Common Services, individual biobanks, users and observers into a single virtual structure, preserving on one hand privacy and autonomy, and supporting communication and collaboration on the other hand.

Harmonization of ethical, legal and societal issues (ELSI). During the Preparatory Phase analysis on the ethical, social and legal issues of the infrastructure resulted in a conceptual paper on ethics related policies for biobanks and biomolecular resources. Bovenberg [19] proposed a WIKI+ platform for legal aspects for uploading and validating existing legal documents in use in BBMRI-ERIC Member and Partner countries which is now available through the BBMRI-ERIC web site.

For efficient running of the BBMRI-ERIC ELSI Common Services each National Node is expected to designate a National ELSI Representative to participate in the ELSI Common Service activities and to interface with National Institutions, Biobanks and BBMRI-ERIC. The ELSI Common Services was to include a "Hot Line" to respond to ethical issues raised by users and a platform that provides access to existing ethical and legal frameworks for the exchange of human biological samples for research use in Europe. Training of biobank managers and ethics and legal officers was also considered an important activity.

7.4 Private Sector Access to Biobanks

Three types of users from private sector, each one interested in specific facilities provided by BBMRI were identified: pharmaceutical industries, diagnostic industries and biotechnology industries. Therefore, establishment of an international network of "Expert Centers" was proposed by SEAB of BBMRI-PP to facilitate international research collaborations by reducing the need for sample shipment and allowing primary data and value generation from biological resources to remain in the country of origin. According to the concept, BBMRI-ERIC affiliated Expert Centers are not-for-profit entities that represent a novel public-private partnership model that 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, data, and their analysis [20].

7.5 Education and Training

One of the objectives of BBMRI-PP was to plan a European Master/PhD curriculum for Biobanking Management and facilitate other types of education and training in biobanking. The European curriculum is currently tested in Lyon, France, to be later spread out over several education centers in Europe. BBMRI-ERIC will play a critical role in establishing and coordinating these programs. Industry has expressed their high interest in these training activities. Through the EMTRAIN

project of the Innovative Medicines Initiative (IMI) BBMRI-ERIC is contributing to a new education and training vision for pharmaceutical R&D, especially in biomarker development.

8 Development of BBMRI-ERIC National Nodes

The enthusiasm about the development of the BBMRI concept was beautifully illustrated by the development of National Nodes already during the progression of the Preparatory Phase. The important role of National Nodes in providing a common access portal to biobank resources, facilities and expertise available in Member States has been recognized. National biobanking communities comprising universities, hospitals, research institutions and resource centres were reorganized under the BBMRI banner, often following the same WP structure as was in place for BBMRI-PP. National Coordinators were nominated to lead the development at national level.

Work on establishment of National Nodes proceeded so fast that the first meeting of BBMRI National Coordinators was organized in Amsterdam on February 10–12, 2013, 10 months before the official establishment of the BBMRI-ERIC legal entity. Thirteen National Nodes were represented by their coordinators or deputies (Austria, Czech Republic, Estonia, Finland, France, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Spain, Sweden). Also the newly funded BBMRI-LPC (Large Population Cohorts) project was appropriately represented, as the aim of this FP7-funded "infrastructure-I3" project was to support the future BBMRI-ERIC in providing access to population biobanks of BBMRI-ERIC and thereby providing a real test bed for organizing scientific and ethical evaluation of research projects and the subsequent access of qualifying projects to BBMRI-ERIC-associated biobanks.

Following the BBMRI-PP tradition, the National Coordinators meeting focused on information exchange and identified a number of important areas for future collaboration. These were further discussed informally in other European biobank meetings/conferences in the second half of 2013; notably the BBMRI-ERIC Kick-off Meeting in Graz on September 26–27 and the HandsOn Biobanks Meeting in den Haag on November 21–22. After the establishment of BBMRI-ERIC, the National Coordinators meetings have become an official part of the Governance structure.

9 End of the Preparatory Phase Is Followed by a Long Interim Phase to Establish BBMRI-ERIC as a Legal Entity

In the original application and grant agreement the duration of BBMRI-PP was 2 years. However, during these 2 years it became clear that more time is needed to reach agreement on the Governance structure and financing of

BBMRI-ERIC. Through two amendments, the duration of BBMRI-PP was extended to 3 years. When the Preparatory Phase came to its end on January 31, 2011, the BBMRI-PP Steering Committee agreed that the current Steering Committee will continue to function as an interim governing body of BBMRI and the current Coordinator as the interim Coordinator until the Preparatory Body described in the Memorandum of Understanding (see below) was established.

Selection of host country for the BBMRI-ERIC legal entity had been done already during the Preparatory Phase. Ministries of BBMRI-PP partner countries received an offer from the Austrian minister for Science and Research, for Austria to serve as a host country for of BBMRI-ERIC. The matter was discussed in a Steering Committee meeting. No other formal offers were made and Austria was subsequently selected as the host country.

9.1 Involvement of Member State Ministries

The Statutes and Business plan for BBMRI-ERIC were produced during the Preparatory Phase with limited commitment of the ministries of potential member countries. Therefore, the procedure to agree on the critical issues of the Statutes (financial contributions towards joint budget, voting rights, language issues etc.) and to decide on the legal entity had to include a process where mandated ministerial representatives were involved. Towards this goal, a Memorandum of Understanding (MoU) was drafted where Member States expressed their aim to establish BBMRI as an ERIC and become Members of BBMRI-ERIC. By December 2011, 13 countries (Austria, Bulgaria, Czech Republic, Estonia, Finland, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Spain, Sweden) had signed the MoU, and a BBMRI Preparatory Body was established comprising representatives of Ministries and chaired by Dr. Hemma Bauer from the Austrian Ministry. Professors Zatloukal and Vuorio served as experts in the Preparatory Body explaining the work conducted by BBMRI-PP. It took eight meetings and about 2.5 years from the BBMRI Preparatory Body to reach agreement on the Statutes and the BBMRI-ERIC Governance structure. During this time period the MoU had been signed by another eight countries (Belgium, France, Germany, Ireland, Luxembourg, Poland, Switzerland, and Turkey). The work of Preparatory Body also included unofficial consultations of the EC by the Austrian Ministry and the Statutes writing group about the acceptability of the Statutes from the perspective of the ERIC regulation.

9.2 The ERIC Application

The application for ERIC status was a two-stage process. The first application was submitted to the European Commission on July 31, 2012 and the Commission's reply came on November 21, 2012. A lot of detail that had been added to the draft

Statutes after long debates by the Preparatory Body was removed by the Commission and transferred to rules of procedures.

The excitement of having reached a consensus on all key issues of setting up BBMRI-ERIC was reflected by the decision of the Austrian Ministry and the Preparatory Body to initiate organization of the Inauguration Ceremony of BBMRI-ERIC. A high-level inauguration ceremony was organized by the Austrian ministry and the BBMRI community in Graz on September 16, 2013. Two other biobank-related events were organized in conjunction with the inauguration: the International Biobanking Summit II (IBS-II) and the first Forum of the BBMRI-LPC project.

10 Establishment of BBMRI-ERIC

On December 3, 2013, 3 days after publication of the Statutes (dated November 22, 2013) in the Official Journal of the European Union on November 30, 2013, BBMRI was officially awarded the Community legal status of a European Research Infrastructure Consortium (ERIC).

During the interim phase the Preparatory Body had realized that establishment of BBMRI-ERIC also needs the key personnel to be in place by the beginning of 2014. A search committee was appointed by the Preparatory Body to plan and implement the selection process of the first Director General for BBMRI-ERIC, followed by a similar process to identify the first Administrative Director. These processes proceeded via drafting of job descriptions for the application process and evaluation criteria to short listing of the applicants based on the curricula vitae, interviews and finally presentation of the top candidates for both positions to the Preparatory Body. Professor Jan-Eric Litton from Sweden was subsequently nominated as the first Director General and Markus Pasterk from Austria as the first Administrative Director first by the Preparatory Body and finally by the Assembly of Members of BBMRI-ERIC in its first meeting. By that time 12 EU Member States (Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Malta, the Netherlands and Sweden) had completed the national process to commit to full membership and four other countries (Norway, Poland, Switzerland and Turkey) as well as the international organization IARC to the status of an observer.

11 BBMRI-PP in Retrospect

Overall the Preparatory Phase of BBMRI can be considered a success. All milestones and deliverables as outlined in the Description of Work were reached and approved by the European Commission. Some additional deliverables, such as the development of the Expert Center concept were an over performance.

In addition to the positive evaluation of BBMRI-PP by the Commission, BBMRI also received a favorable assessment by the ESFRI Expert Panel in 2014 [21]. Thus

BBMRI-ERIC became one of the first ERICs to be implemented, and one of the largest. The facts that the membership of BBMRI-ERIC covered both the largest and the smallest Member States and showed a reasonable good geographical distribution were looked upon very positively. Another indicator of success of the BBMRI concept was the constantly increasing interest to join BBMRI-PP, and later BBMRI-ERIC.

The main weakness of the BBMRI-PP scheme was the overly optimistic estimation (originally 2 years) of the timeline to organize and connect biobanks across the national borders and to commit Members States towards the Construction Phase. When the Statutes and the Governance structure developed during the Preparatory Phase were presented to the Member State ministries with very divergent decision making processes, it took over two and a half years to find agreement. The fact that ERIC was a new legal entity in Europe and establishment of BBMRI-ERIC took place in financially difficult times made the process even more difficult. This also explains why some countries have not yet been able to join BBMRI-ERIC despite their active participation in the Preparatory Phase and Preparatory Body.

A number of bottlenecks were identified during the Preparatory Phase. The most important challenge was created by the heterogeneity of the status of current European biobanks, typically linked to hospitals, universities, different research performing institutions, and national health institutes. The ownership of the biobanked samples was sometimes unclear as was their availability for biomedical research, governed by consent forms, national ethical review systems, and national legislation, which differed from one country to another. Also the molecular, clinical and life-style data attached to biobanked samples were in heterogeneous formats, usually gathered in the respective national languages. Interoperability of the existing data was a major challenge. All these factors form obstacles on the path towards smooth transnational access to biobanks. The BBMRI-LPC project has been testing the access procedure and has shown that transnational access is possible, but still faces many national and institutional regulations that slow down the process of accessing biobanks.

At the time of writing, BBMRI-ERIC has been in existence for a little over 1 year. The first work program has been prepared along the lines outlined in the Business Plan and the central coordination office is now housed in a new office building in Graz, Austria. The Assembly of Members and the Management Committee have been working hard to remove the remaining obstacles and the pan-European biobank BBMRI-ERIC has become a reality.

Acknowledgements Development of the BBMRI concept for a pan-European biobank was a joint effort of a very large number of individuals who contributed to the establishment of BBMRI-ERIC. The author wants to express his gratitude to this large group of individuals, too large to be listed here, for their contributions. The constructive support of Gert-Jan van Ommen and Kurt Zatloukal cannot, however, be left without acknowledgement. The financial contribution from the EC to BBMRI-PP is gratefully acknowledged (Grant Agreement No. 212111).

References

1. GenomeEUTwin project description. http://cordis.europa.eu/project/rcn/64820_en.html
2. Muilu J, Peltonen L, Litton JE (2007) The federated database—a basis for biobank-based post-genome studies, integrating phenome and genome data from 600,000 twin pairs in Europe. Eur J Hum Genet 15(7):718–723
3. PHOEBE project description. http://www.fhi.no/artikler/?id=73793
4. Budin-Ljøsne I, Isaeva J, Knoppers BM et al (2014) Data sharing in large research consortia: experiences and recommendations from ENGAGE. Eur J Hum Genet 22(3):317–321
5. Murtagh MJ, Thorisson GA, Wallace SG et al (2012) On behalf of the P3G consortium, GEN2PHEN and BioSHARE-EU navigating the perfect [data] storm. Norsk Epidemiologi 21(2):203–209
6. BioSHaRE-EU project description. www.bioshare.eu
7. Consortium Catalogue description. http://www.p3gobservatory.org/network/studies.htm?partner=engage
8. OECD Best Practice Guidelines for Biological Resource Centres (2007). http://www.oecd.org/dataoecd/7/13/38777417.pdf
9. OECD Guidelines on Human Biobanks and Genetic Research Databases (2009). http://www.oecd.org/dataoecd/41/47/44054609.pdf
10. European Strategy Forum on Research Infrastructures (2006) European roadmap for research Infrastructures. Luxembourg: Office for Official Publications of the European Communities. ISBN: 978-92-79-10117-5
11. European Science Foundation (2008) Population Surveys and Biobanking. Science Policy Briefing #32. http://www.esf.org/fileadmin/Public_documents/Publications/SPB32_Biobanking.pdf
12. Wichmann HE, Kuhn KA, Waldenberger M et al (2011) Comprehensive catalog of European biobanks. Nat Biotechnol 29(9):795–797
13. Caboux E, Plymoth A, Hainaut P (eds) (2007) Common minimum technical standards and protocols for biological resource centres dedicated to cancer research. WorkGroup Report 2, IARC
14. Guerin JS, Murray DW, McGrath MM et al (2010) Molecular Medicine Ireland guidelines for standardized biobanking. Biopreserv Biobank 8(1):3–63
15. Bravo E, Calzolari A, De Castro P et al (2015) Developing a guideline to standardize the citation of bioresources in journal articles (CoBRA). BMC Med. doi:10.1186/s12916-015-0266-y
16. BBMRI Business Plan. http://bbmri-eric.eu/documents/10181/49443/BBMRI+Business+Plan.pdf/25e8e6e0-c97f-40b2-91fb-ba1b4bf3184b
17. Bourbeillon J, Orchard S, Benhar I et al (2010) Minimum information about a protein affinity reagent (MIAPAR). Nat Biotechnol 28(7):650–653
18. Klingström T, Soldatova L, Stevens R et al (2013) Workshop on laboratory protocol standards for the molecular methods database. Nat Biotechnol 30(2):109–113. doi:10.1016/j.nbt.2012.05.019
19. Bovenberg JA (2007) Legal pathways for cross-border research: building a legal platform for biomedical academia. Eur J Hum Genet 15(5):522–524
20. van Ommen GJ, Törnwall O, Bréchot C et al (2015) BBMRI-ERIC as a resource for pharmaceutical and life science industries: the development of biobank-based expert centres. Eur J Hum Genet 23(7):893–900
21. Calvia-Goetz A, Franciosi A, Larsen S et al (2014) Assessing the projects on the ESFRI roadmap. A high level expert group report. Luxembourg: Publications Office of the European Union. ISBN: 978-92-79-32732-2; doi:10.2777/34016