



## **Deliverable No. 5.3**

# **Legal and ethical issues regarding access to biobanks**

Grant Agreement No.: 270089  
Deliverable No.: 5.3  
Deliverable Name: Legal and ethical issues regarding access to biobanks  
Contractual Submission Date: 31/01/2013  
Actual Submission Date: 31/01/2013

Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	



<b>COVER AND CONTROL PAGE OF DOCUMENT</b>	
Project Acronym:	<b>p-medicine</b>
Project Full Name:	From data sharing and integration via VPH models to personalized medicine
Deliverable No.:	D 5.3
Document name:	Legal and ethical issues regarding access to biobanks
Nature (R, P, D, O) <sup>1</sup>	R
Dissemination Level (PU, PP, RE, CO) <sup>2</sup>	RE
Version:	1
Actual Submission Date:	31/01/2013
Editor: Institution: E-Mail:	Nikolaus Forgó Institute for Legal Informatics, LUH <a href="mailto:forgo@iri.uni-hannover.de">forgo@iri.uni-hannover.de</a>

**ABSTRACT:**

This deliverable highlights the legal and ethical issues affecting access to biobanks by researchers in general and the envisaged solution contributed by the p-medicine metabiobank in particular. A risk-appropriate p-medicine access policy is developed in this report and a prototype of the data transfer agreement between the p-medicine metabiobank and the participating biobanks is annexed. There is also consideration of quality and safety standards for biobanks.

**KEYWORD LIST: Biobank, Access, Legal and Ethical Issues, Quality and Safety**

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 270089.

The author is solely responsible for its content, it does not represent the opinion of the European Community and the Community is not responsible for any use that might be made of data appearing therein.

<sup>1</sup> R=Report, P=Prototype, D=Demonstrator, O=Other

<sup>2</sup> PU=Public, PP=Restricted to other programme participants (including the Commission Services), RE=Restricted to a group specified by the consortium (including the Commission Services), CO=Confidential, only for members of the consortium (including the Commission Services)

<b>MODIFICATION CONTROL</b>			
Version	Date	Status	Author
1.0	10/11/12	Draft	Nikolaus Forgó, Stefanie Hänold, Iheanyi Nwankwo, Wolfgang Kuchinke
2.0	24/12/12	Draft	Nikolaus Forgó, Stefanie Hänold, Iheanyi Nwankwo, Wolfgang Kuchinke, Sebastian Seufert
3.0	16/1/13	Draft	Nikolaus Forgó, Stefanie Hänold, Iheanyi Nwankwo, Wolfgang Kuchinke, Sebastian Seufert
4.0	31/1/13	Final	Nikolaus Forgó, Stefanie Hänold, Iheanyi Nwankwo, Wolfgang Kuchinke, Sebastian Seufert

#### List of contributors

- Nikolaus Forgó, LHU
- Stefanie Hänold, LHU
- Iheanyi Nwankwo, LHU
- Wolfgang Kuchinke, UDUS
- Sebastian Seufert, UDUS
- Christina Schröder, Fraunhofer IBMT
- Gabriele Weiler, Fraunhofer IBMT
- Elias Neri, Custodix
- Norbert Graf, USAAR

## Contents

1	EXECUTIVE SUMMARY .....	6
2	INTRODUCTION .....	7
3	RESEARCHER ACCESS TO BIOBANK RESOURCES.....	9
4	LEGAL AND ETHICAL FACTORS THAT AFFECT ACCESS TO BIOBANKS.....	12
4.1	INFORMED CONSENT FOR THE USE OF BIOMATERIAL AND RELATED PERSONAL DATA.....	13
4.1.1	<i>Features of biobanks and informed consent</i> .....	14
4.1.2	<i>Secondary uses</i> .....	18
4.1.3	<i>Right to withdraw</i> .....	19
4.1.4	<i>Differences between Member States' regulations applicable to the use of samples and personal data associated with samples</i> .....	19
4.2	FURTHER ISSUES IN DATA PROTECTION LAW .....	23
4.2.1	<i>Data associated with samples and data protection law</i> .....	23
4.2.2	<i>Samples as personal data?</i> .....	24
4.2.3	<i>Different interpretations on "anonymous" data</i> .....	24
4.3	THE ISSUE OF DIFFERENT REQUIREMENTS IN THE NATIONAL LAWS WHEN SHARING BIOMATERIAL AND ASSOCIATED PERSONAL DATA AND FUNCTIONAL PARALLELISM .....	26
4.3.1	<i>Transnational sharing of biomaterial</i> .....	26
4.3.2	<i>Transnational sharing of (personal) data</i> .....	31
4.4	CRITERIA FOR ASSESSING REQUESTS AND PROPOSALS .....	33
4.5	INTELLECTUAL PROPERTY.....	33
5	MATERIAL TRANSFER AGREEMENTS .....	35
6	INITIATIVES TO FACILITATE ACCESS TO BIOBANKS IN EUROPE .....	36
7	THE P-MEDICINE METABIOBANK FRAMEWORK .....	40
7.1	THE P-MEDICINE METABIOBANK CONCEPT AND DATA FLOWS .....	41
7.1.1	<i>Uploading data to the metabiobank</i> .....	41
7.1.2	<i>Searching for data in the metabiobank</i> .....	42
7.2	DATA PROTECTION ASPECTS.....	44
7.2.1	<i>Data sets of the donors</i> .....	44
7.2.2	<i>Data of the end-users</i> .....	45
8	THE P-MEDICINE METABIOBANK ACCESS POLICY .....	46
9	QUALITY AND SAFETY STANDARDS IN BIOBANKING .....	49
9.1	NECESSITY FOR QUALITY IN BIOBANKING .....	49
9.2	EUROPEAN REGULATIONS WITH REGARD TO BIOBANKS: PROTECTION OF FUNDAMENTAL RIGHTS AND QUALITY ASSURANCE.....	50
9.3	DIRECTIVE 2004/23/EC .....	52
9.4	RELATED LAWS .....	55
10	BIOBANK BEST PRACTICE GUIDELINES AND STANDARDS .....	57
10.1	OECD: BEST PRACTICE GUIDELINES FOR BIOLOGICAL RESOURCE CENTERS (2007).....	57
10.2	ISBER: BEST PRACTICES FOR REPOSITORIES (2008).....	58
10.3	NCI: BEST PRACTICES FOR BIOSPECIMEN RESOURCES (2007).....	59
10.4	2011 REVISED NCI BEST PRACTICES .....	59
10.5	P3G OBSERVATORY .....	59
10.6	HUMAN TISSUE REPOSITORIES: BEST PRACTICES FOR A BIOSPECIMEN RESOURCE FOR THE GENOMIC AND PROTEOMIC ERA .....	60
10.7	AUSTRALIAN BIOSPECIMEN NETWORK BIOREPOSITORY PROTOCOLS .....	60
10.8	INTERNATIONAL NETWORK OF BIOLOGICAL RESOURCE CENTRES (IARC).....	60
10.9	BIOBANKING GUIDELINES AND REGULATIONS IN BBMRI .....	60
11	GROWTH OF BIOBANKS AND THE ISSUE OF HARMONISATION .....	62
12	SAFETY STANDARDS IN BIOBANKING .....	67
12.1	SAFETY IN THE TISSUE DIRECTIVE .....	67
12.2	SAFETY IN BIOBANKING GUIDELINES .....	68
13	QUALITY ASPECTS ASSIGNED TO THE METABIOBANK FRAMEWORK OF P-MEDICINE ...	69

14	DISCUSSION .....	72
15	SUGGESTIONS TO IMPROVE QUALITY IN P-MEDICINE BIOBANKING .....	75
16	CONCLUSION.....	77
	APPENDIX 1 - ABBREVIATIONS AND ACRONYMS .....	78

# 1 Executive Summary

The significance of biobanks for medical research is increasing rapidly. Huge amounts of samples and data are needed for research studies, especially for examining biomarkers etc., but researchers face many obstacles in the search for suitable biomaterial and data. Those hindrances which have legal, ethical and quality dimensions and that hamper access to biobanks' resources will be investigated in this deliverable in detail:

The need for informed consent by the patient to agree to the collection and use of his or her samples and related data will be elaborated in relation to specific features of biobanks. Issues regarding secondary use, the right to withdraw consent and differences in the national laws will be illustrated.

Further, relevant issues with regard to data protection and privacy will be discussed, in particular the possible extension of the scope of the Data Protection Directive<sup>3</sup> to samples, as well as the different approaches to the question of when data is to be regarded as “anonymous” in a legal sense. Privacy protection is not only of importance to the donor, but it is of utmost importance for researchers too, because where data is found to be anonymous, the restrictions of the Data Protection Directive and the implementing national laws do not apply so that legal risks decrease significantly.

It will be shown how divergent national requirements for the use of samples and (personal) data associated with them impede the transnational sharing of biomaterial and related data. On the other hand, the impact of the principle of mutual recognition in facilitating exchange of samples and data will be examined. It is, however, not enough, to illustrate the problems only. It is the aim of p-medicine to develop working, compliant solutions.

While a lot of initiatives try to facilitate greater access to bio-resources, the contribution of the p-medicine project in this regard therefore will be to develop a first level integration facility that will permit a search of existing biobanks by researchers to obtain information about their material and data. The envisaged technical implementation will be examined with a focus on data protection aspects. In addition, this deliverable sets out an access policy for the use of the p-medicine metabiobank infrastructure. A prototype of the data transfer agreements between the p-medicine metabiobank and the participating biobanks is annexed.

Relevant legislation and a multitude of guidelines concerned with the quality and safety of biobanking are examined for their relevance in p-medicine. Since p-medicine will use cells and tissues not for clinical applications but for research purposes, many regulations do not apply. Nonetheless, collaborative research is dependent on the quality of biosamples to obtain relevant research results. Use cases are examined as to how p-medicine can support the use of harmonised high-quality samples. We suggest that p-medicine should encourage the use of standards, normalization and validated protocols across all biobanks and laboratories involved in its projects. Metadata about how the samples were collected, processed, and stored should be provided in the metabiobank to give researchers the possibility to retrieve quality information.

---

<sup>3</sup> Directive 95/46/EC.

## 2 Introduction

This deliverable aims to analyse the legal and ethical issues regarding access to biobank, with particular focus on the framework of the p-medicine project. In the course of doing this, issues relating to sharing of biomaterial and data within a trans-European framework, as well as quality and safety standards will be discussed.

There have been several acknowledgements that it is in the public interest for biobanks to be accessible by a large group of researchers as possible, in order to ensure optimum utilisation of the potential of biobanks.<sup>4</sup> This makes it imperative to have a framework that will facilitate this access and make it easier for researchers to get the results and resources they need for their investigations in full compliance with all legal and ethical rules. However, there are various obstacles in the bid to achieving this objective within the EU. Paramount factors include the lack of harmonised rules for biobank operations such as SOP and exchange formats, as well as the lack of a harmonised legal and ethical framework for data protection and consent models of sharing data and samples.

It is therefore worth the effort to increase the interoperability between biobanks and the knowledge about data and material that is available in existing biobanks. While the p-medicine project does not aim to establish a new biobank, the framework that is being developed under the project is to build a metabiobank infrastructure. In this framework, information and communication technology will be used to enable access to biomaterial and associated data through a search engine that reveals the availability of resources within the participating biobanks. However, individual-level data will not be transferred. In essence, the metabiobank will facilitate access to statistical or aggregated data about the availability of biomaterials and associated data within the integrated biobanks. Further negotiations for the transfer of biomaterial and data will be made between the researcher and the biobank operator(s) that hold the desired samples.

It has to be stressed that so far, there is no harmonized framework for sharing biosamples (access rules and procedures) within the EU or the world at large. This fragmentation among the EU Member States has a great tendency to hinder cross-border biobank cooperation.<sup>5</sup> Legal and ethical challenges such as the appropriate consent model to cover future (secondary) uses of biobank materials and data, divergent regulatory requirements for access, data protection and security, differences in priority setting and screening of scientific merit of proposals, intellectual property rights, etc. are still prevalent and militate against smooth cross-border cooperation.<sup>6</sup>

Furthermore, there is also a gap in standards for maintaining high-quality samples through good collection and handling techniques. Ensuring that biobanks follow evidence-based standards for collecting, storing, and handling of samples is an imperative that must be pursued vigorously at a global level. Researchers may rightly expect that the biomaterial they receive for further analysis attains a certain level of quality. This implies that biobanks have to implement stringent quality control measures covering, in addition to the material transfer itself, the whole process of material acquisition, transport, pre-analytical handling and

---

<sup>4</sup> German National Ethics Council, Biobank for Research, 2004, viewed 13.12.2012, <[http://www.ethikrat.org/english/publications/Opinion\\_Biobanks-for-research.pdf](http://www.ethikrat.org/english/publications/Opinion_Biobanks-for-research.pdf)>, p. 75.

<sup>5</sup> Zika, E, et. al., Biobanks in Europe: Prospects for Harmonisation and Networking, 2010 viewed 13.12.2012, <<http://ftp.jrc.es/EURdoc/JRC57831.pdf>>.

<sup>6</sup> Ibid.

storage. There is also a need to have metadata describing clinical status and measurements of clinical phenotypes that characterize samples.<sup>7</sup>

Although there have been several initiatives to encourage trans-European cooperation in this regard, especially in disseminating best practices for biobanking, there is a growing need for better harmonisation of their operations to integrate legal, ethical, technical and social frameworks in biobanking. This will play an important role in ensuring the preservation of biosamples - integrity, interoperability as well as facilitate easy access to the valuable resources they hold, including their secondary uses.

This document will look at the issues raised above and how the p-medicine biobank access framework has tackled them. Following this introduction, section three generally looks at biobank resources and how researchers gain access to them. Section four discusses legal and ethical issues that affect access to biobanks, while section five briefly looks at material transfer agreements. Section six examines initiatives that aim at improving access to bio-resources. The p-medicine metabiobank framework is described in section seven, while a p-medicine metabiobank access policy is developed in section eight. In section nine till fourteen quality and safety standards in biobanking will be elaborated, while the final section, ten is the conclusion.

---

<sup>7</sup> Marko-Varga, G, et. al, Standardization and Utilization of Biobank Resources in Clinical Protein Science with Examples of Emerging Applications. *J. Proteome Res.* 2012, 11, pp. 5124–5134.



### 3 Researcher access to biobank resources

The term “biobank” covers a variety of dissimilar facilities (e.g., population biobanks, environmental specimen banks, clinical trial collections, disease-based sample collections, etc.) and this makes it difficult to have a single encompassing definition of the term.<sup>8</sup> These differences could be seen from their range in design and uses – spanning from those established to support clinical health care to those with the primary purpose of research.<sup>9</sup> In general, biobanks are collections of human biospecimen (e.g. tissues, blood and body fluids and their derivatives collected for diagnosis and/or for research projects) and their associated clinical and outcome data.

One of such growing establishments is the longitudinal population-based biobank with biological samples and data from randomly selected individuals of a general population. Typically, samples are stored together with data about family history, lifestyle, environmental exposure etc., collected at the entry time and updated in the future. This format enables researchers to examine biomarkers and to assess the natural frequency of occurrence and progression of common diseases in a priori healthy population, and to investigate putative predisposing genetic variants and environmental risk factors.<sup>10</sup>

In contrast to population biobanks, disease-oriented biobanks store specimen that are collected from individuals in the context of medical diagnosis and treatment. Various collections of diseased human tissues are annotated with detailed information on the existing disease, information on response to therapy as well as the final disease outcome.<sup>11</sup> Almost every major hospital in Europe supports the collection of blood, DNA or tissues.<sup>12</sup> Researchers can use those facilities to compare different disease stages and forms of treatments at a molecular level which is instrumental for the finding of biomarkers for diagnosis or prediction of disease progression. This may include a case control study that contains about an equal number of samples and data from healthy persons.<sup>13</sup>

It is usually not easy to understand the use of the term “access” when it relates to biobanking activities. Generally, access means being allowed to use data or materials.<sup>14</sup> In the context of biobanking, access may include identifying the location of the biomaterial and associated data,<sup>15</sup> visiting a biobank and using resources onsite (this will be the case with the BBMRI Expert Centres), duplicating copies of data or samples of material or storing them, or downloading data through an ICT infrastructure. In extreme cases, this may also include communicating with donors. Transferring biomaterial to researchers is also a form of access that usually takes place after further negotiations with the biobank operators. Some biobanks limit access to their materials and data to a closed community of researchers, while others are open to a wider community. A UK report in 2006 finds that: “Access may amount to a truly cooperative effort – symbiotic collaboration – in which researchers who are not members of the custodial team bring complementary resources or capabilities to a joint project, and the custodians make interpretive or other intellectual contributions beyond merely supplying data or materials [...] Depending on the circumstances, collaboration can

---

<sup>8</sup> See commentary by Hewitt, R, et. al., ‘Defining “biobank”’, ISBER News 2012, vol. 12 no. 4, p. 20.

<sup>9</sup> Watson, P, et. al., ‘Evolutionary Concepts in Biobanking – the BC Bioblibrary’, Journal of Translational Medicine 2009, p. 2.

<sup>10</sup> Asslauer, M and Zatloukal, K, ‘Biobanks: Transnational, European and Global Networks, Briefings in Functional Genomics and Proteomics, vol. 6 no. 3, p. 194.

<sup>11</sup> Ibid, p. 195.

<sup>12</sup> Yuille, M, et. al., ‘Biobanking for Europe’, Briefings in Informatics, vol. 9 no. 1, p. 19.

<sup>13</sup> Asslauer, M and Zatloukal, K, op. cit, p. 195.

<sup>14</sup> Lowrance, M, Access to collections of data and materials for health research, 2006, UK, p. 11.

<sup>15</sup> European Science Foundation, Population Surveys and Biobanking, ESF Science Policy Briefing, 2008, p. 5.

be viewed, by access providers or access requesters, either as an advantage or as a burden.”<sup>16</sup>

The potential for analysis of the samples and associated data is growing constantly and has increased with the development of high-throughput sequencing and genotyping technologies. For instance, it is possible to determine one million genetic variants of an individual within one hour.<sup>17</sup> However, to fully exploit the potential of biobanks and to accelerate the development towards personalized medicine, researchers must be able to use the information of large sample stores of a number of biobanks. For genetic-lifestyle interaction studies for example, 20.000 – 50.000 samples may be required.<sup>18</sup> This large number of resources can only be achieved if researchers have access to various existing biobanks. This will to a great extent, require integrating local and national biobank resources into a coherent research infrastructure that will significantly improve access to large samples and data sets.

Currently, researchers need to surmount a whole lot of challenges if they wish to have access to these biobank resources - spanning from finding the appropriate biobank with suitable data and materials to meeting the costs for granting such access. In practical terms, some of these challenges are partly being tackled through ICT solutions that integrate biobank infrastructures. The BBMRI, CRIP and P3G projects, for example, have tried to bring a solution to biobank access problems by providing an interface where biobanks could collaborate through linking together data and metadata among participating institutions. via these infrastructures, a researcher could query and obtain information about the existence of data and material within a very short time and at a minimal cost.

In a second step however, researchers who target a set of suitable material and data must still overcome a series of ethical, legal and other conditions to access these resources from individual biobanks.<sup>19</sup> Indeed, many factors affect getting real materials from biobanks at this stage. This includes the obligation on biobank operators to manage their sensitive information in a way that will be of optimal use for the scientific community, while at the same time ensuring proper protection and respect for the privacy and confidentiality of the donors. So far, there is no standardised procedure for the evaluation of requests for granting access. The decision is usually affected by a number of considerations including control and confidentiality concerns, or even competition.<sup>20</sup> In most cases, it is completely dependent on the biobank custodian/management. The above issues raise a challenge in establishing an appropriate balance between protecting the biobanks and their volunteer donors and making their resources available to researchers. When interoperation is sought in some cases, specific restrictions concealed in variable policies, procedures and contracts do constitute hurdles. While parties interested in performing studies need to know what data/material is available at the time of study design in order to form their research proposal and determine which biobanks contain the resources that are suitable for their proposed study, it is also

---

<sup>16</sup> Lowrance, M, op. cit., p. 12.

<sup>17</sup> Mascalzoni, D, et. al., ‘Informed Consent in the Genomics Era’, PLOS Medicine 2008, vol. 5 no. 9, p. 1302.

<sup>18</sup> William, R, et. al., ‘Integrating Biobanks: Addressing the Practical and Ethical Issues to Develop a Valuable Tool for Cancer Research’, Nature Reviews Cancer 2010, viewed 28.01.2013, <<http://www.ucd.ie/t4cms/integrating%20biobanks.pdf>>, p.1.

<sup>19</sup> Zielhuis, G, ‘Biobanking for epidemiology’, Public Health 2012, pp. 214-216.

<sup>20</sup> Nobel, S, ‘Biobanks – Integration of Human Information to Improve Health’, 2008, viewed 25.12.2012,

<[http://www.vr.se/download/18.61c03dad1180e26cb8780004896/Spr%C3%A5kgranskad+Biobank\\_report\\_SRC\\_v2.pdf](http://www.vr.se/download/18.61c03dad1180e26cb8780004896/Spr%C3%A5kgranskad+Biobank_report_SRC_v2.pdf)>, p. 11; See also Verlinden, M, ‘Access rules within biobank networks’, 2012, viewed 25.12.2012, <[http://www.esbb.org/nov2011/slides/s11c\\_verlinden.pdf](http://www.esbb.org/nov2011/slides/s11c_verlinden.pdf)>.

important to understand what factors may influence the actual granting of access to these resources.<sup>21</sup> The following sections will discuss these factors in detail.

---

<sup>21</sup> Krestyaninova, M, et. al., 'Biobank Metaportal to Enhance Collaborative Research: sail.simbioms.org', (n.d), viewed 25.12.2012, [http://www.iiisci.org/journal/CV\\$/sci/pdfs/HCT875XS.pdf](http://www.iiisci.org/journal/CV$/sci/pdfs/HCT875XS.pdf).

## 4 Legal and ethical factors that affect access to biobanks

One of the essential factors identified over the years as affecting biobanking is the lack of a harmonized international regulatory framework on its governance. Although one finds a number of international regulations and reports on principles relating to health and biomedicine, only few of them address biobanking specifically, and in most cases they are not binding until domesticated into the local legislation.<sup>22</sup>

One aspect that should be noted right from the beginning regarding the legal situation in the EU is that there are different legal regimes between the use of the samples and the associated data of the participant. Whereas regarding the sharing of personal data, the national laws implementing the Data Protection Directive<sup>23</sup> are in force and we find a more or less coherent framework here,<sup>24</sup> there is however, no such legislative harmonisation on a European level for the sharing of biomaterial. Some EU Member States such as Iceland<sup>25</sup> and Estonia<sup>26</sup> have enacted laws specifically to govern their population database projects. Spain has just recently amended its Biomedical Research Act by the 1716/2011 Royal Decree.<sup>27</sup> Other Member States, such as Germany or France<sup>28</sup>, do not have specific regulatory instruments for biobanking and sharing of biomaterials. In effect this means that one has to search for the relevant statutory provisions in a number of national regulations which are far from uniform.<sup>29</sup> Furthermore, it is not always clear where the borderline is between the scope of these biomedical acts and the national data protection laws that apply in these situations.<sup>30</sup> This has affected to a great extent the interpretation and application of essential concepts such as informed consent, secondary uses of biosamples etc. Thus, access to biosamples and data is to a large extent influenced by the legal rules and obligations faced by biobanks within their jurisdiction of establishment.

---

<sup>22</sup> See for example, WMA, Declaration of Helsinki 2008; WMA, Declaration on the Human Genome Project 1992; CIOMS, Ethical Guidelines for Biomedical Research on Humans 2002; The Convention on Human Rights and Biomedicine; UNESCO, International Declaration on Human Genetic Data 2003; UNESCO, Universal Declaration on the Human Genome and Human Rights 1997; UNESCO International Bioethics Committee, Report on Confidentiality and Genetic Data 1999; HUGO Ethics Committee, Statement on DNA Sampling, Control and Access 1998; Council of Europe, Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo 1997; Council of Europe, Recommendation R (92) 3 on Genetic Testing and Screening for Health-Care Purposes 1992; Council of Europe Recommendation on the Collection of Epidemiological Data on Primary Health Care 1989; Council of Europe, Recommendation R (81) 1 on Regulations for Automated Medical Data Banks 1981 etc. Council of Europe, Recommendation R (94)1 on Human Tissue Banks 1994; Council of Europe, Recommendation R(2006) 4 on Research on Biological Materials of Human Origin.

<sup>23</sup> Directive 95/46/EC.

<sup>24</sup> For more details see D5.1: Setting Up of the Data Protection and Data Security Framework, p. 13.

<sup>25</sup> Biobanks Act, No. 110/2000, as amended by Act No. 27/2008 and Act No. 48/2009, viewed 30.11.2012, [http://eng.velferdarraduneyti.is/media/acrobat-enskar\\_sidur/Biobanks-Act-as-amended.pdf](http://eng.velferdarraduneyti.is/media/acrobat-enskar_sidur/Biobanks-Act-as-amended.pdf).

<sup>26</sup> Human Genes Research Act (RT I 2000, 104, 685), viewed 30.11.2012, <<http://biochem118.stanford.edu/Papers/Genome%20Papers/Estonian%20Genome%20Res%20Act.pdf>>.

<sup>27</sup> Arias-Diaz, J, et. al., 'Spanish Regulatory Approach for Biobanking', European Journal of Human Genetics 2012, p. 1.

<sup>28</sup> Budin-Ljønsne, I, 'ELSI challenges and strategies of national biobank Infrastructures', 2012, viewed 23.12.2012, <<http://www.ntnu.no/ojs/index.php/norepid/article/view/1487/1332>>.

<sup>29</sup> Knoppers, B, et. al., op. cit., p. 299.

<sup>30</sup> European Commission, JRC, Biobanks in Europe: Prospects for Harmonisation and Networking, 2010, viewed 19.12.2012, <[ftp://ftp.jrc.es/pub/EURdoc/JRC57831.pdf](http://ftp.jrc.es/pub/EURdoc/JRC57831.pdf)>, p. 119.

Of particular interest for p-medicine that strives for a European-wide exchange of knowledge, data and biomaterial are the legal and ethical aspects of sharing of biomaterial and data with researchers across Europe. As indicated earlier, regulatory regimes differ and create uncertainties amongst researchers in multinational trials as to which law is applicable. It should be kept in mind that there is no uniform framework for the use of personal data and samples. Below, we will look at the following factors that affect access to biobanks in detail:

- Informed consent for the use of biomaterial and related personal data
- Data Protection Law
- The issue of different requirements in the national laws when sharing biomaterial and associated personal data and functional parallelism
- Criteria for assessing requests and proposals
- Intellectual Property

#### **4.1 *Informed consent for the use of biomaterial and related personal data***

The nature, design and scope of consent that was obtained during the collection of biosamples are part of the critical factors in allowing access to the samples stored in biobanks.<sup>31</sup> As one of the most important and acknowledged principles in medical research, informed consent of the person who is going to donate biomaterial or data is meant to preserve the self autonomy and protection of the donor. In the context of biobanking, informed consent concerns the process in which the envisaged participant receives the relevant information and decides whether or not to authorize the storage and use of his or her samples and pertaining personal data.<sup>32</sup>

With regard to the use of (sensitive<sup>33</sup>) personal data for research purposes, the Data Protection Directive and the implementing national laws have to be considered. Principally, every kind of processing of sensitive personal data, e.g. health data, is forbidden; but exemptions are provided: for instance, when the informed consent of the patient is obtained. The Data Protection Directive also allows Member States in Art. 8 (4) to implement exceptions in their national laws for reasons of substantial public interest if they provide suitable safeguards for the privacy protection of the data subjects. According to Recital (34) scientific research is a possible example for an important public interest within the context of the Data Protection Directive.<sup>34</sup> Concerning the use of samples for research, many Member States have laid down the requirement of informed consent, but in a lot of cases also provide exemptions.<sup>35</sup> In practice, it is not always clear whether the obtained informed consent covers the use of both the samples and the use of the personal data, especially if just one consent form is used.<sup>36</sup>

---

<sup>31</sup> Kiehntop, M and Krawezak, M, 'Biobanking and international interoperability: samples', Hum Genet 2011, vol. 130, pp. 369-376.

<sup>32</sup> European Commission, JRC, Biobanks in Europe: Prospect for Harmonisation and Networking, 2010, viewed 02.12.2012, <<http://ftp.jrc.es/EURdoc/JRC57831.pdf>>, p. 122.

<sup>33</sup> "personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life" (Art. 8 Data Protection Directive).

<sup>34</sup> For more details see D5.1: Setting up of the Data Protection and Data security Framework, p. 17-19.

<sup>35</sup> See point 4.1.4.1.

<sup>36</sup> Stefanini, E, 'The Need for Italian Biobank Regulation', SCRIPTed 2010, vol. 7 no. 1, p. 74.

The debate is still ongoing as to whether broad consent can be used to permit third party access and sharing without the need for a re-consent for a future use of the samples. While most States have recognised the enormous burden of re-consenting for future use of biosamples and personal data and are easing the requirements, such as in the UK, others still impose the classical rule which seems to pose hurdles for the access to the biobank resources within such jurisdictions. In France, for instance, researchers have a legal obligation to renew consent before reusing donors' samples for a new purpose.<sup>37</sup>

#### 4.1.1 Features of biobanks and informed consent

As stated above, biobanking has not only become a common feature in clinical trials, but there is also a development in many countries to establish stores of samples and associated data of millions of donors in population biobanks, which are deemed as essential research tool to scrutinize human diseases<sup>38</sup>. These biobanks are typically set up as long-term resources that could be used for a wide range of investigations which could not be foreseen on the day of collecting the samples.<sup>39</sup> The increasing pressure for flexibility in the use and sharing of samples made the consent process even more complicated.<sup>40</sup> One also has to consider that genomic research by nature also touches on the interests of others such as relatives or other genetic communities of the participant. Though in Western countries, consent is a very individualistic notion, however, in genetic research, sensitivity to familial or cultural considerations may require consent to be sought also from wider groups.<sup>41</sup> So far, there is still an unsettled discussion on how informed consent (not only in connection with biobanking) should be designed, and national laws differ considerably regarding the strictness and procedures in obtaining valid informed consent. This is a potential problem for international collaboration in the exchange of samples and data.<sup>42</sup>

There are several types of consent under discussion in the literature which differ in terms of the information given to the donor and the level of authorization obtained from them. The following table shows general types of informed consent, albeit not exhaustive, and not exclusive of each other, e.g. broad consent and opt-out solutions can be combined (see table 1).

---

<sup>37</sup> Zika, E, op. cit., p. 147.

<sup>38</sup> Caulfield, T, 'Biobanks and Blanket Consent: the Proper Place of the Public Good and Public Perception Rationales', KLJ 2007, pp. 211-212.

<sup>39</sup> NHMRC, Biobanks Information Paper 2010, viewed 28.11.2012, <[http://www.nhmrc.gov.au/files/nhmrc/file/your\\_health/egenetics/practioners/biobanks\\_information\\_paper.pdf](http://www.nhmrc.gov.au/files/nhmrc/file/your_health/egenetics/practioners/biobanks_information_paper.pdf).

<sup>40</sup> Watson, R, et. al., op. cit., p. 648.

<sup>41</sup> NHMRC, op. cit, p. 24.

<sup>42</sup> Salvaterra, E, 'Banking together', EMBO Reports 2008, vol. 9 no. 4, p. 309.

Models of informed consent <sup>43</sup>	Level of information and authorization
Specific consent	Allows the use of biological specimens and related data only in immediate research; forbids any future study that is not foreseen at the time of the original consent
Partially restricted consent	Allows the use of biological specimens and related data in specific immediate research and in future investigations directly or indirectly associated with them
Multi-layered consent	Requires several options to be explained to the research subject in a detailed form and samples and related data can be used for any research that is covered by the donor's consent
Broad consent	Allows the use of biological specimens and related data in immediate research and in future investigations of any kind at any time
Opt-out method	The tissue is stored and used for research unless a person explicitly refuses <sup>44</sup>

Table 1: (Non exhaustive) Listing of the different types of informed consent

From the table above, one could see a divide as to how informed consent can be construed. Proponents of broad consent claim that it will facilitate research. They argue that re-consenting the participants for every new research project would be far too costly, time consuming and could even falsify research results because it is highly probable that a considerable number of participants will be lost, e.g. due to the fact that they have moved, died or are annoyed by repeated enquiries for their consent.<sup>45</sup> Due to the long term nature of population biobanks, broad consent would be the more suitable option in their opinion.<sup>46</sup> They also associate a lower risk of harm with the samples in biobanks in relation to the benefits that could be generated from such potential future research for the society,<sup>47</sup> since there is no risk for physical harm – except when samples are extracted from the body- as is

<sup>43</sup> Ibid.

<sup>44</sup> Giesbertz, N, et. al., 'Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out', PLoS Biology 2012, vol. 10 no. 8, p. 1; relevant in some Member States for the storage and use of residual tissue.

<sup>45</sup> Knoppers, B and Abduhl-Rahman, M, 'Biobanks in the Literature', viewed 21.11.2012, <[http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CElQFjAB&url=http%3A%2F%2Fwww.p3gobservatory.org%2Fdownload%2Fpublications%2FEthicsChapter\\_2.doc&ei=yRCtUMetEonltAbetlGACw&usq=AFQjCNEEnXEawk5RSBjb1jPol8f-8aPaVPw&cad=rja](http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CElQFjAB&url=http%3A%2F%2Fwww.p3gobservatory.org%2Fdownload%2Fpublications%2FEthicsChapter_2.doc&ei=yRCtUMetEonltAbetlGACw&usq=AFQjCNEEnXEawk5RSBjb1jPol8f-8aPaVPw&cad=rja)>, p. 4; Elger, B and Caplan, A, 'Consent and Anonymization in Research Involving Biobanks', EMBO Reports 2006, vol.7 no. 7, p. 662.

<sup>46</sup> Knoppers, B and Abduhl-Rahman, M, Ibid.

<sup>47</sup> Watson, R, et. al., op. cit., p. 649.

the case in clinical trials.<sup>48</sup> Where appropriate protection has been put in place to ensure safe handling of samples and data, the approval of an ethical committee is obtained and there is the possibility for participants to withdraw their samples and data, this school of thought believes that broad consent is appropriate.<sup>49</sup>

On the other hand, when a closer assessment is made at the very nature of informed consent, it may seem that relying on the concepts of broad or blanket consent may be problematic. The idea behind informed consent is that the patient and/or donor can make up his or her mind on whether the participation in medical research is in his or her interests or not. The point is that such a donor can only do that if he or she knows about the nature of the research, the risks and the benefits. Proponents of specific consent have criticized broad consent on the premise that the more general the consent is, the less informed it becomes and that the use of the term informed consent is misleading for participation in research that is not foreseen and not specified in a research protocol.<sup>50</sup> But it has to be noted that using specific consent for large scale biobanks may hamper their status as “research platforms” that will be used by many researchers, for various research purposes over decades. It is impossible to tell in advance for what kind of research the samples and data will be used. However, it seems that the proposition on modifying the requirements for informed consent with special focus on biobanks is pretty strong. When potential risks of harms are deemed to be minimal, strong emphasis is put on the need to use the samples for progress in medical research.<sup>51</sup> There are a number of international guidelines that allow blanket or broad consent under certain circumstances in order to facilitate research. The UNESCO International Bioethics Committee for instance has stated that: “blanket consent covering all forms of future research might be preferable”.<sup>52</sup> Some countries such as Belgium have even adopted ‘opt out’ systems for residual tissue<sup>53</sup>, whereby the patients are not asked for their consent, but can indicate that they do not want their tissue to be used for research purposes.<sup>54</sup>

With regard to informed consent for the processing of personal data the definition in the Data Protection Directive of informed consent needs to be considered. According to Art. 2 (h) ‘the data subject’s consent’ shall mean any freely given specific and informed indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed. The Article 29 Data Protection Working Party stated in its opinion on the definition of informed consent:

*“To be valid, consent must be specific. In other words, blanket consent without specifying the exact purpose of the processing is not acceptable. To be specific, consent must be intelligible: it should refer clearly and precisely to the scope and the consequences of the data processing. It cannot apply to an open-ended set of processing activities. This means in other words that the context in which consent*

---

<sup>48</sup> Erikson, S & Helgesson, G, ‘Potential Harms, Anonymization, and the Right to Withdraw Consent to Biobank Research’, *European Journal of Human Genetics* 2005, vol. 13, p. 1702; Watson, R, et. al., op. cit., p. 649.

<sup>49</sup> Hofman, B, ‘Broadening Consent – and Diluting Ethics’, *J Med Ethics* 2009, vol. 35, p. 125.

<sup>50</sup> Arnason, V, ‘Coding and Consent: Moral Challenges of the Database Project in Iceland’, *Bioethics* 2004, vol. 18 no. 1, pp. 27–49.

<sup>51</sup> Maschke, K, ‘Navigating an Ethical Patchwork – Human Gene Banks’, *Nature Biotechnology* 2005, vol. 23 no. 5, p. 542.

<sup>52</sup> UNESCO: IBC, *Human Genetic Data: Preliminary Study by the IBC on its Collection, Processing, Storage and Use*, 2002, viewed 02.12.2012, <[http://portal.unesco.org/pv\\_obj\\_cache/pv\\_obj\\_id\\_2E70F2D0A959F04F9450E8AD1F27E168E1FA0500/filename/Rapfinal\\_gendata\\_en.pdf](http://portal.unesco.org/pv_obj_cache/pv_obj_id_2E70F2D0A959F04F9450E8AD1F27E168E1FA0500/filename/Rapfinal_gendata_en.pdf)>, p. 16.

<sup>53</sup> Tissue that was taken in the course of clinical care and is leftover (Giesbertz, N, et. al. op. cit., p. 4).

<sup>54</sup> Wagstaff, A, ‘International Biobanking Regulations, the Promise and the Pitfalls’, *Cancer World* 2011, p. 26.



*applies is limited. Consent must be given in relation to the different aspects of the processing, clearly identified. It includes notably which data are processed and for which purposes. This understanding should be based on the reasonable expectations of the parties. "Specific consent" is therefore intrinsically linked to the fact that consent must be informed. There is a requirement of granularity of the consent with regard to the different elements that constitute the data processing: it cannot be held to cover "all the legitimate purposes" followed by the data controller. Consent should refer to the processing that is reasonable and necessary in relation to the purpose. It should be sufficient in principle for data controllers to obtain consent only once for different operations if they fall within the reasonable expectations of the data subject.*

[...]

*The Working Party has clarified this aspect of consent in WP131 on electronic health records (EHR): "Specific" consent must relate to a well-defined, concrete situation in which the processing of medical data is envisaged. Therefore a "general agreement" of the data subject - e.g. to the collection of his medical data for an EHR and to any future transfers of these medical data to health professionals involved in treatment - would not constitute consent in the terms of Article 2(h) of the Directive."*<sup>55</sup>

This indicates that broad consent could be questioned when relied upon in processing personal data in a health related scenario. Art. 6 (1 (b)) of the Data Protection Directive which provides that personal data must be collected only for specified explicit and legitimate purposes may be used to supports this conclusion. However, Member States vary in their practical implementation of informed consent for using personal data for research purposes. The Medical Research Council from the United Kingdom promotes broad consent.<sup>56</sup> UK Biobank also uses broad consent regarding the use of data (and samples), justifying this with the long term nature of the project. It is also not possible to foresee all kinds of research to which the data and samples in the UK Biobank will be used for.<sup>57</sup> Norwegian law also gives biobanks the option of broad consent, but the regional committee for medical and health research ethics may specify conditions for its use and may order the project manager to obtain new consent if the committee deems it necessary. According to § 4 a BDSG (Bundesdatenschutzgesetz (Federal Data Protection Act)) data subjects shall be informed of the purpose of collection, processing or use and, as necessary in the individual case or on request, of the consequences of withholding consent. In the literature it is mainly argued on that point that consent has to be sufficiently precise. It must be clear for the patients under which conditions they agree to the processing of their personal data. Blanket consent and generalized consent are therefore no option.<sup>58</sup> In Belgian data protection law consent for the processing of personal data must relate to a well-defined, concrete situation in which the processing of medical data is envisaged. Therefore a 'general agreement' of the data subject e.g. to the collection of his medical data for an EHR and to subsequent transfers of these medical data of the past and of the future to health professionals involved in treatment would not constitute consent in the terms of article 1 DPA.<sup>59</sup>

---

<sup>55</sup> Article 29 Data Protection Working Party, Opinion 15/2011 on the Definition of Informed Consent, adopted 13.07.2011, pp. 17-18.

<sup>56</sup> MRC, Study policy on sharing research data, viewed 28.01.2013, <<http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/datasharing/Policy/PHSPolicy/studypolicy/index.htm>>.

<sup>57</sup> UK BIOBANK Ethics and Governance Framework Version 3.0, October 2007, viewed 28.01.2013, <<http://www.ukbiobank.ac.uk/wp-content/uploads/2011/05/EGF20082.pdf>>.

<sup>58</sup> Simitis, S, Simitis – Kommentar zum Bundesdatenschutzgesetz (Commentary on Federal Data Protection Law) edited by Simitis, S, pp. 387-389; Gola, P and Schomerus, R, Commentary on Bundesdatenschutzgesetz (Federal Data Protection Law), 2005, pp. 166-167.

<sup>59</sup> CONTRACT, D3.1: Initial Report and Guidelines on Identified Good Practice Cases, 2011, not published, p. 92.

### 4.1.2 Secondary uses

A related issue to the design of informed consent is the secondary uses problem which refers to such cases where the samples have been collected for a particular research programme and will, in addition, be used for a purpose that is not covered by the informed consent originally obtained, e.g. sharing the samples with a third party that has not been foreseen at the time of collection of the samples. In a statement by the HUGO Ethics Committee on DNA Sampling,<sup>60</sup> the following position on the issue can be found: “Research samples obtained with consent and stored may be used for other research if; there is general notification of such a policy, the participant has not yet objected, and the sample to be used by the researcher has been coded or anonymized. For the use of research samples obtained before notification of a policy, these samples may be used for other research if the sample has been coded or anonymized prior to use.” Also, opinions on national level such as that of the British Medical Research Council Working Group<sup>61</sup> support secondary use without obtaining re-consent: “It is acceptable to use human material surplus to clinical requirements for research without consent if it is anonymous and unlinked.” This issue also occurs when tissue has been removed originally for medical diagnosis or treatment purposes (residual tissues).<sup>62</sup> It has to be noted, however, that not all national frameworks cover the issue (e.g. there is no regulation in Germany or Italy<sup>63</sup>), and this leaves some level of uncertainty on this matter.

The secondary uses problem occurs as well with respect to personal data. The use of personal data for another study that is not covered by the informed consent requires a legal basis: e.g. obtaining new consent. One way to overcome the practical hurdles of obtaining re-consent, as discussed above, is by using anonymized data.<sup>64</sup> Member States can also implement national regulations that allow processing of personal data for a substantial public interest (e.g. research for improving health care), if suitable safeguards are provided (Art. 8 (4) Data Protection Directive).<sup>65</sup>

Many physicians, ethicists and policy makers regard the current heterogeneity in the regulatory systems as a serious obstacle to biomedical research.<sup>66</sup> A review of studies also shows that people are aware of the sensitive nature of genetic data and have an interest to be informed about what is going to happen with their genetic material.<sup>67</sup> Ideally, participants should be actively involved in information exchange and decision making processes. Contacts between participants and researchers could easily be managed via e-mail, sms or regularly updated webpages and local press. Participants then may decide if they want their samples and pertaining data to be used for future analysis. The advantage of such an ongoing contact is that researchers also could ask for new information. This could also

---

<sup>60</sup> HUGO Ethics Committee, Statement on DNA Sampling: Control and Access, 1998, viewed 20.11.2012, <[http://www.hugo-international.org/img/dna\\_1998.pdf](http://www.hugo-international.org/img/dna_1998.pdf)>.

<sup>61</sup> MRC, Human Tissue and Biological Samples for use in research, Operational and Ethical Guidelines, 2001, viewed 20.11.2012, <<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002420>>.

<sup>62</sup> Stefanini, E, op. cit., p. 73.

<sup>63</sup> Stefanini, E, op. cit., p. 75; Tubafrost, D.7.1: Ethical and Legal Aspects, p. 40.

<sup>64</sup> For more details on the issue when data is anonymized in a legal sense see point 4.2.3., for the issue of anonymization of personal data as a step of processing in the sense of Art. 2 (b) Data Protection Directive see point 4.2.1.

<sup>65</sup> For further detail on the issues of secondary uses of personal data, see Elger, B, ‘Strategies for Health Data Exchange for Secondary, Cross Institutional clinical Research’, Comput. Methods, Progras Biomed. 2010, pp. 1-22; EURECA, D7.1: Initial Legal and Ethical Requirements, (not published yet).

<sup>66</sup> Salvaterra, E, et. al., op. cit., p. 307.

<sup>67</sup> Caulfield, T, ‘Biobanks and Blanket Consent: The Proper Place of the Public Good and Public Perception Rationales, KLJ 2007, pp. 218-222.

facilitate a new level of transparency in medical research and build up trust between science and society.<sup>68</sup> EnCoRe, for instance, is a multi-disciplinary research project that aims to improve the rigor and ease with which individuals can grant and revoke their consent to the use, storage and sharing of their personal data by others with the development of IT-solutions.<sup>69</sup>

### 4.1.3 Right to withdraw

The right to withdraw consent to participation in medical research can be found in many national and international guidelines and national laws, and has its historical background from the Nuremberg Code and the Declaration of Helsinki.<sup>70</sup> The concept of informed consent as a process, demands that participants in medical trials should be allowed to take a free decision on risk of participating. This invariably means that if during the course of a study, new information become available to the sample providers, which instigate them to make a change in their decision whether participating is still in their interests or not, such should not be impeded. This is in line with the autonomy perspective and also raises trust and support in medical research.<sup>71</sup>

There are issues around the realization of this right: what can be withdrawn and when? Will samples and data have to be deleted or is it sufficient to anonymize those? What happens to already shared samples and data? Can those be recalled? Participants need to be aware of the fact that data and samples that were used in completed research studies cannot be extricated from the research results. There is no reactive effect: it is to be seen as a prohibition to further analyse the data in future research programs.<sup>72</sup> Practices vary in relation to the options for withdrawal offered to the providers of samples and data. Whereas UK Biobank offers a set of graded options (complete withdrawal, discontinued participation and no further contact requested), in Estonia, donors have the right to have their data deleted.<sup>73</sup> In Germany, the German Ethics Council notes that there should be a provision that samples and data could be used for further research despite the withdrawal of the participant if the link to him or her is eliminated.<sup>74</sup> The German option seems to beg the question as to how to render samples and data truly anonymous.

### 4.1.4 Differences between Member States' regulations applicable to the use of samples and personal data associated with samples

#### 4.1.4.1 Examples of National provisions

As already mentioned, different regulatory framework apply for the use of tissues and the processing of personal data, and it is not always clear where the borderline is. In the

---

<sup>68</sup> Mascalzoni, D, et. al., op. cit., pp. 1304-1305.

<sup>69</sup> Whitley, A and Kanellopoulou, N, 'Privacy and Informed Consent in Online Interactions: Evidence from Expert Focus Groups', EnCoRe Publications 2010, viewed 30.01.2013, <[http://www.encore-project.info/other\\_publications\\_material/EnCoRe%20Publication%20Privacy%20and%20Informed%20Consent%20%28ICIS%202010%29.pdf](http://www.encore-project.info/other_publications_material/EnCoRe%20Publication%20Privacy%20and%20Informed%20Consent%20%28ICIS%202010%29.pdf)>, p. 10.

<sup>70</sup> Helgesson, G and Johnson, L, op. cit., p. 315.

<sup>71</sup> Ibid., pp. 318-319.

<sup>72</sup> Watson, R, et. al., op. cit., p. 650.

<sup>73</sup> William, R, et. al., op. cit., p. 5.

<sup>74</sup> Deutscher Ethikrat, Opinion on Human Biobanks for Research 2010, viewed 29.11.2012, <[http://www.ethikrat.org/files/der\\_opinion\\_human-biobanks.pdf](http://www.ethikrat.org/files/der_opinion_human-biobanks.pdf)>, p. 14.

following sections, we will provide an insight into the national regulations in Spain, Sweden, Norway, Denmark and Germany to underscore these differences.<sup>75</sup>

#### 4.1.4.1.1 Spain

The Spanish Biomedical Research Act (BRA) 2007 and the Royal Decree (1716/2011) provide a situation where donors of biosamples have a choice between giving consent to the storage and use of their samples in a specific research project, to the storage in a collection or the storage in a biobank. Samples collected for a specific project are time-restricted and must be destroyed at the end of that particular project. In the second alternative the participant consents to the long-term storage of samples meant to be used within the frame of a particular research line. These samples can only be used by the investigator who requested them and cannot be shared with third parties or used in research projects outside the particular research line foreseen in the original informed consent. The third option is to give consent to the storage of the samples in a biobank which implies that the sample can be used for any research and shared with third parties.<sup>76</sup>

Samples that were obtained before the BRA came into force, where no informed consent exists, may be used for research if it takes unreasonable effort for receiving re-consent, or if it is not possible at all because the donor had died or was untraceable. In these cases the favourable opinion of a research ethics committee will be required which has to consider if the use of the samples was in public interest, that there is no known objection to the use and the anonymization of the samples. Such an option for the re-use of samples does not exist for samples that have been collected after the BRA has come into force.<sup>77</sup>

#### 4.1.4.1.2 Sweden

Sweden is one of the European Member States that has a specific regulation on biobanks. It enacted in 2003, the Biobanks in Medical Care Act (SFS 2002:297)<sup>78</sup> and later complemented with Regulation ("Förordning") (SFS 2002:746) regarding biobanks in areas such as health and medical services.<sup>79</sup> The Swedish Biobanks in Medical Care Act (chapter 2, section 1) provides principally that tissue samples may not be collected and preserved in a biobank without informing the donor of that intention, and about the purpose(s) for which the biobank may be used, as well as obtaining his or her consent. Sweden thereby requires specific informed consent.<sup>80</sup> With regard to minors it provides in chapter 3, section 2 that the parent or guardian of the minor must be informed of that intention and about the purpose(s) for which the biobank may be used, and obtaining the consent of the parent or guardian. The minor can decide when reached such an age and level of maturity that he or she can make a decision on the matter. There is also a special provision on embryos and fetuses (chapter 3, section 3).

In chapter 3, section 5 it is stated that tissue samples preserved in a biobank may not be used for other purposes than those indicated in information submitted previously for which consent had been granted. Principally in the event of a new purpose, the person who

---

<sup>75</sup> See the webpage of PRIVELEGED for a comprehensive overview, viewed 28.12.2012 <http://www.privileged.group.shef.ac.uk/>.

<sup>76</sup> Ariaz-Diaz, J, et. al., op. cit., p. 1-3.

<sup>77</sup> Ibid.

<sup>78</sup> Swedish Biobanks in Medical Care Act, English translation, viewed 27.12.2012, <[http://www.genomeutwin.org/member/cores/ethics/docs/Swedish\\_Biobank\\_law\\_english\\_version.pdf](http://www.genomeutwin.org/member/cores/ethics/docs/Swedish_Biobank_law_english_version.pdf)>

<sup>79</sup> CODEX, viewed 28.12.2012, <<http://www.codex.uu.se/en/manniska4.shtml>>.

<sup>80</sup> Salvaterra, E, et. al., op. cit., p. 308; Scott, C, Personal Medicine – the New Banking Crisis, Nature Biotechnology 2012, vol. 30 no. 2.

previously granted consent must be informed and grant new consent. If the person who originally granted the consent has deceased, the deceased's next of kin shall be informed of the new purpose and, after a reasonable period of reflection, must not be opposed to the new purpose. Exceptionally, in case the new purpose is research or clinical trials, the research ethics committee that approves the new purpose shall also determine the requirements concerning the information and consent regulations that shall apply so that the tissue samples in the bank may be used for the new purpose.

The Swedish Act also allows withdrawal of consent at any time. If the withdrawal of consent refers to all use, the tissue sample shall be immediately destroyed or depersonalized.

Personal data of participants is not considered by the Biobanks in Medical Care Act. Here the regulations in the Personal Data Act (SFS 1998:204) as well as other legislations regarding personal information and health-related data in the healthcare area apply.<sup>81</sup>

#### **4.1.4.1.3 Norway**

The Act on Medical and Health Research (Health Research Act)<sup>82</sup>, implemented on 1 July 2009, replaced the Personal Data Act, the Personal Health Data Filing System Act, the Act on Biobanks and the Act on the Application of Biotechnology in Human Medicine Health with regard to medical and health research<sup>83</sup>. The Health Research Act states in chapter 4, section 14 that research participants may consent to human biological material and personal health data being used for specific, broadly defined research purposes. The regional committee for medical and health research ethics may specify conditions for use of broad consent and may order the project manager to obtain new consent if the committee deems it necessary. Participants who have given broad consent are entitled to receive information about the project at regular intervals. Consent is not required for research on anonymous human biological material and anonymous data, but for the collection of material and data for subsequent anonymization consent is needed (chapter 4, section 20).

According to chapter 6 section 28, the regional committee for medical and health research ethics may rule that human biological material collected by the health service in connection with diagnosis and treatment may be used for research purposes without the patient's consent being obtained. This may only be applied if the research in question is of significant interest to society, and the participants' welfare and integrity are ensured. The regional committee for medical and health research ethics may specify conditions for the use. The patient must have been informed in advance that in some cases human biological material may be used for research and must have been given the opportunity to refuse to be involved in research on human biological material. An electronic register must be established with the details of the patients that have stated that they do not wish their biological material to be used for research. A similar provision has been enacted in chapter 7, section 35 regarding the use of personal health data collected by medical staff, but without the possibility to opt out. Referring to the issue of secondary uses the act provides that In the event of substantial changes to the research project, new consent must be obtained if the changes are deemed to have consequences for the participant's consent. In case it is difficult to obtain new consent, the regional committee for medical and health research ethics may approve new or changed use of previously collected human biological material or personal health data without new consent being obtained. This may only be applied if the research in question is of significant interest to society and the participants' welfare and integrity are ensured. The

---

<sup>81</sup> CODEX, op. cit.

<sup>82</sup> Norwegian Act on Medical and Health Research (Health Research Act) 2008-06-20 no. 44, English translation, viewed 28.12.2012, <<http://www.ub.uio.no/ujur/ulovdata/lov-20080620-044-eng.pdf>>.

<sup>83</sup> PRIVILEGED, viewed 28.12.2012, <<http://www.privileged.group.shef.ac.uk/projstages/stage-2-genetic-databases-and-biobanks/genetic-databases-and-biobanks-by-country/norway>>.

regional committee for medical and health research ethics may specify conditions for the use.

Regarding withdrawal of consent, the law states in chapter 4, section 16 that consent to take part in a research project may be withdrawn at any time. If a participant withdraws his/her consent, research on their biological material or personal health data must stop. A person who has withdrawn their consent may demand that their biological material is destroyed and that the personal health data are deleted or surrendered within 30 days. The right to demand destruction, deletion or surrender of biological material or health data does not apply if the material or data have been anonymized, if the material has been processed and is now part of another biological product, or if the data have already been included in completed analyses. If particularly strong social or research considerations so warrant, the regional committee for medical and health research ethics may allow continued research on the material and defer destruction, deletion or surrender until the research project is concluded.

#### **4.1.4.1.4 Denmark**

Denmark does not have a separate biobanks act. The Danish Data Protection Agency has declared that the data protection framework also applies to the collection, storage and use of biomaterial. Today, biobanks are covered by the same Acts and institutions as other biomedical and health research, i.e. The Act on Processing of Personal Data, the Act on Scientific Ethical Committees, the Act on Scientific Ethical Handling of Health Sciences Research and the Health Act (2-5) and the Data Protection Agency and the Committees on Biomedical Research Ethics. Researchers cannot ask for consent in the form of a “blank cheque” for all future uses. If researchers want to do new analysis, for example, some years later, or if they want to analyze biological markers not specified in the original application, they need to re-consent the donors of the biological material, but it is possible for the ethics committees to give exemption from this requirement if a considerable number of donors are unavailable, e.g. if they are dead.<sup>84</sup> Whereas samples taken specifically for research must be collected with consent, no consent is needed for using a tissue sample for research if it is taken for diagnostic purposes and used for research only at a later stage. Patients have the option to refuse from tissue storage and/or use.<sup>85</sup> This decision will be entered in a national registry.<sup>86</sup>

#### **4.1.4.1.5 Germany**

In Germany there is no specific law on the sharing of biomaterial. The long planned law on genetic testing/diagnosis was enacted in spring of 2009, but due to political wrangling the envisaged key area of regulation of research that should have dealt with all relevant ethical issues such as informed consent and secondary uses was dropped.<sup>87</sup> Germany is one of the instances where one needs to search in a number of laws to find out the legal requirements for the use and storage of samples and pertaining data. The former German National Ethics Council and the Study Commission of the Bundestag (German Federal Parliament) have

---

<sup>84</sup> Kyvik, K, ‘Danish Biobank Legislation: a Simple Approach?’, *Norsk Epidemiologi* 2012, pp. 161-162.

<sup>85</sup> Hoeyer, K, An Opt Out System for Tissue Storage: Lessons from Denmark, viewed 04.01.2012, <<http://www.bmj.com/rapid-response/2011/11/02/opt-out-system-tissue-storage-lessons-denmark>>.

<sup>86</sup> Ursin L, et. al, The Informed consenters Governing Biobanks in Scandinavia in *Biobanks Governance in Comparative Aspects*, edited by Herbert Gotweiss & Alan Petersen, 2008, p. 181.

<sup>87</sup> European Commission, JRC, op. cit., p. 74; German Ethics Council (Deutscher Ethikrat), *Opinion on Human Biobanks for Research*, 2010, op. cit, p. 8.

considered biobanks in earlier opinions and have formulated recommendations on dealing with samples and data of human origin.<sup>88</sup>

The Federal Data Protection Act and the Data Protection Acts of the Federal States of Germany have to be considered for the processing of personal data. In contrast to Denmark, DNA samples are not treated as personal data, but the information contained in the sample are.<sup>89</sup> Thus only the collection, storage and use of data must be in compliance with the German data protection framework. In case data is anonymized, it falls out of the scope of the data protection laws. For processing of personal data, informed consent is needed or the preconditions of one of the research exceptions implementing the provided national research exemptions in the Data Protection Directive must be fulfilled. The legal situation in Germany on research exceptions is confusing. There are differing provisions for scientific research in public and private agencies. In some Federal States of Germany, the consent may be dispensed only for research carried out by the relevant hospital itself; in other Federal States of Germany, the law is less strict, permitting also the use of personal data for scientific research outside the relevant hospital without the person's consent.<sup>90</sup> Another important issue is that there is no uniform position on the question of how specific the consent must be. The data protection laws set no provision with sufficient clarity. The views of data protection officers and ethics commissions on this aspect vary widely: from consent for a specific research project to the information about the research field (e.g. cancer research, dementia research). Others are satisfied with an even broader consent ("medical research").<sup>91</sup>

With regard to the collection of samples it is provided that encroachments upon bodily integrity require the express consent of the persons affected, if not otherwise permitted by law (e.g. provisions in German criminal law). In cases where samples were taken for the sole purpose of diagnosis and therapy, and shall be used for medical research later on, a weighing of interest is suggested analogous to the German data protection laws.<sup>92</sup>

## 4.2 *Further issues in data protection law*

### 4.2.1 Data associated with samples and data protection law

As already mentioned above, for the use of tissue and the use of data different regulatory frameworks apply.<sup>93</sup> For processing of personal data, the Data Protection Directive and the implementing national laws have to be considered. Accordingly, researchers need a legal ground for processing of personal data. Processing of data shall mean any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction (Art. 2 (b) Data Protection

---

<sup>88</sup> German Ethics Council (Deutscher Ethikrat), Opinion on Human Biobanks for Research, 2010, op. cit, p. 8.

<sup>89</sup> Kühn, H, The Implementation of the Data Protection Directive 95/46/EC in Germany in Implementation of the Data Protection Directive in Relation to Medical Research in Europe, edited by Beyleveld, D, et. al., 2004, p. 138.

<sup>90</sup> German Ethics Council (Deutscher Ethikrat), Opinion on Human Biobanks for Research, 2010, op. cit., p. 17.

<sup>91</sup> Ibid, p. 18.

<sup>92</sup> Ibid, pp. 15-16.

<sup>93</sup> See Introduction of point 4.

Directive). This is a comprehensive definition which covers all forms of research on the data, including transfer or disclosure to third parties. It is controversial if anonymization of personal data is to be seen as a form of processing of personal data.<sup>94</sup>

#### 4.2.2 Samples as personal data?

For the Data Protection Directive to apply in any data processing, personal data must be involved. Personal data in the sense of the directive means “any information relating to an identified or identifiable natural person ('data subject')” (Art. 2 (a) Data Protection Directive). In this context, the question is whether samples and tissues themselves can be subsumed under this definition. According to the Article 29 Data Protection Working Party, samples are sources of data, but cannot be regarded as data in the sense of the Data Protection Directive.<sup>95</sup> However, in contrast to this, the Danish Data Protection Agency has stated that collections of human biomaterial can be considered as covered by the Act on Processing of Personal Data.<sup>96</sup> Having in mind that the samples are the containers of (partly very sensitive) data, the principles applying to the retention and circulation of biological samples that relate to identified or identifiable individuals should not differ significantly from personal data protection principles even if the legal framework devised for personal data were not found to be directly applicable.<sup>97</sup> Indeed national regulatory instruments require suitable security measures to protect the confidentiality of the samples.<sup>98</sup> In any case, as soon as data is extracted from samples this information needs to be seen as (potentially) personal data.<sup>99</sup>

#### 4.2.3 Different interpretations on “anonymous” data<sup>100</sup>

Data is personal if it relates to an identified or identifiable person. An identifiable person is one “who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity” (Art. 2 (a) Data Protection Directive). In order to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person. This criterion should in particular take into account all the factors at stake, whereby e.g. the cost of conducting identification or the intended purpose, the way the processing is structured, the advantage expected by the controller, the interests at stake for the individuals, as well as the

---

<sup>94</sup> Casabona, C, Anonymization and Pseudonymization: The Legal Framework at a European Level, in: *The Data Protection Directive and Medical Research Across Europe*, 2005, pp. 42-43.

<sup>95</sup> Article 29 Data Protection Working Party, Working Document, Opinion 4/2007 on the Concept of Personal Data, adopted 20.06.2007, p. 9.

<sup>96</sup> Danish Data Protection Agency, *Biobanks Are Covered by the Act on Processing of Personal Data*, viewed 18.12.2012, < <http://www.datatilsynet.dk/english/health-research-and-statistics-projects/biobanks-are-covered-by-the-act-on-processing-of-personal-data/>>.

<sup>97</sup> European Commission, *Biobanks for Europe – A challenge for Governance*, Report of the Expert Group on Dealing with Ethical and Regulatory Challenges of International Biobank Research, 2012, viewed 18.12.2012, < [http://www.coe.int/t/dg3/healthbioethic/Activities/10\\_Biobanks/biobanks\\_for\\_Europe.pdf](http://www.coe.int/t/dg3/healthbioethic/Activities/10_Biobanks/biobanks_for_Europe.pdf)>, p. 38.

<sup>98</sup> See, e.g. section 27, chapter 6, Norwegian Health Research Act.

<sup>99</sup> Article 29 Data Protection Working Party, Working Document, Opinion 4/2007 on the Concept of Personal Data, adopted 20.06.2007, p. 9.

<sup>100</sup> For more information see Forgó, et. al., *Ethical and Legal Requirements for Transnational Genetic Research*, 2010, op. cit., pp. 90-112; EURECA, D7.1: *Initial Legal and Ethical Requirements*, p.19f (not published yet); Linked2Safety, D2.1 *Legal and Ethical Requirements*, p.15, viewed 29.01.2013, < <http://www.linked2safety-project.eu/node/30>>.



risk of organisational dysfunctions and technical failures have to be considered.<sup>101</sup> Thereafter, the extent to which certain identifiers are sufficient to achieve identification is something dependent on the context of the particular situation.<sup>102</sup> The mere hypothetical possibility to single out the individual is not enough to consider the person as “identifiable”. If that possibility does not exist or is negligible, the person should not be considered as “identifiable”, and the information would not be considered as “personal data” with the consequence that the Data Protection Directive and the implementing national laws do not apply.<sup>103</sup> That is of importance because this interpretation of ‘anonymous data’ does not demand that there is an irrevocable breach of the link to the participant. It allows the use of linkable coded information as long as there are sufficient safeguards to restrict access to the link.<sup>104</sup> Thus, researchers or their treating physicians can go back to the participants to get updates on how a patient’s disease progressed or how it responded to various treatments or to ask for additional information e.g. on side-effects.<sup>105</sup> It is also for the benefit of the patients if re-identification is possible to get back to them in case there has been found a treatment that could cure the patients disease or at least provide relief.<sup>106</sup>

What seems to be required from a legal point of view for having anonymized data can be hard to achieve if it comes to practical implementation, because detailed medical data or genetic information is needed in personalised medicine.<sup>107</sup> Genetic analyses aggravate this problem, since they often create an individual genetic pattern or “profile” of a person. If identifiable reference material is available elsewhere, the participant could be identified despite de-identification procedures of the data.<sup>108</sup> Nevertheless, as long as the risk for re-identification is negligible data is regarded anonymous and data protection regulations have not to be observed which facilitates (transnational) exchange of data immensely as e.g. notification requirements come off. Researchers also do not have to invest time and money for identifying data protection obligations and implementing compliance measures.<sup>109</sup>

This concept of “reasonable or proportional anonymity”<sup>110</sup> is prevailing in the Member States, but there are differences in the implementation. Whereas in Belgium<sup>111</sup> and Denmark<sup>112</sup> amongst other Member States, it is required that nobody is able to re-identify with reasonable

---

<sup>101</sup> Article 29 Data Protection Working Party, Working Document, Opinion 4/2007 on the Concept of Personal Data, adopted 20.06.2007, p. 15.

<sup>102</sup> Ibid, p. 13.

<sup>103</sup> Ibid, p. 15.

<sup>104</sup> Forgó, N, et. al., op. cit., pp. 90-94; Elger, B, op. cit., p. 4.

<sup>105</sup> Wagstaff, A, op. cit., p. 25.

<sup>106</sup> D5.1: Setting up of the data protection and data security framework, op. cit., p. 76; Forgó, N, et. al., op. cit., pp. 102-104.

<sup>107</sup> Eder, J, et. al., ‘IT Solutions for Privacy Protection in Biobanking’, Public health Genomics 2012, p. 255.

<sup>108</sup> German Ethics Council (Deutscher Ethikrat), Opinion on Human Biobanks for Research, 2010, viewed 04.01.2013, <[http://www.ethikrat.org/files/der\\_opinion\\_human-biobanks.pdf](http://www.ethikrat.org/files/der_opinion_human-biobanks.pdf)>, p. 11.

<sup>109</sup> Reetzer, K., et. al., ‘Navigating the Sea of Data Protection Law in European Medical Research’, 2011, viewed 19.12.2012, <<http://www.mofo.com/files/Uploads/Images/111201-Data-Privacy-SRC.pdf>>, p. 16.

<sup>110</sup> European Commission, JRC, Biobanks in Europe: Prospects for Harmonisation and Networking, 2010, viewed 19.12.2012, <<ftp://ftp.jrc.es/pub/EURdoc/JRC57831.pdf>>, p. 120.

<sup>111</sup> Nys, H, Report on the Implementation of Directive 95/46/EC in Belgian Law, in: Implementation of the Data Protection Directive in Relation to Medical Research in Europe, edited by Beyleveld, D, et. al., 2004, p. 30.

<sup>112</sup> Hartlev, M, The Implementation of Data Protection Directive 95/46/EC in Denmark, in: Implementation of the Data Protection Directive in Relation to Medical Research in Europe, edited by Beyleveld, D, et. al., 2004, p. 60.

means. Member States such as Germany<sup>113</sup> and UK<sup>114</sup> take a relatively different approach, judging from the data controller's point of view. This means that coded data can be regarded as anonymous for those who do not hold the key if it will be unreasonable for them to obtain the key. The consequence of these divergent interpretations is that the same set of data can be regarded in one Member State as personal, whereas they are viewed as anonymous in a another Member State with a less strict interpretation.

#### **4.3 The issue of different requirements in the national laws when sharing biomaterial and associated personal data and functional parallelism**

As mentioned regulatory regimes differ and spread uncertainties amongst researchers in multinational trials as to which law is applicable. Again, we have to approach data and tissue separately due to the distinct frameworks that apply.

##### **4.3.1 Transnational sharing of biomaterial**

We have figured out that for sharing of biomaterial no international or European unified binding legal framework exists, but national jurisdictions determine the legal situation. The already mentioned differences in the national legislations lead us to the question: what happens if two regimes collide? If biomaterial is exchanged between two Member States, can an authority from a Member State with a stricter regime ban the use of biomaterial that has been collected in a Member State with a less strict regime? Can a Member State set out conditions in its national law for the export of biomaterial to another Member State?

Tubafrost has investigated this issue in detail and came to an interesting conclusion: Whereas the suggestion of a creation of a harmonized standard for Europe was rejected because the finding of an “average standard” would have the tendency to the strictest regime and would be detrimental for researchers of countries with a less strict regime, they brought into play the principle of mutual recognition<sup>115</sup> which has its legal basis in the Treaty on the Functioning of the European Union (TFEU).

---

<sup>113</sup> Authors argueing for a relative approach: Forgó, N, et. al., op. cit., p. 90-94; Gola, P and Schomerus, R, Kommentar zum Bundesdatenschutzgesetz (Commentary on Federal Data Protection Law), 2005, pp. 118-120; Plath, K-U and Schreiber, L, Kommentar zum Bundesdatenschutzgesetz sowie den Datenschutzbestimmungen von TMG und TKG (Commentary on Federal Data Protection Law as well as TMG and TKG (Law on Telemedia as well as Telecommunication), 2013, pp. 61-62; taking an absolute approach: Dammann, U, Simitis – Kommentar zum Bundesdatenschutzgesetz (Commentary on Federal Data Protection Law) edited by Simitis, S, 2006, pp. 310-313.

<sup>114</sup> Beyleveld, D, et. al., The UK's Implementation of Directive 95/46/EC, in: Implementation of the Data Protection Directive in Relation to Medical Research in Europe, edited by Beyleveld, D, et. al., 2004, pp. 407-408; Information Comissioner's Office, Anonymisation - Managing Data Protection Risk, Code of Conduct, 2012, p. 21.

<sup>115</sup> Van Veen, E.-B., et. al., 'TubaFrost 3: Regulatory and Ethical Issues on the Exchange of Residual Tissue for Reseach Across Europe', EJC 2006, pp. 2914-2923.

#### 4.3.1.1 The European fundamental freedoms and the principle of mutual recognition (functional parallelism<sup>116</sup>)

Since there has been no harmonisation on the matter of sharing of biomaterials on a European level, the standard clauses of the TFEU on the European fundamental freedoms apply. For the sharing of biomaterial the principles of the free movements of goods (Art. 34) and the free provision of services (Art. 56) have to be considered depending on the nature of the agreement (e.g. purchase or loan).

##### 4.3.1.1.1 Field of application of the European fundamental freedoms

Principally, it needs to be stated that the application of the European fundamental freedoms and the entailed prohibitions of discrimination and restrictions is confined to cases with cross-border implications, for instance, samples are sold to a research entity that is established in another Member State of the European Union. Sellings and services within a Member State are not covered by the provisions regarding the European fundamental freedoms laid down in the TFEU.

For the transnational sharing of biomaterial a very relevant issue is, whether such material can be regarded as “goods” within the meaning of the treaty. From an ethical aspect it might appear inappropriate to speak of goods. The same problem is posed in connection with the application of the free provision of services (e.g. the loaning of biomaterial for research purposes). Many authors seem to orientate in their interpretation on the fact that the trade with human biomaterial and any products derived from it are already part of the EU common market.<sup>117</sup> Schwarzburg<sup>118</sup> investigated this issue in detail thereby taking into account the jurisdiction of the European Court of Justice (ECJ) and came to a persuasive conclusion on the issue: Principally, biomaterial<sup>119</sup> can be regarded as goods in the sense of Art. 35 TFEU unless trade with it is impossible in all Member States because of ethical or legal aspects. The same applies regarding the free provision of services (Art. 56).<sup>120</sup>

Analysis of the jurisdictions of the ECJ show that the term “goods” or “services” is interpreted rather neutral in an economic direction.

For instance, abortions were principally subsumed by the ECJ in a preliminary ruling procedure in the year 1991 as services in the sense of Art. 51 TEC (today Art. 56 TFEU):

*“services are to be considered to be “services” within the meaning of the Treaty where they are normally provided for remuneration, in so far as they are not governed by the provisions relating to freedom of movement for goods, capital or persons. [...] It must be held that termination of pregnancy, as lawfully practised in several Member States, is a medical activity which is normally provided for remuneration and may be carried out as part of a professional activity.” [...] The Society for the protection of unborn children maintains “that the provision of abortion cannot be regarded as being a service in the sense of the treaty, on the grounds that it is grossly immoral and involves the destruction of the life of a human being, namely the unborn child. Whatever the merits of those arguments on the moral plane, they cannot influence the answer to the national court's first question.*

---

<sup>116</sup> Russi, L, ‘Economic Analysis of Article 28 EC after the Keck Judgment’, German Law Journal 2006, vol. 7 no. 5, p. 483.

<sup>117</sup> Schwarzburg, K, Die Menschenwürde im Recht der Europäischen Union, 2012, p. 180.

<sup>118</sup> Ibid, pp. 178-184.

<sup>119</sup> Special features of cells as in the case of stem cells may require a different evaluation (see, e.g., Schwarzburg, K, op. cit., pp. 182-184).

<sup>120</sup> Ibid, p. 181.

*It is not for the Court to substitute its assessment for that of the legislature in those Member States where the activities in question are practised legally.*<sup>121</sup>

In a decision regarding narcotic drugs covered by the 1961 Single Convention and marketable the court declared:

*“goods taken across a frontier for the purposes of commercial transactions are subject to Article 30 (today Art. 35) of the Treaty (regulating the free movement of goods), whatever the nature of those transaction is” and “since they have those characteristics, the drugs covered by the Convention and marketable under it are subject to Article 30”*<sup>122</sup>

In another judgement the ECJ stated that customs duty cannot be determined for goods if in every Member State the trade in such a good is forbidden and seizing of the good is prescribed if discovered, as e.g. in case of heroin.<sup>123</sup> Similarly the ECJ stated in a judgement regarding the selling of marihuana in coffee shops in The Netherlands:

*“It follows that narcotic drugs which are not distributed through channels which are strictly controlled by the competent authorities to be used for medical and scientific purposes are, because of their very nature, subject to a prohibition on importation and offering for sale in all the Member States [...] The fact that some Member States describe a narcotic drug as a ‘soft’ drug is not capable of calling that finding into question (see, to that effect, Vereiniging Happy Family Rustenburgerstraat, paragraph 25). As narcotic drugs which are not distributed through such strictly controlled channels are prohibited from being released into the economic and commercial channels of the European Union, a coffee-shop proprietor cannot rely on the freedoms of movement or the principle of non-discrimination, in so far as concerns the marketing of cannabis, to object to municipal rules such as those at issue in the main proceedings.”*<sup>124</sup>

These decisions mirror a constrained ethical neutrality of the ECJ’s approach when interpreting the scope of application for the European fundamental freedoms because those decisions also indicate that the ECJ does consider legal aspects.<sup>125</sup> National regulations of Member States seem to be considerable in two ways: in the case that the legal situation in all Member States forbids the practice of a profession or the trade in specific goods; then the field of application of the respective European fundamental freedom is not opened. This is a teleological constraint, but should only apply if there is a common sense between the Member States, e.g. on a selling prohibition. It would be contradictory to the European approach if a Member State could escape from the obligations of the TFEU by declaring a specific service or the selling of a specific good as illegal. That does not mean that Member States cannot enact prohibitions or constraints on the European fundamental freedoms. The TFEU entails the possibilities for national restrictions and the jurisdiction of the ECJ has widened the scope of national derogations, but certain preconditions such as a reasonable justification for the restriction on a European fundamental freedom need to be fulfilled. This, however, is dogmatically to be localized in the area of justification of a hinderance for a European fundamental freedom (see point 4.2.1.1.3).

---

<sup>121</sup> Case C-159/90 The Society for the Protection of Unborn Children Ireland Ltd v Stephen Grogan and others [1991] ECR I-04685.

<sup>122</sup> Case C-324/93 The Queen v Secretary of State for Home Department, ex parte Evans Medical Ltd and Macfarlan Smith Ltd [1995] ECR I-00563.

<sup>123</sup> Case 50/80 Jozsef Horvath v Hauptzollamt Hamburg-Jonas [1981] ECR 00385.

<sup>124</sup> Case C-137/09 Marc Michel Josemans v Burgemeester van Maastricht [2010] ECR I-13019.

<sup>125</sup> See also Schwarzburg, K, op. cit., p. 181.

Conclusively, it is to state that principally the selling or loaning of human biomaterial is covered by the European fundamental freedoms because Member States basically allow the exchange of human specimen etc. One finds in the national regulations a number of restrictions and notification requirements. The requirements for the validity of such rules will be discussed in point 4.2.1.1.3.

#### **4.3.1.1.2 Hindrance of the free movement of goods/ provision of services**

Article 34 TFEU, prohibits quantitative restrictions on imports and all measures having equivalent effect between the Member States. Art. 35 TFEU, which relates to exports from one Member State to another Member State, prohibits quantitative restrictions and also all measures having equivalent effect. Art. 56 TFEU guarantees the freedom to provide services within the European Union. A cross-border element is a prerequisite for applying the freedom of movements of goods and providing services. Those freedoms are endangered if a measure of the Member State, be it a law or some administrative measure, is capable of indirectly or potentially hindering intra-EU trade. This could also be occurred by a measure that sets conditions for the use of a good.<sup>126</sup> In case the law of the receiving Member State sets stricter regulations on the use of the samples, this might be a potential hindrance for the trade of samples between those Member States.

#### **4.3.1.1.3 Reasons for justification and the principle of mutual recognition (functional parallelism<sup>127</sup>)**

However, not in every case a factual hindrance might be a violation of European Law. The treaty provides in Art. 36 TFEU exceptions on grounds of public morality, public policy or public security; the protection of health and life of humans, animals or plants; the protection of national treasures possessing artistic, historic or archaeological value; or the protection of industrial and commercial property as long as those national regulations do not constitute a means of arbitrary discrimination or a disguised restriction on trade between the Member States. For the free movement of services Art. 61 and 62 TFEU provide exceptions for similar reasons. Besides the written exceptions in the TFEU the European Court of Justice has carved out unwritten exceptions that could justify potential hindrances for intra-community trade.<sup>128</sup> In its decision referring the prohibition of resale at a loss from the year 1993 the court stated:

*“It is established by the case-law beginning with "Cassis de Dijon" (Case 120/78 Rewe-Zentral v Bundesmonopolverwaltung fuer Branntwein [1979] ECR 649) that, in the absence of harmonisation of legislation, obstacles to free movement of goods which are the consequence of applying, to goods coming from other Member States where they are lawfully manufactured and marketed, rules that lay down requirements to be met by such goods (such as those relating to designation, form, size, weight, composition, presentation, labelling, packaging) constitute measures of equivalent effect prohibited by Article 30. This is so even if those rules apply without distinction to all products unless their*

---

<sup>126</sup> European Commission, Free Movement of Goods, Guide to the application of Treaty provisions governing the free movement of goods 2010, viewed 27.12.2012, <[http://ec.europa.eu/enterprise/policies/single-market-goods/files/goods/docs/art34-36/new\\_guide\\_en.pdf](http://ec.europa.eu/enterprise/policies/single-market-goods/files/goods/docs/art34-36/new_guide_en.pdf)>, p. 14.

<sup>127</sup> Russi, L, ‘Economic Analysis of Article 28 EC after the Keck Judgment’, German Law Journal 2006, vol. 7 no. 5, p. 483.

<sup>128</sup> Starting with the judgement in the case 120/78 Rewe-Zentral AG v Bundesmonopolverwaltung für Branntwein ECR [1979] 00649.

*application can be justified by a public-interest objective taking precedence over the free movement of goods.*<sup>129</sup>

In its famous Gebhard-judgment<sup>130</sup> the ECJ declared the unwritten exceptions - allowing (potential) trade hinderances - applicable also to the other European fundamental freedoms. Thereafter, measures that constitute an indirect discrimination will also be in accordance with the TFEU insofar as

*“they must be applied in a non-discriminatory manner; they must be justified by imperative requirements in the general interest; they must be suitable for securing the attainment of the objective which they pursue; and they must not go beyond what is necessary in order to attain it”*<sup>131</sup>.

Consequence of this regulatory framework is in non harmonized areas the ‘mutual recognition principle’ that consists of a rule and an exception:

- “the general rule that, notwithstanding the existence of a national technical rule in the Member State of destination, products lawfully produced or marketed in another Member State enjoy a basic right to free movement, guaranteed by the TFEU;
- the exception that products lawfully produced or marketed in another Member State do not enjoy this right if the Member State of destination can prove that it is essential to impose its own technical rule on the products concerned based on the reasons outlined in Article 36 TFEU or in the mandatory requirements developed in the court’s jurisprudence and subject to the compliance with the principle of proportionality.”<sup>132</sup>

The principle of mutual recognition also applies for the free movement of services.<sup>133</sup>

Thereafter, the Member State with the stricter regime cannot impose its regulatory framework with its tighter regulations as far as there is no mandatory reason for this, as e.g. the protection of consumers<sup>134</sup>. In case of the import of tissue which has become available under a less strict regime such a justification cannot be found because the research does not affect the rights of their people or obligations of their researchers.<sup>135</sup> On the other hand, if Member States put restrictions on the export of samples those might be justified for reasons laid down in one of the exception rules in TFEU or developed by the European Court of Justice. Here the Member States enact those regulations for the good of their people where their jurisdiction applies, but the conditions set out in the jurisprudence and the treaty must be met. An example for a reasonable justification is the requirement of informed consent for the use of a sample for research. This potentially hinders the export of human specimen

---

<sup>129</sup> Joined cases C-267/91 and C-268/91 Criminal proceedings against Bernard Keck and Daniel Mithouard [1993] ECRI-06097.

<sup>130</sup> Case C-55/94 Reinhard Gebhard v Consiglio dell’Ordine degli Avvocati e Procuratori di Milano [1995] ECR I-04165.

<sup>131</sup> Ibid.

<sup>132</sup> European Commission, Free Movement of Goods, Guide to the application of Treaty provisions governing the free movement of goods, 2010, op. cit., p. 15.

<sup>133</sup> Gekiere, W, et. al., Free movement of services in the EU and health care, viewed 27.12.2012, <[http://www.euro.who.int/data/assets/pdf\\_file/0003/138180/E94886\\_ch11.pdf](http://www.euro.who.int/data/assets/pdf_file/0003/138180/E94886_ch11.pdf)>, p. 470.

<sup>134</sup> Case 120/78, op. cit.

<sup>135</sup> Van Veen, E-B, et. al., op. cit., p. 2919.

because it requires financial and arbitrary efforts to first inform patients and convince them to take part in a clinical trial and, therefore, researchers could refrain from buying samples collected in such Member States. As elaborated in the chapter on informed consent<sup>136</sup> the prior obtained approval of the patient for the use of his samples serves the self autonomy of the patients and their protection and is, therefore, reasonably justified. Many Member States also lay down exceptions from this general requirement in the case it is impossible or would require unreasonable efforts to obtain informed consent, such as Norway or Sweden. Spain, for instance, on the contrary excluded such a derogation from the consent requirement.<sup>137</sup> This does not necessarily mean that such national regulations have to be seen as unlawful potential hinderances for the European fundamental freedoms. The right of self autonomy and the protection of the patients are so valuable goods that a higher standard of protection could be regarded as reasonable without an infringement of the standards on free movement of services and goods.

### 4.3.2 Transnational sharing of (personal) data

If it comes to sharing of personal data between researchers in different Member States the Data Protection Directive and the implementing national laws have to be considered. In a transnational setting the question arises which national data protection framework does apply. Two situations have to be distinguished:

- the transferring entity stays data controller and the receiving entity becomes data processor or
- the receiving entity becomes a data controller (as well).

The sharing of anonymous data is not governed by the data protection frameworks. Here again arises the issue of truly “anonymizing” data in a legal sense.<sup>138</sup> If such data can be qualified as anonymous the details provided in the following subsections do not apply.

#### 4.3.2.1 Data controller and data processor

Firstly, the terms ‘data processor’ and ‘data controller’ need to be explained. The Data Protection Directive defines in Art. 2 (d) ‘data controller’ as the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing of personal data. ‘Data Processor’ is defined as a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller (Art. 2 (e)). Those definitions imply that it is a question of control whether a person processing personal data is qualified as data controller or data processor. In clinical trial settings often researchers want to use (personal) data and samples for their self-managed research projects. In such cases one would qualify the recipient of the personal data as a data controller. The providing biobank supplies only the samples and related data, but is not defining the research proceedings (of course the providing biobanks and/or their ethical committees consider the research purpose when they grant access to their resources). In contrast to this if the recipient is only following the instructions from the sending party then this implicates that he is a data processor.<sup>139</sup>

---

<sup>136</sup> See point 4.1.

<sup>137</sup> See point 4.1.4.1.1.

<sup>138</sup> See point 4.2.3.

<sup>139</sup> D5.1, pp. 21-22, 80-81.

#### 4.3.2.2 Receiving entity becomes data processor

In the case where the receiving entity becomes a data processor only one national data protection regime applies. According to Art. 4 of the Data Protection Directive shall each Member State apply the national provisions it adopts pursuant to this Directive where the processing of personal data is carried out in the context of the activities of an establishment of the controller on the territory of the Member State. When the same controller is established on the territory of several Member States, he must take the necessary measures to ensure that each of these establishments complies with the obligations laid down by the national law applicable. Thus, the processing of personal data underlies the national law of the country in which the controller is established, regardless of where the actual processing takes place.<sup>140</sup>

Significant differences in the implementation of Art. 4 Data Protection Directive cause uncertainties: e.g. Finnish law bases on the controller's place of activity while Swedish law puts emphasis on the place of the "establishment". This again shows that EU data protection laws are far from being a single coherent regime, which causes confusion and difficulties to comply with the relevant national laws.<sup>141</sup> The heterogeneity in the national data protection frameworks might be a hindrance especially when a multitude of parties are involved such as clinical investigators, research organizations, sponsors and monitors from different Member States.<sup>142</sup> It is time-consuming and costly to identify data protection obligations and implement compliance measures. Failing with the requirements could jeopardize a whole research project because apart from fines and reputational damages national data protection authorities also have the power to terminate a project if appropriate.<sup>143</sup>

#### 4.3.2.3 Receiving entity becomes data controller

The situation where the recipient becomes data controller is to be treated differently. Following Art. 4 of the Data Protection Directive the territorial principle will apply as soon as the receiving entity becomes a data controller. Here the same question arises as above regarding to the use of tissues: can an authority abandon the use of data if they have been collected under a less strict regime than the regime of the Member State where the new data controller is established?<sup>144</sup> The answer can be found in Art. 1 Data Protection Directive on the Object of the Directive:

"1. In accordance with this Directive, Member States shall protect the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data.

2. Member States shall neither restrict nor prohibit the free flow of personal data between Member States for reasons connected with the protection afforded under paragraph 1."

This means that if one Member State implements the Directive correctly then another Member State may not impose restrictions on the flow of personal data to that other Member

---

<sup>140</sup> Ibid, pp. 15-16.

<sup>141</sup> BBMRI, Joint Deliverable of WP 5 and WP 6, To Explore Pan-European Solutions for the Cross Border Data Protection Issues Associated with BBMRI, 2011, p. 13.

<sup>142</sup> Reetzer, K, et. al., op. cit., p.15.

<sup>143</sup> Ibid, p. 16.

<sup>144</sup> See point 4.3.1.



State because it does not consider the level of protection adequate and the other way around.<sup>145</sup>

#### 4.4 **Criteria for assessing requests and proposals**

One other factor affecting access to biorepositories is the lack of standard for evaluating requests made to use such resources. Different criteria are applied by biobanks when setting priorities between competing applications, and they can arbitrarily take a decision based on their individual policies and procedures. Verlinden (2012) indicates that criteria could range from giving priority to researchers working in the same institution to lottery.<sup>146</sup> Precedence of application and comparative scientific merit of proposal also count, however, the criteria for evaluation may differ depending on whether the application is coming from academic or commercial applicant. Industrial or commercial access requests tend to be treated differently in some cases as a result of public image, consent and intellectual property concerns.<sup>147</sup> The OECD have tried to address this issue by stating that: “Access to human biological materials and data should be based on objective and clearly articulated criteria, and should be consistent with the participants’ informed consent”.<sup>148</sup> But this is yet to be properly represented in biobank policies.

Similarly, the governance structures, often consisting of several boards or groups that evaluate biobank policies, documents and research proposals also have a bearing on the issue at stake. When a proposal is submitted to a biobank to get access to samples and data, often an additional group such as external ethics committee is also involved in the approval process, which means that a lengthy process may be involved. While the outcome of these reviews may affect access, it is not static what the screening factors are. The mandates of the access committees vary and they evaluate access requests in accordance with the rules or guidelines of the biobanks establishing them.<sup>149</sup> Though most public funded biobanks aim at promoting access, some institutions tilt more towards protecting the infrastructure and maximizing the use of their repository. Access can sometimes be restricted to researchers within particular institution where the samples are collected.<sup>150</sup> Other considerations may include availability of adequate portion of sample, the qualification of the researcher and the scope of the research.

#### 4.5 **Intellectual property**

The biobank’s policy for the IP rights derived from research conducted with its data or samples, such as new medications usually affects how access is granted in a number of cases.<sup>151</sup> Hellstadius, Wolk and Wessman (2003) point out that “the existence of exclusive rights in biobank structures, or rights to forbid extraction from or reutilisation of the collection in a biobank, or to hold a biobank trademark or trade name to an exclusive basis always

---

<sup>145</sup> Beyleveld, D, op. cit., 2004, p. 6.

<sup>146</sup> Verlinden, M, op. cit, p. 12.

<sup>147</sup> Lowrance, M, op. cit., p. 12.

<sup>148</sup> See Principles 7.A of the OECD Guidelines.

<sup>149</sup> Fortin, S, et. al., ‘Access Arrangements’ for Biobanks: A Fine Line between Facilitating and Hindering Collaboration’, Public Health Genomics 2011, vol.14, pp. 104–114.

<sup>150</sup> Zika, E, et. al., op. cit., p. 22.

<sup>151</sup> Fortin, S, op. cit.

restricts the access of other parties to the protected objects".<sup>152</sup> An important distinction must be made between biobanks created within the frame of public health and medical services, and those created by private companies such as pharmaceutical companies. Public law applies to biobanks established within the realm of public health and medical services and there are provisions prohibiting the exportation of biobanks for commercial gain. This in effect means that publicly funded biobanks exclude themselves from partaking in IP rights generated with their resources, thereby promoting access. But there may be some caveat in some instances forbidding the researchers from imposing unreasonable restrictions from the inventions they generated from this public resources as seen in the UK biobank access policy.<sup>153</sup> This may not be the case with private biobank, whose policy usually is to negotiate and partake in IP proceeds. Resolving IP issues in some cases may linger the time it takes between access request and actual grant.

---

<sup>152</sup>Hellstadius, A, et. al., 'Intellectual Property and Biobanks' in Hansson, M and Levin, M (eds.) *Biobanks as Resources for Health*, Universitetstryckeriet (2003), Uppsala, p. 209.

<sup>153</sup> See the UK Biobank Access Procedure, version 1.0, November 2011.

## 5 Material Transfer Agreements

Access to materials is treated differently from access to data, and in some situations it is subject to separate oversight.<sup>154</sup> Biomaterial transfer is usually carried out under an agreement (Material Transfer Agreement (MTA)) between the biobank and the researcher. MTAs also echo the general view that the best way to avoid legal conflicts in biobank collaboration is via the use of bilateral contracts.<sup>155</sup> These agreements are meant to ensure that the collaboration proceeds in the best interest of all partners. There is at present no standardized format for MTA within the EU, even though there have been some efforts to harmonize it in the past such as the Uniform Biological Materials Transfer Agreement (UBMTA).<sup>156</sup> However, the core elements of such agreement have been generally identified to include among other things: obligations of the investigator, safe handling, transfer and storage, use of material and restrictions, requirements for maintaining privacy /confidentiality and non transfer, intellectual property rights, return of material, etc.<sup>157</sup> It has also been found that such agreements are very jurisdiction specific due to their legal nature, though there are some commonalities in the context of populational biobanks.<sup>158</sup>

At present, each institution has to negotiate its material transfer, which can be so protracted and complex in some cases. While it is desirable that a harmonised approach be adopted, jurisdictional nature of the contracts, as well as the differences in biobanking regulations may still form militating factors for such objectives. It should also be noted that some biobanks make their MTA non-negotiable.<sup>159</sup>

---

<sup>154</sup> Lowrance, M, op. cit., p. 31.

<sup>155</sup> Goebel, J et. al., 'Legal and ethical consequences of international biobanking from a national perspective: the German BMB-EUCoop project', *Eur J Hum Genet* 2010; 18(5), pp. 522–525.

<sup>156</sup> Science Common Background Briefing, viewed 23.12.2012, <<http://sciencecommons.org/projects/licensing/background-briefing/>>.

<sup>157</sup> Chalmers, D, 'From Contracts to Generic MTA's: International Governance and Access', International Biobank Summit 2012, viewed 24.12.2012, <<http://www.p3g.org/sites/default/files/site/default/files/Don%20Chalmers%20-%20Uppsala%20Sept.pdf>>.

<sup>158</sup> Pathmasiri, S and Knoppers, B, 'Material and Data Access Agreement: Core elements', P3G Ethics and Policymaking Core, (n.d).

<sup>159</sup> See for instance the UK Biobank Access Procedure.

## 6 Initiatives to facilitate access to biobanks in Europe

In spite of the above hurdles, there have been several initiatives at both EU and global level that tend to facilitate access to biomaterials and associated data. In terms of location of resources, a meta-model that describes information about various biobanks and their heterogeneities is being built across the globe.<sup>160</sup> These infrastructure will make it possible to link and network biobanks with the aim that researchers can make one inquiry that will enable them to access a number of biobanks and datasets.<sup>161</sup> In Europe, such initiative is being carried out in several formats such as integrating national biobanks under the auspices of the Biobanking and Biomolecular Resources Research Infrastructures Initiative (BBMRI); integrating local biobanks under the auspices of the national biobank such as the BBMRI.se, Danish National Biobank; or various institutions integrating their resources such as universities biobanks within a state such as the String of Pearls Initiative in Netherlands. Below, we shall briefly evaluate few examples. Worthy of note also is the trend in most states where National Registry of Biobanks and their collections is being created such as in Germany<sup>162</sup>, Spain, Denmark, etc.

**The BBMRI:** The BBMRI is now a network of over 225 established biobanks throughout Europe, and is expected to become a legal entity (BBMRI-ERIC) in the second half of 2013.<sup>163</sup> BBMRI aims to improve biobanking accessibility and interoperability by establishing a clear access procedure that complies with the general access procedures and conditions of BBMRI-ERIC.<sup>164</sup> The infrastructure seeks to harmonise the rules for access to samples and data that will honour commitments to donors and follow the principles of “fair access” and scientific excellence. BBMRI has a catalogue of existing major population-based and clinical (or disease-orientated) biobanks in Europe. And to bridge the gap in private sector access to biomaterial and data, it is developing the concept of Expert Centres (public-private partnerships) that will be responsible for the analysis of samples in the country of origin under internationally standardised conditions and the generation of primary data.<sup>165</sup> Under BBMRI framework, a common IT-infrastructure of BBMRI-ERIC, will be used to connect the different national nodes, which are geographically spread through Europe. The planned IT-infrastructure employing federated database architecture will integrate the complex network of hubs, members and associated partners in the implementation phase of BBMRI.<sup>166</sup> National chapters of BBMRI have emerged in some European countries such as in Sweden, Finland, Italy, etc, with similar motive to increase the potential of biobanks.

BBMRI has proposed a three phase scheme for access to biobanks which consists of:

---

<sup>160</sup>Harris, J, et. al., ‘Toward a Roadmap in Global Biobanking for Health’ *European Journal of Human Genetics* (2012) 20, 1105–1111, viewed 10.01.2013, <[http://www.redbiobancos.es/Pages%5CDocs%5CToward a roadmap in global biobanking for health.pdf](http://www.redbiobancos.es/Pages%5CDocs%5CToward%20a%20roadmap%20in%20global%20biobanking%20for%20health.pdf)>, p. 1106.

<sup>161</sup> Kaye, J, ‘From single biobank to international networks: developing e-governance’, *Hum Genet* 2011, 130:, pp. 377-382.

<sup>162</sup> See German Biobank Registry, viewed 12.01.2013, <<http://www.tmf-ev.de/BiobankenRegisterEN/Registry.aspx>>.

<sup>163</sup> See, BBMRI during the transition phase, viewed 29.01.2013, <[http://www.bbmri.eu/index.php?option=com\\_content&view=frontpage&Itemid=27](http://www.bbmri.eu/index.php?option=com_content&view=frontpage&Itemid=27)>.

<sup>164</sup> The European Research Infrastructure for Bio-Banking and Biomolecular Resources Partner Charter (Draft version 4; 06.12.2010).

<sup>165</sup> BBMRI Final Report, 2011, viewed 29.1.13, < [http://www.bbmri.eu/index.php?option=com\\_content&view=article&id=99&Itemid=78](http://www.bbmri.eu/index.php?option=com_content&view=article&id=99&Itemid=78) >, p. 16.

<sup>166</sup> *Ibid*, p. 5.

- 1) Acquiring material and data – where a researcher investigates which of the biobanks participating in a consortium store data that may be relevant for a proposed study. In this phase, the researcher has no access to data detailed enough to violate anonymity requirements and has no access whatsoever to biomaterials.
- 2) Based on the results of this research, the researcher in stage 2 formulates a project proposal and submits it to the institution's ethics committee for approval. Additionally, the proposal is reviewed by the biobank, so it can manage access to rare resources. Part of the approval process is the analysis of whether all the data requested is indeed necessary for the project ('need to know' principle).
- 3) Only after approval from the ethics committee is the researcher granted, in stage 3, access to detailed data and material. In this phase, the actual research project is performed and the researcher is bound to observe all necessary precautions to maintain the security of the data and the confidentiality of the donors.<sup>167</sup> It should be noted however that under the BBMRI infrastructure, partners can decide whether access will be granted for a specific request or not. This decision, however, has to follow transparent decision making procedures.<sup>168</sup>

**BioSHaRE:** Another initiative is the Biobank Standardisation and Harmonisation for Research Excellence in the European Union (BioSHaRE).<sup>169</sup> BioSHaRE aims to coordinate the sharing of data and biological samples from different biobanks for the purpose of research. The overall aim of the project is to build upon available tools and methods in order to achieve solutions for researchers to use pooled data from different cohort and biobank studies. The mission of BioSHaRE is to ensure the development of harmonised measures and standardised computing infrastructures enabling the effective pooling of data and key measures of life-style, social circumstances and environment, as well as critical sub-components of the phenotypes associated with common complex diseases.<sup>170</sup>

**STORE:** The STORE (Sustaining access to tissues and data from radiobiological experiments) project aims to create a platform for the storage and dissemination of both data and biological materials from past, present, and future radiobiological research. The platform will consist of a combined "Data Warehouse" and physical repository that will enable the sharing of experimental data sets and materials. STORE will provide a single portal to radiobiological information that is presently distributed over scientific centres worldwide, and will also provide the necessary Standard Operating Procedures (SOPs) for the evaluation of archived tissue usability.<sup>171</sup> Basically, it will provide a "one-stop-shop" portal integrating international databases, such as e.ERA, Chernobyl Tissue Archive, JANUS, and other repositories currently active, such that the user can find material and data held remotely.

**SAIL:** The Sample avAILability System, is a web-based resource, which allows researchers to locate and estimate the amount of relevant biomaterial available from a sample collection.<sup>172</sup> It is a biomedical informatics solution developed under the ENGAGE project which takes the form of a central and controlled meta-portal for data release by biobanks to

---

<sup>167</sup> Eder, J; Gottweis, H and Zatloukal, K, 'IT Solution for privacy protection in biobanking', Public Health Genomics 2012; vol. 15, pp. 254-262.

<sup>168</sup> Ibid.

<sup>169</sup> <http://www.bioshare.eu/>.

<sup>170</sup> <http://www.bioshare.eu/?q=content/our-mission>.

<sup>171</sup> Sustaining access to Tissues and data frOm Radiobiological Experiments, viewed 12.12.2012, <<http://fp7store.de/pages/home.php?lang%4EN>>.

<sup>172</sup> [sail.simbioms.org](http://sail.simbioms.org).

potential and existing partners. It also provides information for each sample as to whether a value for a given phenotypic variable exists or not, without storing or disclosing the value per se. In summary, SAIL provides an interface for harmonisation and submission of sample and phenotype information that is available in various biobank collections; and a search engine for surveying which data from which cohorts could be combined for specific tasks such as study construction and sample selection. It has a database that is populated with information about metadata and availability of biomaterial within various collections. One important feature of this infrastructure is that it facilitates resource discovery across biobanks at the level of a single individual samples, rather than presenting summary content for an entire collection.<sup>173</sup>

At the national level are initiatives such as the **String of Pearls Initiative** in the Netherlands comprising of eight university medical centres (teaching hospitals) in the Netherlands. The project started in 2007, but began a compilation of database in 2008 with a view to making the information and physical specimens they hold available for scientific research. Interested researchers have no direct access to the facility, but can consult an online catalogue to find out what material has been collected by each “pearl”. Data and biomaterials are released for research purposes only after ethical checks have been carried out and the scientific relevance of the proposed study has been assessed. Once an application has been approved, the requested data is retrieved from the central system and made available to the researcher.<sup>174</sup>

**The Danish National Biobank** also aims to offer scientists a unique overview and access to more than 15 million biological samples. To facilitate this, it created a registry that gives researchers online access to combined data from all the biobanks participating in the Danish National Biobank initiative.<sup>175</sup> Through national collaboration, large biobanks based at hospitals, universities and other research institutions in Denmark, will regularly submit data to the Biobank Register. Data from the biobanks can be linked to disease codes and demographic information from national administrative registries on an individual level. So, when searching the biobank register for example, it will be possible to look up the number of biological samples available from patients with certain diagnosis. Anonymous data sets can be made available to researchers around the world through a web-based search system.<sup>176</sup> And after conducting a search, the next step for researchers will be to contact the Coordinating Centre for the materials.<sup>177</sup>

**CRIP:** The German-Austrian Central Research Infrastructure for molecular Pathology (CRIP) is another example of transnational networking between tissue banks in Europe.<sup>178</sup> It provides a metabiobank - a common infrastructure and attuned workflow permitting access to participating biobanks’ data and materials. The core components of the project are the

---

<sup>173</sup> Krestyaninova, M, op. cit.

<sup>174</sup> The String of Pearls Initiative Factsheet, viewed 12.12.12, <<http://www.string-of-pearls.org/uploaded/FILES/htmlcontent/Factsheets%20Engels/Factsheet%20String%20of%20Pearls%20Initiative.pdf>>.

<sup>175</sup> Danish National Biobank Register, viewed 22.12.2012 <<http://www.biobanks.dk/?locale=en>>.

<sup>176</sup> The Danish National Biobank Register – overview and access, viewed 22.12.2012, <<http://www.biobankdenmark.dk/The%20Biobank%20Register/More%20about%20Biobank%20Register.aspx>>.

<sup>177</sup> Ibid.

<sup>178</sup> Schröder, C, et. al., ‘Safeguarding donors’ personal rights and biobank autonomy in biobank networks: the CRIP privacy regime’, viewed 12.12.2012, <[http://www.crip.fraunhofer.de/htdocs/pdf/135\\_Schroeder\\_CRIPPrivacy.pdf](http://www.crip.fraunhofer.de/htdocs/pdf/135_Schroeder_CRIPPrivacy.pdf)>.

Database Partners, the CRIP project management and an Advisory Board. The Database Partners contribute anonymized data for biomedical research to the CRIP infrastructure, while the CRIP project management is under the auspices of Fraunhofer IBMT which acts as a metabiobank operator that coordinates and maintains the CRIP database. The Advisory Board for CRIP is acting independently to establish guidelines, advice and comment on problems and questions arising from the project.

On the global level, there are initiatives such as the **Public Population Project in Genomics (P3G) and Society**.<sup>179</sup> P3G is an international consortium dedicated to the development and management of a multi-disciplinary infrastructure that can compare and merge results from studies, biobanks, research databases and other similar health and social research infrastructures conducted around the world. It is building an open, public and accessible knowledge database called the P3G Observatory. Through its tools, support and network, P3G is enabling wide access to research tools and expertise. The P3G is currently in collaboration with various EU institutions and projects such as BBMRI, BioShare and national biobanks.

From our evaluation of the above infrastructure, it could be distilled that access is facilitated in diverse ways such as by having a catalogue (P3G) or creating a search engine (Danish National Biobank, CRIP) or by creating both catalogue/search engine and further avenue to share both data and material (BBMRI). Furthermore, a general platform for global cooperation where institution can publish their access to data and sample information such as P3G is also a valuable tool in this regard.<sup>180</sup> One other useful information that could be gathered from the above infrastructures is how they handle the legal, ethical and social issues that may arise as a result of their initiatives. The CRIP project for instance has a separate advisory board that takes care of ELSI, while some others have work packages that are dedicated to ELSI. The p-medicine project has a combination of both – an international ethical committee and work package 5 that deals with legal and ethical issues. Below we will look at the p-medicine framework in detail.

---

<sup>179</sup> Public Population Project in Genomics (P<sup>3</sup>G) and Society, viewed 12.12.12, <<http://www.p3g.org/about-p3g/glance>>.

<sup>180</sup> See P3G Access Description form.

## 7 The p-medicine metabiobank framework

The p-medicine metabiobank aims at facilitating the linking, pooling, or comparing of data sets/materials within the participating biobanks. It is a web application and database architecture and will be accessible via the p-medicine portal.<sup>181</sup> As indicated in Deliverable 10.1, the biobank access framework will assist in two broad ways: facilitating researchers' access to biomaterial with specific characteristics that match their intended research purpose; and from the perspective of a biobank operator, to make their own biomaterial stock and characterising data available to the research community. This framework does not attempt to build a new biobank, but facilitates access to already existing biobanks for researchers. Registered researchers (users) will have the possibility to search this metabiobank for suitable biosamples and data and can further request access to these resources through the infrastructure. Deliverable 10.1 has made an elaborate analysis of the metabiobank architecture, including the functionalities of its tools.<sup>182</sup> Deliverable 10.2. describes in more detail the correspondent functionalities of the p-medicine biobank access framework which is being developed along two user scenarios on acute lymphoblastic leukemia (ALL) and Wilmstumor.<sup>183</sup>

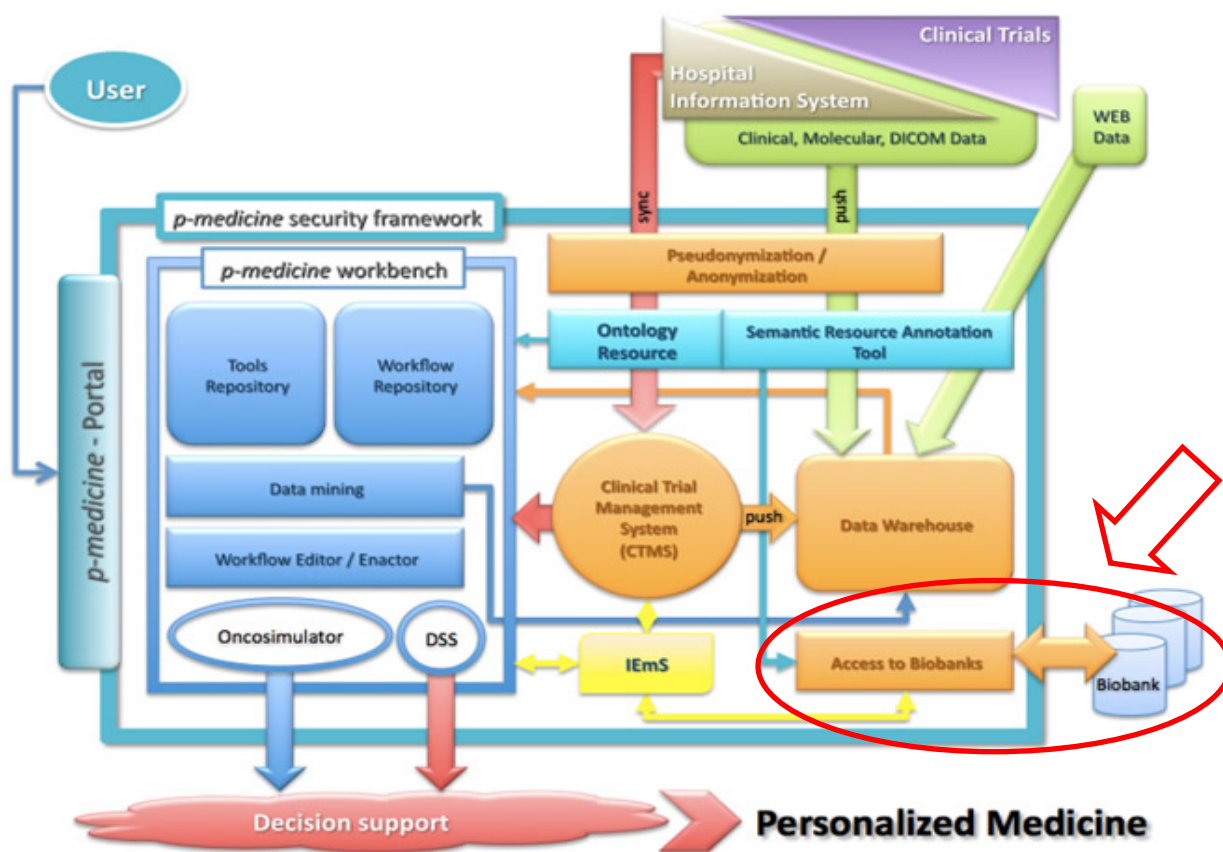


Figure 1: p-medicine infrastructure

<sup>181</sup> D10.2: Initial Implementation of the Components of the p-medicine Biobank Access Framework, p. 15.

<sup>182</sup> D10.1: Analysis report about existing Tools, Platforms, and Initiatives for Integrated Biobanking, pp. 112-128.

<sup>183</sup> D.10.2, op. cit., pp. 7-12.



## 7.1 **The p-medicine metabiobank concept and data flows**

The p-medicine metabiobank is technically based on the CRIP (Central Research Infrastructure for molecular Pathology) metabiobank concept which has been found most suitable for the purposes of integrating a search tool for biomaterial in the p-medicine infrastructure. It enables the exchange of information about stored biomaterials in participating biobanks in a manner that respects the donor's privacy and biobank autonomy.<sup>184</sup> The CRIP data protection scheme was developed in close collaboration with the Berlin Data Protection Commissioner, who acknowledged CRIP as a benchmark.<sup>185</sup>

The main component of the p-medicine framework will be **p-BioSPRE** - the p-medicine Biomaterial Search and Project Request Engine, which will enable researchers to search for biomaterial and data. Furthermore, the framework comprises the **p-Biobank Wrappers**, which are tools to support biobank owners to offer their biomaterial and related data, which can be stored in any biobank information system, in p-BioSPRE and manage associated requests. In order to enable users of the p-medicine trial management system ObTiMA to integrate biomaterial data in clinical trials and offer it in p-BioSPRE, a **Trial Biomaterial Manager** will also be provided.<sup>186</sup>

### 7.1.1 Uploading data to the metabiobank

Participating biobanks that are willing to share data about their stored samples will be able to use the p-Biobank wrappers to upload data into p-BioSPRE. Core of the p-Biobank Wrappers is an Inhouse Database (IDB)<sup>187</sup> which is technically comparable to the CRIP "Inhouse Research Database" (IRDB).<sup>188</sup> The p-Biobank Wrappers are local servers installed at the site of a biomaterial owner and configured to link one or more of his biobank management systems that store data. The user will be able to extract research relevant data and is provided with an interface that is supporting the import of pseudonymized sample data from the linked biobank information management systems (BIMS). Research data that has been imported into the IDB will be harmonized and further de-identified: e.g. by converting patients' data (e.g. converting patients' exact age into full years), but the pseudonym still exists on this stage. The keyholder, however, is only the hospital or biobank holding the samples and pertaining data (BIMS). Data will not be exported automatically to p-BioSPRE, it can only be triggered by the participating biobank operators. Before data will be sent to the p-BioSPRE database, the pseudonymization key will be replaced by a randomly generated number.<sup>189</sup>

---

<sup>184</sup> D10.1, op. cit., pp. 46-51; 112-128; Schröder, C, et. al., op. cit, p. 1.

<sup>185</sup> Schröder, C, et. al., op. cit., p. 5.

<sup>186</sup> D10.1, op. cit., p. 113.

<sup>187</sup> D10.2, op. cit., p. 13.

<sup>188</sup> D10.1, op. cit., p. 114; for more details about CRIP see Schröder, C, et. al., op. cit, pp. 1-8.

<sup>189</sup> D10.2, op. cit., p. 18.

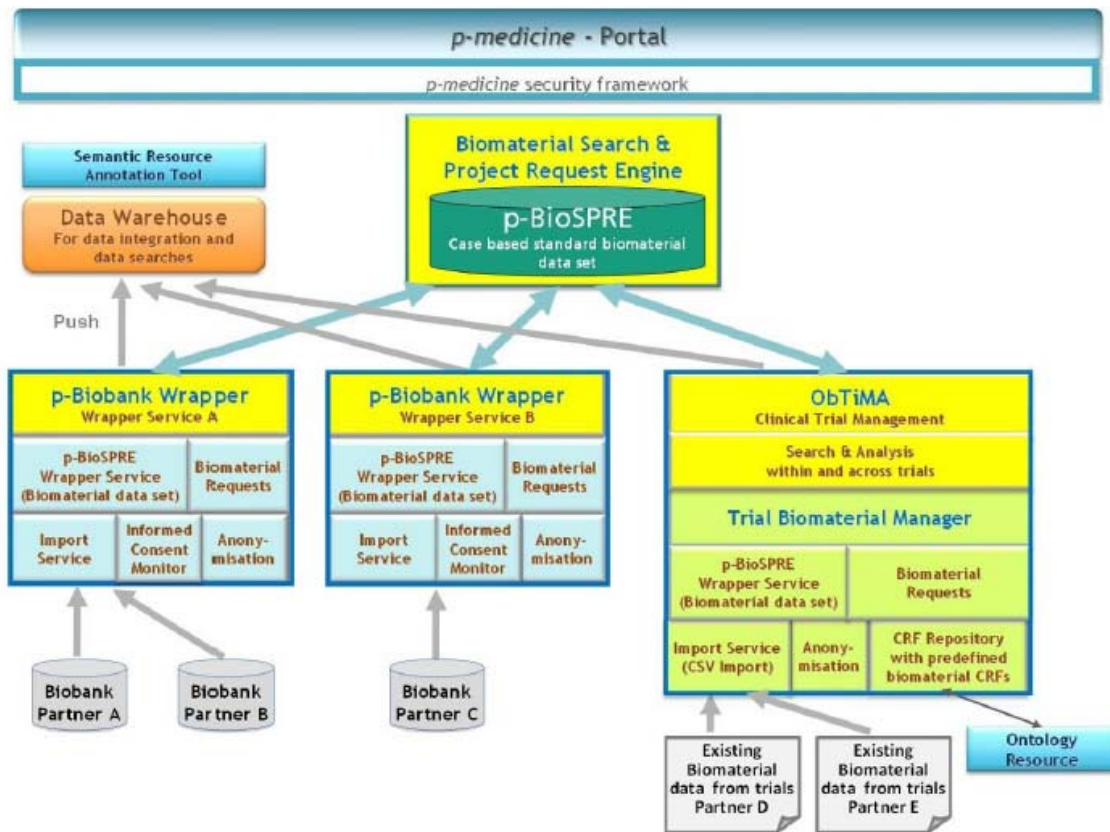


Figure 2: Basic architecture of the p-medicine Biobank Framework

If patients decide to withdraw their consent, the biobank operator that has provided the respective data to the metabiobank will replace their old data sets by uploading the updated sets (excluding the data set of the patient who withdrew his consent). The data sets uploaded to the p-BioSPRE metabiobank are still traceable to their original source, so that the concerned biobanks are able to update their data sets.

To enforce patients' decisions on the research use of their specimen p-BioSPRE will be equipped to record tiered informed consent and provide this information, if available, to the metabiobank query.<sup>190</sup>

### 7.1.2 Searching for data in the metabiobank

After authentication, registered users can search for biomaterial using the p-BioSPRE tool according to the standard biobank dataset. The interactive search tool allows the selection of the localization of the organ/organ system, the disease, the type of specimen, clinical data and information on informed consent.<sup>191</sup> The search result displayed from the infrastructure contains only the number of cases ("pool") fulfilling the scientist's search query. In other words, results are represented as statistical groups. The minimum threshold for the number of displayed cases can be defined over the software by the p-medicine metabiobank in cooperation with the biobank operators. With the statistical data the providing biobank entity can be shown and/or the BioSPRE tool can be launched to send requests for research projects to the biobank operator. It has to be decided by the p-medicine consortium if a

<sup>190</sup> D10.2, p. 17.

<sup>191</sup> D10.2, p. 16.

uniform approach shall be taken here or if participating biobanks can choose the option that they prefer. In respect of protecting privacy of the donors, biobank operators should keep in mind that revealing the location where the sample is stored might make it easier for matching data sets. Request files (search parameters of the user) can be sent to the participating biobanks in any case.

The user who wants to get in contact with the respective biobank can send a request specifying the amount of biomaterial needed and prescribing the envisaged study in detail. It is up to the respective biobank to decide on the actual sharing of biomaterial and data, but according to the p-BioSPRE policy the decision needs to be made within five workdays in order to avoid unnecessary delays.



Figure 3: p-BioSPRE search interface

**Project Details**

**Scope of Project**

Please give us an idea and a short outline of your work and the question(s) this project shall answer. This will help our partners to tailor their proposals to your research needs. Thank you.

Select	Required Cases	Localization	Disease	Specimen
<input checked="" type="checkbox"/>	<input type="text" value="30"/> Further specification of cases/specimens	C50 - Breast	814-838 - Adenomas and Adenocarcinomas	Tissue (FFPE)
<input checked="" type="checkbox"/>	<input type="text" value="50"/> Further specification of cases/specimens	C50 - Breast	850-854 - Ductal and Lobular Neoplasms	Tissue (FFPE)
<input checked="" type="checkbox"/>	<input type="text" value="8"/> Further specification of cases/specimens	C50 - Breast	856-857 - Complex Epithelial Neoplasms	Tissue (FFPE)

**Requested Methods**

Select checkboxes from the list of scientific services available at the partners' institutes.

<input checked="" type="checkbox"/> DNA-PCR	<input type="checkbox"/> Tissue microarray	<input checked="" type="checkbox"/> Gene expression profiling
<input type="checkbox"/> RNA-(RT)-PCR	<input type="checkbox"/> W/N/S blot	<input type="checkbox"/> Genomic losses/gains
<input type="checkbox"/> Morphology	<input type="checkbox"/> In-situ hybridization	<input type="checkbox"/> FISH
<input type="checkbox"/> Immunohistology	<input type="checkbox"/> Functional assays	<input type="checkbox"/> Macro-/Microdissection

Other/Comments:

I accept the supply conditions.

Back

Figure 4: p-BioSPRE request form

## 7.2 Data Protection Aspects

### 7.2.1 Data sets of the donors

The data flow within the metabiobank infrastructure shows that the access tool (p-BioSPRE) only processes anonymized/aggregated data that do not reveal any individual identity when performing a search. This does not in fact pose data protection issues as only statistical results, guaranteeing a k-anonymized<sup>192</sup> view on the data, devoid of any personal information of the donors. The researcher will enter his stratification criteria step by step and retrieve the number of cases which are available and matching his request. Processing only anonymous data thus relieves the infrastructure from the rigorous requirements for personal data processing as required by the national laws implementing the Data Protection Directive.

To maintain security and confidentiality of the infrastructure by controlling the context in which data is processed, the metabiobank portal will be used only by registered users and the infrastructure will be exploited under a clear guide as will be set up in this deliverable. In the first instance, data transfer agreement will be concluded between the participating

<sup>192</sup> See point 7.1.2.

biobank operators and the p-medicine metabiobank operator. This agreement indicates clearly that only anonymous data will be processed in the framework. Secondly, researchers wishing to use the infrastructure will complete registration requirements and agree to the terms of use. Through this regime, the biobanks' autonomy and users' confidentiality are efficiently protected.<sup>193</sup>

## 7.2.2 Data of the end-users

It should be noted that personal data of the researchers (end-users) will be processed by the p-medicine metabiobank operator for the purposes of registration and authentication. The registration form will be downloadable from the metabiobank portal. The researcher will have to send the completed form by fax or email to the p-medicine metabiobank operator. Negotiation proceedings regarding the content of the registration are ongoing. It is foreseen at the moment that a scientist will have to state his name, e-mail address, phone and fax number, the name and address of the organization or company he or she is working for, its legal representative and the name and the head of the laboratory research group. Additionally, he or she has to make credible his or her research interest. Data to be collected from the researcher will be specifically used for registration and validation purposes, and not further processed for any incompatible purpose. This processing is under the established data protection and data security framework of the project, (having first obtained the explicit consent of the researcher for such data processing during registration) as described in Deliverable 5.1.<sup>194</sup> The protection and security of the processed data will be in accordance with the data protection law applicable in Germany where the p-medicine metabiobank operator is established (according to the territorial principle laid down in Art. 4 of the Data Protection Directive).

---

<sup>193</sup> [http://www.crip.fraunhofer.de/en/ethics\\_policy/privacy\\_regime](http://www.crip.fraunhofer.de/en/ethics_policy/privacy_regime).

<sup>194</sup> See Deliverable No. 5.1 Setting up of the data protection and data security framework for p-medicine, pp. 67-88.

## 8 The p-medicine metabiobank access policy

From the remarks above, the data flow via the p-medicine biobank access infrastructure indicates a minimal risk of data protection and confidentiality violation. However, as pointed out by Eder et. al., there is always a possibility of subtle risk even with aggregated information, such as when there is a motivated snooping or tracking.<sup>195</sup> While these incidents could be tackled technically<sup>196</sup>, there is also a need to have a policy framework that outlines what is permissible in biobank procedures. Below we will set up a guideline that will incorporate non-technical measures to safeguard the p-medicine metabiobank infrastructure. As lessons are learned, this guide may be reviewed to keep up with the changing times.

### 1. Data Transfer Agreement

Data integrated in the p-medicine metabiobank will be based on data transfer agreement between the participating biobanks and the p-medicine metabiobank operator (see the annex to this deliverable for a sample of such a contract).

### 2. Access to the infrastructure and data protection principle

Access to the p-medicine metabiobank will be restricted to registered end-users who will have to show their identity and their affiliations to a company or research institution. Access will only be granted after a due process of registration done by the p-medicine metabiobank operator. This includes authenticating the identity of the person seeking to use the resources. Information that will be required at this stage include: name, address, institutional email, telephone number, research department, address, telephone and website of institution where researcher is affiliated. At the moment it is foreseen that the process will involve a “break of media” where intending users need to download, fill in and sign a form and send it by fax or email attachment to the p-medicine metabiobank operator. This will include signing the required consent for the processing of the users’ personal data by the metabiobank operator. A copy of the form will be downloadable from the p-medicine biobank portal. A successful registration will be communicated to the intending user who can then proceed to access the infrastructure. The SOP for this registration process is still under discussion and will have to be agreed upon by the p-medicine consortium. While consent will be the basis for the processing of the registration data, the protection and security of the processed data will be in accordance with the data protection law applicable in Germany where the p-medicine metabiobank operator is established.

### 3. Registration timeline

Review of registration request will be conducted within five workdays after all the relevant questions and documents have been forwarded to the p–medicine metabiobank operator. A confirmatory email will be sent to the applicant.

### 4. Documentation of request

All access requests to the infrastructure shall be logged by the p-medicine metabiobank operator for audit purposes and shall not be stored longer than required by the applicable data retention law.

### 5. Infrastructure management

The p-medicine biobank access is managed by Fraunhofer IBMT (metabiobank operator). The operator will take the necessary steps to ensure that the Metabiobank is accessible to the users and regularly updated. This however does not imply a guarantee of accessibility to a given moment or for a given period of time.

---

<sup>195</sup> Eder, op.cit

<sup>196</sup> E.g. by k- anonymity implementation, D10.2., p. 18.

## 6. Fees

It will have to be decided by the p-medicine consortium if end-users will have to pay a fee, and whether fees shall be restricted to industrial users and public institutions exempted. Other forms of contributions may be considered e.g. passing on knowledge that has been gained out of the data. In case the consortium is deciding for a fee, it further needs to be clarified to whom the contribution will have to be made: e.g. to the manager of the metabiobank infrastructure, to the p-medicine consortium etc. This might be an important aspect to ensure sustainability of the p-medicine infrastructure.

## 7. Eligibility

The p-medicine biobank access framework will be open for personally registered users who need to be affiliated to research institutions or companies that have been granted a user account. The p-medicine consortium will have to decide if the p-BioSPRE will be open only to a closed community of biobanks and researchers or if a more open policy will be followed. An open policy that enables also external researchers to use the research facilities could be essential for the p-medicine sustainability concept and does not necessarily implicate a significantly lower security standard as long as researchers have to go through the admission process.

## 8. Intellectual property

Intellectual property aspects will be resolved in accordance with the p-medicine Consortium Agreement, the FP7 Grant Agreement – Annex II- General Conditions as well as Regulation No 1906/2006.

## 9. Material request

Request for material could be made using the metabiobank portal, and this will be automatically forwarded to the responsible biobank partner. The conditions under which the Biobank partner might provide samples are subject to a bilateral project agreement between such Biobank partner and the research organisation/Metabiobank user.

## 10. Maintaining confidentiality

Technically confidentiality is provided by

- restricting access only to authenticated users who have sufficient access rights.
- encrypting all communication through SSL.

For authentication p-BioSPRE relies on the p-medicine security framework<sup>197</sup>. This security framework provides brokered authentication to services. To access p-BioSPRE a user is redirected to the p-medicine central identity provider which is responsible for authenticating the user. On successful authentication the user is redirected to p-BioSPRE with a SAML 2.0<sup>198</sup> identity token which proves the user's identity<sup>199</sup>. The p-medicine security framework is based on open commonly used stable standard such as SAML 2.0, SSL and X.509<sup>200</sup>.

---

<sup>197</sup> D5.1: Setting up of the data protection and data security framework.

<sup>198</sup> Security Assertion Markup Language 2.0 (<http://docs.oasis-open.org/security/saml/v2.0/saml-core-2.0-os.pdf>).

<sup>199</sup> SAML 2.0 Web Browsers SSO Profile (<http://docs.oasis-open.org/security/saml/v2.0/saml-profiles-2.0-os.pdf>).

<sup>200</sup> X.509 is a standard for public key infrastructure (<http://www.ietf.org/html.charters/pkix-charter.html>).

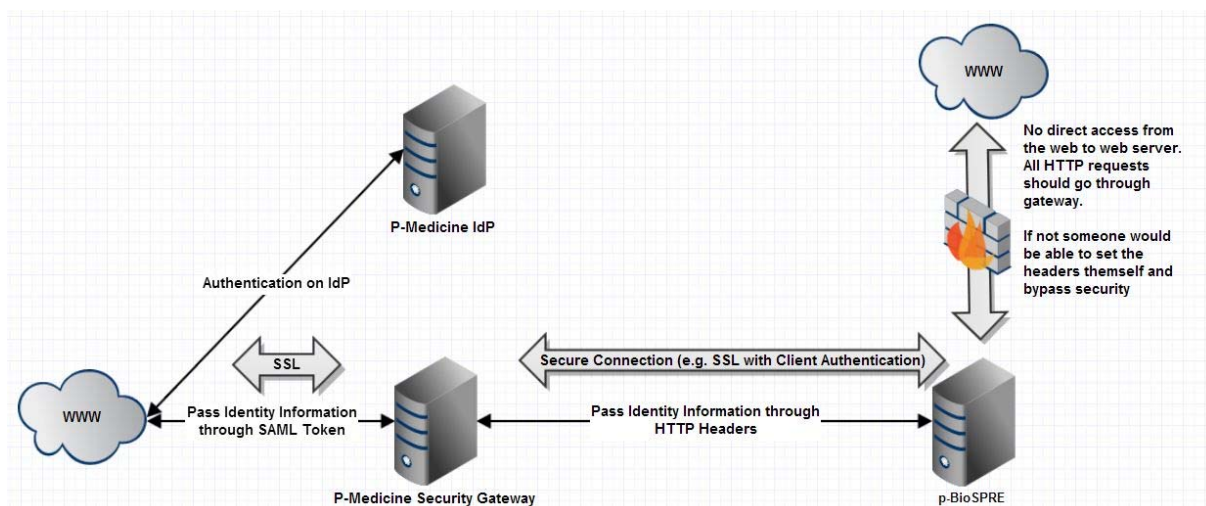


Figure 5: Access to p-BioSPRE via p-medicine security gateway

Integration into the p-medicine security framework implies that p-BioSPRE needs to support the SAML 2.0 standard as defined in D3.4<sup>201</sup>. For easy integration and to avoid a tight coupling between p-BioSPRE and SAML, p-medicine provides a security gateway. It is the responsibility of the gateway to handle the SAML protocol. Once a user is successfully authenticated, the gateway will pass all identity related information (e.g. user's name, identifier, roles) to the shielded web application (p-BioSPRE). It is hereby very important that p-BioSPRE is only accessible through the security gateway. To ensure this, p-BioSPRE should only allow connections from the gateway by using SSL client authentication. Over this gateway, it might be feasible to assign researchers/users of the metabiobank different access rights.

<sup>201</sup> D3.4: Service Integration Guidelines.



## 9 Quality and safety standards in biobanking

### 9.1 *Necessity for quality in biobanking*

A major drawback with many biobanks is that samples have been collected and stored under varying conditions. Thus, it may become difficult for researchers to compare results from different studies. In addition, the amount of clinical information collected with samples varies considerably. Recently, in an effort to standardise biobanking, a number of international organisations have produced detailed guidelines for biobanking<sup>202</sup> (see below). When taken together, these guidelines can provide a reference source for biobanking best practices which can be applied to biobanks in all countries once local legislative considerations have been taken into account. If samples from different collection sites have to be compared, they must be collected in a standardised way, must be processed and stored according to the same protocols and provided with a similar amount of clinical data. Implementation of biobanks with quality assurance can ensure that international best practices are followed and enable that these biobanks can easily become part of initiatives such as the BBMRI. For many cancer clinical trials, biobanks are at a central place to promote such collaboration. But not only for cancer research, medical research is being increasingly conducted at a global level, with large inter-national research collaborations pooling and sharing their samples and data. In these collaborations biobanks can be used as a basic resource for research carried out by these consortia. This collaborative way of carrying out scientific research is challenging the still nationally based systems of biobank governance<sup>203</sup>. Within the European Union, the principles and legal requirements for biobanking have been drawn from more general documents for data protection and clinical trials – but neither of these directives explicitly covers human tissue. An experts group has recommended that member states and European institutions should develop a consistent and coherent legal framework for biobanking that should protect participants' fundamental rights, consider the areas of privacy, data protection and the use of human tissue in research and improve the coordination and collaboration between national oversight bodies.<sup>204</sup> Benefits of the harmonisation of governance to enable collaboration cover the avoidance of duplication of research projects, receipt of samples not available in a country, provision of samples to external studies that might otherwise go unused and in this way increasing the power of statistical studies.

Personalized medicine and biobanking are tightly connected. Today biomedical and pharmaceutical research requires the selection and analysis of large numbers of human samples. These must be of high quality and often for each sample a considerable amount of clinical data must be available to fulfil the requirements of the study protocol. To guarantee that new drugs can effectively reach a large number of patients, it is important to harmonize biobanking procedures, and to support biobank interoperability, biobank quality and specimen sharing<sup>205</sup>. Nevertheless, European biobanks are still widely fragmented with regard to technical, ethical, legal, and quality standards<sup>206</sup>. Biomedical relevant, quality-assessed samples and data as well as associated biomolecular resources are essential for clinical, academic and commercial research to treat and prevent common and rare human

---

<sup>202</sup> Zatloukal K.: Biobank quality management and harmonization: current guidelines, evidence-based standards. Presentation at “Biobanking in Biomedical Research in Siena, Italy”, June 2009.

<sup>203</sup> EUROPEAN COMMISSION, Directorate-General for Research and Innovation: Biobanks for Europe - A Challenge for Governance EU, EUR25302EN (2012).

<sup>204</sup> Ibid, recommendations.

<sup>205</sup> Zatloukal K, Hainaut P.: Human tissue biobanks as instruments for drug discovery and development: Impact on personalized medicine. *Biomark Med.* 2010 Dec;4(6): pp. 895-903.

<sup>206</sup> European Science Foundation: Science policy briefing: population surveys and biobanking (2008).

diseases. ESF identified several key challenges of European biobanking, stating that at present, there is little collaboration between European biobanks<sup>207</sup>. This is largely because of ethical, legal, practical and financial difficulties in sharing or exchanging material and/or data. The lack of standardized and quality-controlled protocols for data and sample collection, storage, retrieval, analysis, and access, presents problems for collaboration, as does a lack of knowledge about where collections exist and what samples they contain<sup>208</sup>. Here the p-medicine biobank access infrastructure comes into play aiming to provide a user interface with metabiobank enabling the search for and the sharing/exchange of biosamples and data. As stated above, as the lack of high-quality clinically annotated biospecimen is seen as a major bottleneck in medical research and a barrier to the development of new treatments, standardization of sample handling and storage protocols are an important requirement. There are very few standardized and quality controlled protocols for pre-analytical procedures, which make it difficult to compare and share samples from different studies, particularly as the sample sizes often need to be large. There is a need for international efforts to agree on standardized, or at least harmonized or cross-convertible protocols, infrastructure and sample formats to ensure that these resources can be utilised fully. To reach this goal pan-European quality assurance schemes and guidelines for pre-analytical procedures for sample collection, handling, transport, processing and storage need to be worked out. In this regard, the ISBER<sup>209</sup> protocol on best practice for repositories might serve as a useful guideline. Although, this guideline, like all other guidelines concerned with biobanking quality, has no legally binding character.

## 9.2 ***European regulations with regard to biobanks: protection of fundamental rights and quality assurance***

With regard to market authorization of medicinal products, the Union adopted the Clinical Trials Directive<sup>210</sup> to provide all the European members with requirements for the conduct of clinical trials, the protection of fundamental rights of study participants and common research protocols. Although this Directive ensures a high level of protection for research subjects, it focuses on the clinical trials procedures to be respected before, during, and after the trial. In summary, demands for harmonised high quality biobanking capabilities in Europe have been recognised by the legislative authority and three European Directives (2004/23/EC, 2006/17/EC (first technical Directive), 2006/86/EC (second technical Directive)) were issued setting standards of quality and safety for the donation, procurement, testing, and processing of samples. In addition to the definition of safety and quality measures for human tissues and cells, these Directives contain requirements on the protection of human rights and privacy, confidentiality of any health related information, and the full traceability of tissues and cells. In addition, the access to quality products for patients is guaranteed by proposing the establishment of common procedures ensuring the traceability of products derived from the human body.<sup>211</sup> Although this legislation does apply to biobanks storing cells and tissues, it

---

<sup>207</sup> Ibid. ESF.

<sup>208</sup> Promoting Harmonisation of Epidemiological Biobanks in Europe (FP6-2004-LIFESCIHEALTH-5) and Eleni Zika, Daniele Paci, Tobias Schulte in den Bäumen, Anette Braun, et.al.: Biobanks in Europe: Prospects for Harmonisation and Networking. JRC Scientific and Technical Reports, European Commission EUR24361EN-2010 (2010).

<sup>209</sup> <http://www.isber.org/>.

<sup>210</sup> Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, JO L 121 of 1.5.2001.

<sup>211</sup> Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004, on setting standards of quality and safety for the donation, procurement, testing, processing, preservation,

only covers those having a therapeutic goal. Only clinical research with the aim of clinical use or to market a product is concerned. In contrast, in vitro research falls outside the field of the directive. Thus, questions arising in the large collaborative research projects which are searching for common instruments to preserve, exchange and use biological samples and data, are not addressed.

In addition, in case cells and tissues are used as medicinal product in interventional Clinical Trials Directive 2001/20/EC<sup>212</sup>, the Clinical Trials Directive applies. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products. The Directive does not specifically refer to research based on biobanks and doesn't mention biobanks and tissues. But it refers to products intended for gene therapy or cell therapy and trials involving medicinal products for gene therapy or somatic cell therapy. It requires that the principles of good manufacturing practice (GMP) should be applied to the production of investigational medicinal products. The same is true for the Directive 2005/28/EC<sup>213</sup> (Good Clinical Practice Directive) which further concretises the Directive 2001/20/EC by laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

The EU Tissue Directive sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human application. It was adopted by the European Parliament on 7 April 2004 and came into effect between 2006 and 2007. Member States were obliged to comply with its provisions from 7 April 2006. Implementation of the Directive is supported by two additional regulations: the technical Directives 2006/17/EC<sup>214</sup> and 2006/86/EC<sup>215</sup>. The Tissue Directive demands that only licensed centres are allowed to handle human tissues and cells intended for human application and in this way sets a standard for the quality of biobank organisations ("Tissue establishments").

---

storage and distribution of human tissues and cells, Directive 2006/17/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, Directive 2006/86/EC implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

<sup>212</sup> EU Directive 2001/20/EC. European Parliament and the Council of the European Union: Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities, L 121:34-44 (2001).

<sup>213</sup> EU Directive 2005/28/EC: Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Official Journal of the European Union L 91/13. Brussels 2005.

<sup>214</sup> COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

<sup>215</sup> COMMISSION DIRECTIVE 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. 25.10.2006.

### 9.3 **Directive 2004/23/EC**<sup>216</sup>

The EU Tissue Directive sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human application. It was adopted by the European Parliament on 7 April 2004 and came into effect between 2006 and 2007. Member States were obliged to comply with its provisions from 7 April 2006. Implementation of the Directive is supported by two additional regulations: the technical Directives 2006/17/EC<sup>217</sup> and 2006/86/EC<sup>218</sup>.

The Directive aims to facilitate exchange of human material within the EU, whilst ensuring a high level of health protection and reassuring patients that tissues and cells derived from donation in another Member State, or originating outside of the EU, carry the same guarantees as those in their own country. Therefore human biobanks containing human body material that is intended for research purposes only are not covered by the scope of this Directive. Nonetheless, the requirements expressed in this Directive can serve as a standard for how to establish quality in biobanks concerned with in-vitro research only. If the human tissue held in a biobank is intended for human use, the rules set by Directive 2004/23/EC establishing specific standards and technical requirements for each one of the steps in the human tissue and cell application process have to be taken into account. The Tissue Directive demands that only licensed centres are allowed to handle human tissues and cells intended for human application and in this way sets a standard for the quality of biobank organisations (“Tissue establishments”). Tissues and cells intended to be used for industrially manufactured products, including medical devices, are covered by the Directive only as far as donation, procurement and testing are concerned, where the processing, preservation, storage are regulated by other Community legislation. The further manufacturing steps are covered by Directive 2001/83/EC<sup>219</sup> relating to medicinal products for human use<sup>220</sup>.

The entire life cycle of a sample, including donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells should comply with high standards of quality and safety in order to ensure a high level of health protection (Figure 6). This Directive therefore establishes standards for each one of the steps in the human tissues and cells application process<sup>221</sup>. In addition, confidentiality and data protection play an important part to guarantee quality of biobanking and are of importance for the donor. Therefore, all necessary measures should be taken into account to provide donors of tissues and cells with assurances regarding the confidentiality of any health-related information, the results of tests on their donations, as well as any future traceability of their donation<sup>222</sup>. Biobanks should also have a quality system in place. Important components of such a quality system are an accreditation process for biobanks and a system for notification of adverse

---

<sup>216</sup> DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. 7.4.2004.

<sup>217</sup> COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

<sup>218</sup> COMMISSION DIRECTIVE 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union. 25.10.2006.

<sup>219</sup> DIRECTIVE 2001/83/EC of the European parliament and of the council of 6 NOVEMBER 2001 on the community code relating to medicinal products for human use. Official Journal L – 311, 28/11/2004, p. 67 – 128.

<sup>220</sup> The Annex currently in force is laid down in Commission Directive 2003/63/EC of 25 June 2003.

<sup>221</sup> Directive 2004/23/EC, Nr. (13).

<sup>222</sup> Ibid, 23 and 24.

events linked to the procurement, testing, processing, preservation, storage and distribution of human tissues and cells.<sup>223</sup> In addition, the Directive requires that an adequate system to ensure the traceability of human tissues and cells should be in place. Such a system can support the verification of compliance with quality and safety standards. Traceability should be enforced through accurate substance, donor, recipient, tissue establishment and laboratory identification procedures as well as record management and appropriate labelling systems.

Article 5 demands the building of an Infrastructure for supervision and accreditation of human tissue and cell procurement on a European level<sup>224</sup>. Member States are required to ensure that tissue and cell procurement and testing are carried out by persons with appropriate training and experience and that they take place in conditions accredited, designated, authorised or licensed for that purpose by the competent authority. The necessary laboratory tests shall be carried out by a qualified laboratory. Article 6 is concerned with the accreditation, designation, authorization or licensing of biobanks (tissue establishments) and tissue and cell preparation processes<sup>225</sup>. Member States shall ensure that all tissue establishments where activities of testing, processing, preservation, storage or distribution of human tissues and cells intended for human applications are undertaken, have been accredited, designated, authorised or licensed by a competent authority.

Notification of serious adverse events and reactions plays an important part for including biobanking in research. The Directive demands that member states shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells.

Quality management has become a necessity for biobanks<sup>226</sup> and the Directive demands that member states shall take all necessary measures to ensure that each tissue establishment puts in place and updates a quality system based on the principles of good practice. The Commission shall establish the Community standards and specifications referred to in Article 28(c) for activities relating to a quality system. Tissue establishments shall take all necessary measures to ensure that the quality system includes at least the following documentation:

- Standard operating procedures
- Guidelines
- Training and reference manuals
- Reporting forms
- Donor records
- Information on the final destination of tissues or cells

All necessary measures to ensure that this documentation is available for inspection by the competent authority or authorities must be ensured. To this extent, every tissue establishment shall designate a responsible person. Personnel directly involved in activities relating to the procurement, processing, preservation, storage and distribution of tissues and cells in a tissue establishment shall be qualified to perform such tasks and shall be provided with the training referred to in Article 28(c). Tissue establishments shall include in their standard operating procedures (SOPs) all processes that affect quality and safety and shall

---

<sup>223</sup> Ibid, issue 25.

<sup>224</sup> Ibid, article 5.

<sup>225</sup> Ibid, article 6.

<sup>226</sup> Ibid, article 16.

ensure that they are carried out under controlled conditions<sup>227</sup>. Furthermore, tissue establishments shall ensure that the equipment used, the working environment and process design, validation and control conditions are in compliance with the requirements referred to in Article 28(h).

Concerning the important topic of tissue and cell storage conditions, tissue establishments shall ensure that all procedures associated with the storage of tissues and cells are documented in the standard operating procedures and that the storage conditions comply with the requirements referred to in Article 28(h).<sup>228</sup> They shall ensure that all storage processes are carried out under controlled conditions. Member States shall ensure that tissue establishments have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason, stored tissues and cells shall be transferred to other tissue establishment or establishments accredited, designated, authorised or licensed in accordance with Article 6, without prejudice to Member States' legislation concerning the disposal of donated tissues or cells, according to the consent pertaining to them.

Always together with the above mentioned Tissue Directive other Directives are mentioned and should be considered, although they all apply only for application on humans.

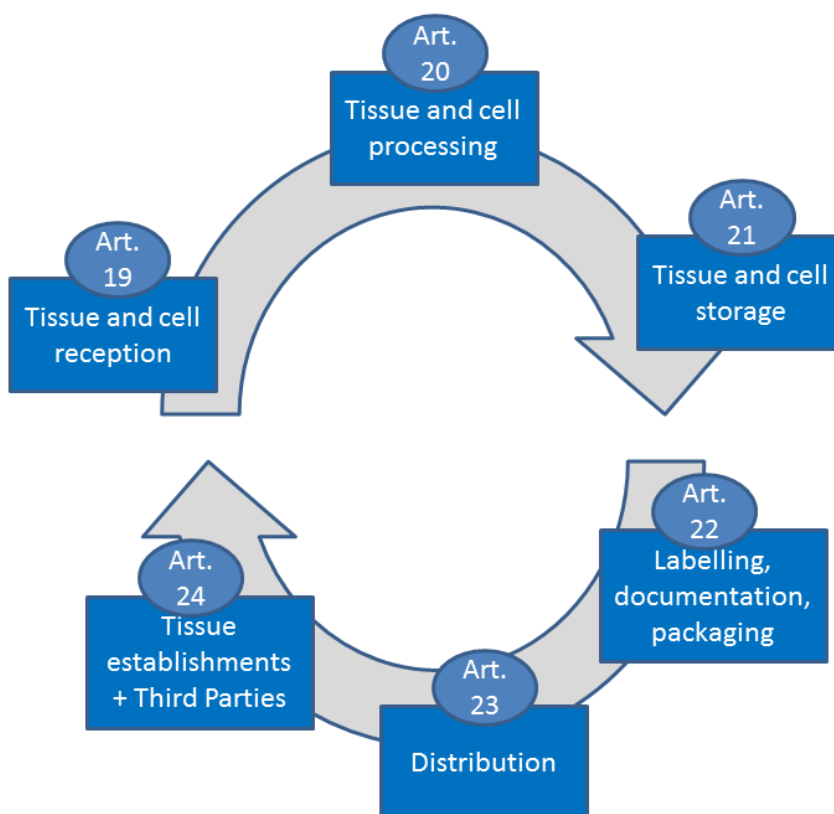


Figure 6: The different components of the biobank quality management in relation to the sample life cycle and the relevant articles of Directive 2004/23/EC

<sup>227</sup> Ibid, article 20.

<sup>228</sup> Ibid, article 21.

The Commission Directive 2006/17/EC<sup>229</sup> establishes specific technical requirements for each step in the human tissue and cell preparation process, in particular regarding the requirements for the procurement of human tissues and cells, the selection criteria for donors of tissues and cells, and laboratory tests required for donors, tissue and/or cell donation and procurement procedures and reception at the tissue establishment as well as requirements for direct distribution to the recipient of specific tissues and cells.

Commission Directive 2006/86/EC defines the technical standards and requirement as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, and products derived from human tissues and cells. The requirements for accreditation, designation, authorisation or licensing of tissue establishments are regulated in Annex I of the Commission Directive, which provides detailed prerequisites as to the organisation and management, the personnel, the equipment and materials, facilities as well as the documentation and records

The Directive 2002/98/EC<sup>230</sup> is concerned with the quality of blood cells. The purpose of this Directive is to set standards of quality and safety for blood and blood components throughout the entire blood transfusion chain. It applies to the collection and testing of human blood and blood components, irrespective of their final destination. It also applies to the processing, storage and distribution of human blood and blood components. In order to prevent the transmission of diseases by human tissues and cells for human applications and to ensure an equivalent level of quality and safety, Directive 2004/23/EC calls for the establishment of specific technical requirements for each one of the steps in the human tissue and cell application process. Important components that should be established are:

- Standard operating procedures (SOPs): written instructions describing the steps in a specific process
- Validation: establishing documented evidence that provides a high degree of assurance that a specific process, SOP, piece of equipment or environment will consistently produce a product meeting its predetermined specifications and quality attributes

#### 9.4 **Related laws**

Commission Directive 2005/62/EC (Standards relating to a quality system for blood establishments)<sup>231</sup>. This Directive lays down the specific technical requirements for a quality system for blood establishments. Member states must ensure that the quality system in place in all blood establishments and hospital blood banks complies with the Community standards and specifications set out in the Annex to the Directive.

---

<sup>229</sup> COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

<sup>230</sup> Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (2003).

<sup>231</sup> Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments [Official Journal L 256 of 1.10.2005].

Commission Directive 2005/61/EC (Traceability requirements and notification of serious adverse reactions and events)<sup>232</sup>. This Directive lays down the technical requirements to ensure traceability of blood and blood components from the donor to the recipient, and the procedures. Member States must ensure that the systems and procedures for traceability and notification of serious adverse reactions in place at national level and in all blood establishments and hospital blood banks comply with the Community standards and specifications set out in the Annex to the Directive.

Commission Directive 2004/33/EC (Certain technical requirements for blood and blood components)<sup>233</sup>. In application of Directive 2002/98/EC, this text provides more detailed information, criteria and requirements relating to donations and donors, storage, transport and distribution of blood and blood components and to the quality and safety of blood and blood components.

---

<sup>232</sup> Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events [Official Journal L 256 of 1.10.2005].

<sup>233</sup> Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components [Official Journal L 91 of 30.3.2004].



## 10 Biobank best practice guidelines and standards

In principle, biobanks are structured collections of biological samples stored for the purposes of present and future research. Therefore, the quality of the samples and the associated data plays an important role that is only partly covered by the EU Directives that focus only on usage with a therapeutic goal. Therefore, for the area of in-vitro research one has to consider existing guidelines for biobanking of cells and tissues. For biobank quality management, a number of Best Practices guidelines have been developed.<sup>234</sup> These guidelines and recommendations define general principles and Best Practices for establishing and organising biobanks and address all processes from sample processing to long-term storage. Nevertheless, progress in harmonisation of Best Practices on a detailed and technical level is still only emerging. In consequence, large collaborative research projects employing biobanking are still searching for common instruments to preserve, exchange and use biological samples and data and to guarantee and maintain high quality and traceability of tissues and data for research purposes. In research, most quality aspects have two aspects: the protection of the patient and the quality of the data. ESF has recognised this quality lag<sup>235</sup> and states that ethical, legal, practical and financial difficulties in sharing or exchanging material and/or information. The lack of standardized and quality-controlled protocols for data and sample management are missing. Here the use of Best Practice guideline can be helpful and represent a first step to harmonise and enable interoperability of sample sharing. Several guidelines are discussed according to their recommendations to establish quality.

### 10.1 *OECD: Best Practice Guidelines for Biological Resource Centers (2007)*<sup>236</sup>

This document provides a collection of guidelines for biological resource centers (BRC) based on the experience of expert groups of OECD members and the influence of scientific community. The Guidelines comprise of Best Practice Guidelines for all types of BRCs and guidelines for microorganism domain and human derived materials. They include organizational requirements, staff, premises, equipment, documentation, informatics, services, preparation and preservation of samples, quality audits and reviews. Biological resource centres<sup>237</sup> are an essential part of the infrastructure supporting life sciences and biotechnology. They are biobanks that collect annotated biological samples from various sources (human, animal, plant, bacteria...) and consist of service providers and repositories of cells, genomes of organism, and associated information<sup>238</sup>. Because research requires reproducibility, BRCs need to provide greater quality assurance than is currently ensured by most collections and databases. The guideline states, that users of BRCs must receive the same level of sample quality and service irrespective of the source of the materials or information requested.

---

<sup>234</sup> Zatloukal, K, Biobank quality management and harmonization: current guidelines, evidence-based standards. Presentation at Biobanking in Biomedical Research. Siena, June 2009.

<sup>235</sup> European Science Foundation (2008) Science policy briefing: population surveys and biobanking. <http://www.esf.org/>.

<sup>236</sup> Organization for Economic Co-operation and Development <http://www.oecd.org/dataoecd/7/13/38777417.pdf>.

<sup>237</sup> Biological resource centres (BRCs) are both service providers and repositories of the living cells, genomes of organism, and related information.

<sup>238</sup> OECD: Biological Resource Centres. Underpinning the future of life sciences and biotechnology. 2001.

Chapter 3 of the guideline<sup>239</sup> gives recommendations for the development and implementation of Best Practices for all kind of BRCs; especially issues of quality management and safety. The most important ones are:

- Building consensus on Best Practices
- Pilot studies on Best Practice Guidelines
- General structure of Best Practice Guidelines
- First-party assessment (self-audit)
- Second-party assessment
- Third-party assessment (certification)

The General Best Practice Guidelines for all BRCs<sup>240</sup> give more specific but still general recommendations for maintaining a biobank, including the aspects concerned with:

- Responsibilities of management
- Qualifications and training
- Safety
- Documentation management
- Data processing
- Accession
- Quality checks on biologic material
- Storage of preserved biological materials
- Supply
- Packaging
- Traceability
- Confidentiality
- Quality audit and quality review

## 10.2 **ISBER: Best Practices for Repositories (2008)**<sup>241</sup>

This guideline provides Best Practices of human specimen and environmental collections reflecting in some aspects national, regional and local regulations that are based on the experiences of ISBER members. The Best Practices contain quality control procedures and

---

<sup>239</sup> OECD Best Practice Guidelines for BRC (2007), p. 21.

<sup>240</sup> OECD Best Practice Guidelines for BRC (2007), p. 32-44.

<sup>241</sup> ISBER (International Society for Biological and Environmental Repositories): 2008 Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Human Biological Materials for Research (2007). 2<sup>nd</sup> edition. <http://www.isber.org/Pubs/BestPractices2008.pdf>.

considerations for specific types of biosamples. Many of the quality control processes are generic across all types of material and repositories and focus on<sup>242</sup>:

- Authenticity: ensuring a correctly assigned identity
- Purity: freedom from contamination
- Stability: capability of a sample to retain the initial value of a measured quantity for a defined period of time when stored under defined conditions

This Guideline comprises also of organizational issues, management of records, facilities, storage equipment and environments, quality assurance and quality control, safety, training, material tracking, packaging and shipping, specimen collection, processing and retrieval relating matters.

### 10.3 **NCI: Best Practices for Biospecimen Resources (2007)**<sup>243</sup>

This guideline outlines the Best Practices for biospecimen collected by the NCI<sup>244</sup> that is part of the National Institute of Health and Department of Health and Human Services in the US. It comprises of technical, operational, ethical, legal and policy Best Practices optimizing biospecimen for cancer research. Recently new updates of this guideline are available, the newest ones from 2010 and 2011.

### 10.4 **2011 Revised NCI Best Practices**<sup>245</sup>

This recent version considers input received during a public comment period. Major revisions in this new text include the addition of new sections on biospecimen resource management and operations and conflicts of interest (COI). Expansion of recommendations relate to custodianship and informed consent (based on the consensus of the 2007 NCI- Workshop on Custodianship and Ownership Issues in Biospecimen Research).

### 10.5 **P3G Observatory**<sup>246</sup>

The P3G Observatory is an internet repository of information, scientific tools and catalogues for the development and harmonization of research projects worldwide. It comprises of various catalogues of information concerning population-based biobanks, harmonization tools, technical and scientific information on different areas of repositories; including a comparison chart of guidelines for sample collection and processing.

P3G provides a repository of Guidelines<sup>247</sup> consisting of several documents. One is the Comparison Chart of Guidelines. This document compares selected referenced Guidelines that cover all biobanking steps, i.e. sample collection, labelling, processing, and storage applied to a wide range of sample types. A P3G-prepared document (2008).

---

<sup>242</sup> ISBER (International Society for Biological and Environmental Repositories): 2012 Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Human Biological Materials for Research (2011).

<sup>243</sup> NCI (National Cancer Institute): Best Practices for Biospecimen Resources (2007). [http://biospecimens.cancer.gov/global/pdfs/NCI\\_Best\\_Practices\\_060507.pdf](http://biospecimens.cancer.gov/global/pdfs/NCI_Best_Practices_060507.pdf).

<sup>244</sup> National Cancer Institute (USA).

<sup>245</sup> National Cancer Institute Best Practices for Biospecimen Resources, NCI 2011.

<sup>246</sup> Population Project in Genomics: <http://www.p3gobservatory.org/repository/guidelines.htm>.

<sup>247</sup> <http://www.p3gobservatory.org/repository/ethics.htm>.

## 10.6 ***Human tissue repositories: Best Practices for a Biospecimen Resource for the Genomic and Proteomic Era***

This document written by RAND Science and Technology organisation is a blueprint for a high-quality biospecimen network of biobanks<sup>248</sup>. RAND Corporation (Research AND Development) is a non-profit global research organization that assists in improving policy and decision making by providing research and analysis. It provided case studies of twelve existing human tissue repositories to evaluate their utility for genomics- and proteomics-based cancer research. The guideline identifies "Best Practices" necessary for establishing a national tissue resource and databank to optimize and accelerate genomics- and proteomics-based research<sup>249</sup>.

## 10.7 ***Australian Biospecimen Network Biorepository Protocols***

This document aims to provide information for new biorepositories or biorepositories that need to develop new protocols and to add Best Practice principles in tissue banking. Prepared by the Australian Biospecimen Network (2007).

## 10.8 ***International Network of Biological Resource Centres (IARC)***

This document focuses on the development of recommendations towards common minimal technical standards in order to stimulate the creation, development and networking of Biological Resource Centres (BRCs) at an international level. Prepared by the International Agency for Research on Cancer (IARC) (2007).

## 10.9 ***Biobanking Guidelines and Regulations in BBMRI***

The global integration of BBMRI is supported by the implementation of the OECD GBRCN Concept in Europe. In 2001 OECD introduced a new concept of repositories and providers of high quality biological materials, the so-called Biological Resource Centres (BRCs). OECD experts called upon national governments to undertake a number of actions to bring the BRC concept into being in concert with the international scientific community. The Best Practices Guidelines for all BRCs<sup>250</sup> are subdivided in different areas, for example Guidelines on biosecurity, Guidelines for the micro-organism domain, Guidelines on human-derived material. The Guidelines on Human-Derived Material lists a number of organizational requirements (e.g. staff-qualifications and training, equipment, documentation, preparation of samples, preservation), research topics (e.g. ethical and legal clearance, quality control, IT-Infrastructure (diff. structured data, confidentiality), sample preservation (new fixatives, cryobiology) and requirements for an interdisciplinary research infrastructure (e.g. integration of different sample types and medical data, harmonization/standardization, data protection) (Figure 9).

---

<sup>248</sup> Case Studies of Existing Human Tissue Repositories: "Best Practices" for a Biospecimen Resource for the Genomic and Proteomic Era. Published date (2003).

<sup>249</sup> Ibid, addressed are: biospecimen collection, processing, annotation, storage, distribution; bioinformatics; consumer and user needs; business plans and operations; privacy, ethical concerns, and consent issues; intellectual property rights and legal issues; public relations, marketing, and education.

<sup>250</sup> OECD Best Practice Guidelines for Biological Resource Centers.

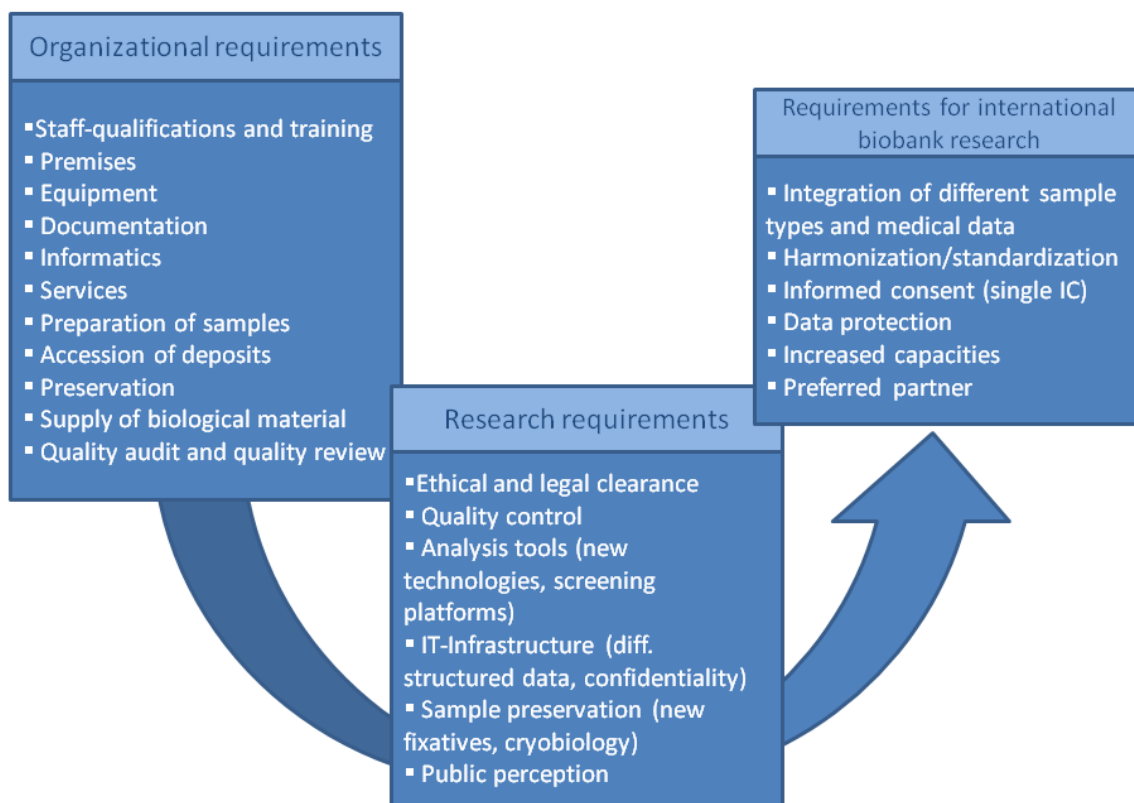


Figure 7: Best Practices and requirements for biobanking of human-derived material<sup>251</sup>

<sup>251</sup> Zatloukal, K, Biobanking in Biomedical Research Part 4 - Biobank quality management and harmonization: current guidelines, evidence-based standards; Presentation in Siena, Italy, June 2009.

## 11 Growth of biobanks and the issue of harmonisation

Whereas biobanking concerned with providing cells and tissues for the clinical treatment is regulated by EU directives and national laws, research with biosamples is not regulated in this way. For research guidelines offer a method to establish a common quality and safety level. Later it will be discussed how p-medicine can participate lifting the quality of biobanking.

Medical research to improve health care faces a major problem in the relatively limited availability of adequately annotated and quality-collected biospecimen<sup>252</sup>. This limitation may create a gap between the pace of scientific discoveries and successful exploitation of this knowledge. Several projects have been designed to address the problem of the lack of harmonisation in biobanking, such as: PHOEBE<sup>253</sup> Promoting Harmonization of Epidemiological Biobanks in Europe, P3G and BBMRI. BBMRI is focused on the design and management of biobanks, standard protocols for sample handling, cataloguing and comparing information, and coordinated bioinformatics. In addition, the bioinformatics challenges comprises of the lack of associated phenotype and study data with samples, and the accessibility of biobank information to clinicians and researchers. Because biobanks have become very large, increasing amounts of data, including genotypic, proteomic, clinical, and demographic information, have to be associated with the samples. In this way, for many biobanks the implementation of a Biobank Information Management Systems to trace samples and their metadata has become unavoidable.

The implementation and use of a quality system by UK Biobank can serve as a standard for harmonisation efforts. UK Biobank is a large, prospective UK study to investigate the role of genetic factors, environmental exposures and lifestyle for the development of major diseases, recruiting about 500000 study participants. UK Biobank has developed a number of protocols. The sample handling and storage protocol describes methods for the collection and storage of samples in a way to give maximum scientific return<sup>254</sup>, including processing or storage methods that are supposed to avoid the exclusion of assays and tests (Figure 8). The data and samples are linked to the participant's medical records to allow longitudinal follow-up of disease incidence and mortality. For UK Biobank, the scientific need for high-quality data was the overriding consideration to develop these protocols. Because of higher costs, it was decided that samples should undergo minimal local processing in the assessment centres before being shipped to a central high-throughput facility as soon as possible.

Summary of quality related principles implemented in the UK Biobank sample handling and storage protocol<sup>255</sup>:

- **Quality control and assurance**
  - Protocols with rigorous quality assurance and control procedures<sup>256</sup>
  - Standardization of processing methodology (high-throughput, high-quality, data trail)

---

<sup>252</sup> Watson PH, Wilson-McManus JE, Barnes RO, Giesz SC, Png A, Hegele RG, Brinkman JN, Mackenzie IR, Huntsman DG, Junker A, Gilks B, Skarsgard E, Burgess M, Aparicio S, McManus BM.: Evolutionary concepts in biobanking - the BC BioLibrary. *J Transl Med.* 2009 Nov 12;7:95.

<sup>253</sup> Promoting Harmonisation of Epidemiological Biobanks in Europe (FP6-2004-LIFESCIHEALTH-5).

<sup>254</sup> Paul Elliott, Tim C Peakman: The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *International Journal of Epidemiology* Volume 37, Issue 2, pp. 234-244.

<sup>255</sup> Ibid, p.236.

<sup>256</sup> Ibid, p.236: Develop and thoroughly test protocols with rigorous quality assurance and control procedures built-in.

• **Sample security**

- Sample fraction storage in ultra-low temperatures to ensure long-term stability
- Sample fractions are stored in two geographically separated archives (long-term integrity)
- Protection of samples from freeze-thaw degradation by storing multiple aliquots
- Selection of the preservatives and additives
- Maintenance of a detailed and secure data audit trail (Laboratory Information Management System and inventory systems)

It is exemplary that a principle of UK Biobank is the use of standardized procedures such that each sample is collected, transported, processed and stored in the same way with strict quality assurance and quality control for the prevention and detection of errors<sup>257</sup>. Sample security is focused on conserving sample integrity. Thus, design and testing of the sample handling protocol considers key factors that affect the stability of biological samples, including: anti-coagulants, stabilizing agents, temperature, elapsed time from collection to initial processing and endogenous degrading properties (enzymes, cell death).<sup>258</sup> All these factors may serve as quality indicators for biosamples and are of potential interest for a research to evaluate the quality of a sample for research.

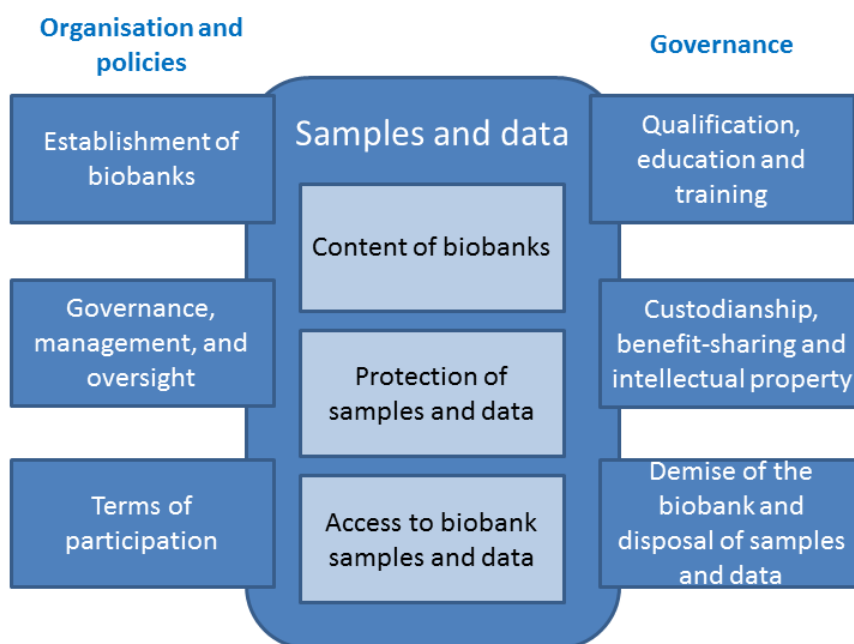


Figure 8: Implementation of Best Practice principles at UK Biobank. Groups of policies, governance, and management issues

<sup>257</sup> Ibid, p. 236.

<sup>258</sup> Ibid, p. 240.

A review of the different guidelines mentioned showed that guidelines for human biobanks list certain common overarching principles that are important for all biobanks<sup>259</sup>.

Following principles and objectives deal with the governance of biobanks:

- Provision of resources for research, conducted within applicable laws, regulations and ethical frameworks
- Ensuring that collection, storage, transfer, access, use and disposal of samples and data are scientifically, legally and ethically appropriate
- Securing the sustainability of the biobank, the protection of participants privacy and confidentiality of their data and, public trust
- Operating the biobank with integrity, transparency, accountability and respect for human rights and freedoms
- Engagement of independent members in decisions about its establishment, governance and use
- The biobank should be independently monitored for compliance with applicable domestic law, guidelines and international instruments
- The financial feasibility of the biobank should be assessed, the scientific need demonstrated, and the financial resources secured prior to establishment. A statement what happens with material, if the biobank has no further money to continue to work has to be provided (analogous to the ones in document archives)
- The biobank custodian should ensure data and materials are shared with others in the research community
- The governance structure (management and oversight roles and responsibilities) should be clearly formulated
- The governance structure of the biobank should ensure the rights and well-being of the participants and the common good should prevail over research interests
- The governance structure of the biobank should be subject to independent ethical review, approval and monitoring
- It is the responsibility of all biobank personnel, researchers and partners to ensure that activities are carried out in accordance with prevailing norms and ethical principles

The British Columbia BioLibrary (Canada) aims to maximize the accrual of high-quality, annotated biospecimens into biobanks<sup>260</sup>. It is suggested that such a framework connecting different biobanks leads to enhanced biospecimen accrual and high quality, reduced competition between biobanks, and a transparent process for donors that in general will enhance public trust in biobanking. The quality management of the framework consists of several components (Figure 9):

- Maintaining high-quality samples / donor clinical information
  - Facility design and safety
  - Samples collection and processing

---

<sup>259</sup> See above.

<sup>260</sup> British Columbia BioLibrary: <http://www.bcbiolibrary.ca/>.



- Samples storage and retrieval
- Data systems and record management
- Quality management and process improvement
  - Standard operating instructions
  - Biobanks quality systems / QA for biobanks
  - Good Biobanking Practices
- Preserving the integrity of samples
- Internal analysis standards
  - Stable storage
  - Clinical annotation of samples
  - Clinical phenotyping
  - Clinical sample collection
- Use of biobanks for research, genomic and proteomic studies
- Biobanks and governance
  - Biobank constitution
  - Research ethics committee
  - Re-use of data: concordance, result feedback, level of confidentiality
  - Informed consent model
- Harmonisation and standards
  - Quality standards in biobanking
  - Authentication
  - Sample genotyping
- Ethical and societal considerations for harmonisation
- Sustainability
- Certification of biobanks
- Certificate - Principles of Biobanking

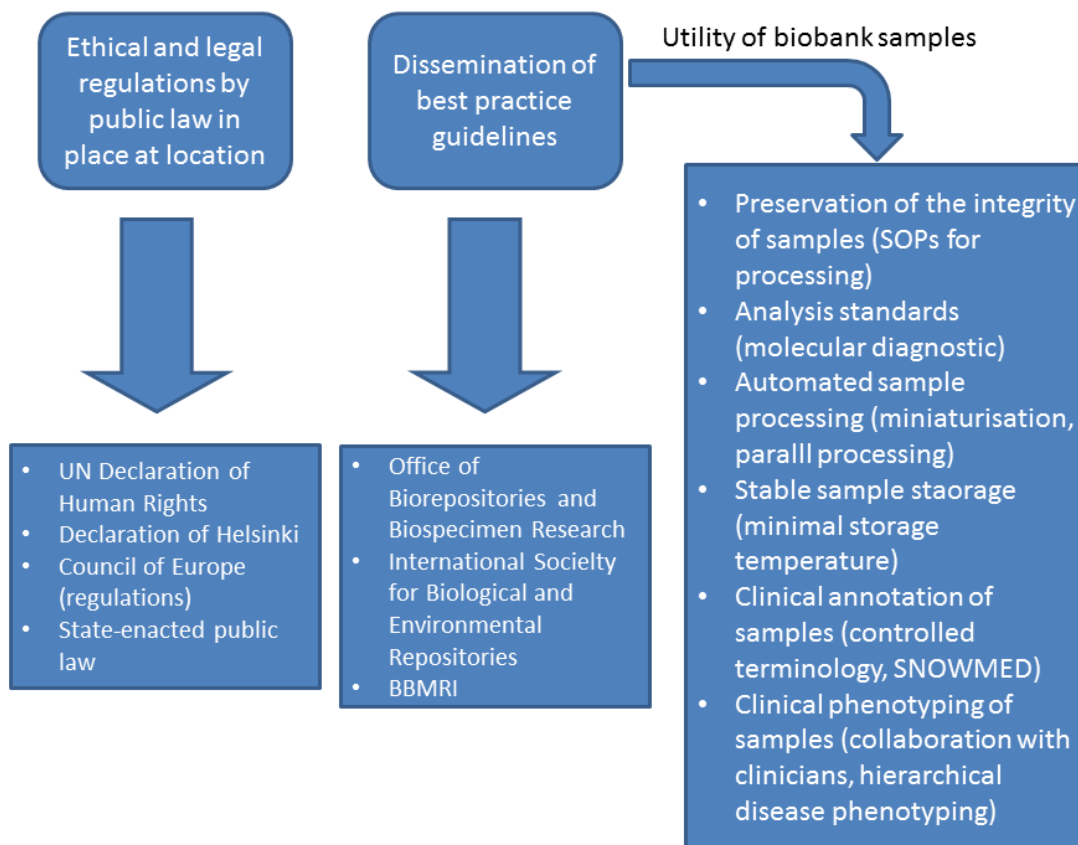


Figure 9: Components of a better quality management of biobank samples (according to BioLibrary and other biobank policies). This chapter concentrates less on the ethical and legal regulations, but on the best practice guidelines (therefore the UN Declaration and the Declaration of Helsinki are not discussed).

## 12 Safety standards in biobanking

### 12.1 Safety in the Tissue Directive

What does the Directive 2004/23/EC say about safety? For the directive the focus is on guaranteeing public health. It is of primary importance that quality and safety of cells and tissues should be ensured, particularly in order to prevent the transmission of diseases.<sup>261</sup> In order to safeguard public health and to prevent the transmission of infectious diseases by these tissues and cells, all safety measures need to be taken during their donation, procurement, testing, processing, preservation, storage, distribution and use. Because the Directive extends the safety target, it is essential, that community provisions ensure that human tissues and cells, whatever their intended use, are of comparable quality and safety.<sup>262</sup> These safety requirements apply to human application of cells and tissues. Because the Directive does not cover research using human tissues and cells, only those cells and tissues that are applied to humans, for example in the course of a clinical trial, should comply with these quality and safety standards.<sup>263</sup>

In clinical trials the term safety relate to the capture and reporting of adverse events. According to GCP, an adverse event (AE) can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.<sup>264</sup> In clinical trials the investigator should promptly report to the ethics committee all adverse drug reactions (ADRs) that are both serious and unexpected and all new information that may affect adversely the safety of the subjects or the conduct of the trial<sup>265</sup>. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting<sup>266</sup>. SAEs are any medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity<sup>267</sup>.

Consequently, for clinical trials with cells / tissues applied in humans, the Directive demands the notification of serious adverse events and reactions. Member States shall ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or after clinical application which may be linked to the quality and safety of tissues and cells.<sup>268</sup> In addition, all persons or establishments using human tissues and cells regulated by this Directive shall report any relevant information to establishments engaged in the donation, procurement, testing, processing, storage and distribution of human.<sup>269</sup>

---

<sup>261</sup> Directive 2004/23/EC, op.cit. (1) and (2).

<sup>262</sup> Directive 2004/23/EC, op.cit. (4).

<sup>263</sup> Directive 2004/23/EC, op.cit. (11.)

<sup>264</sup> EMA: ICH Topic E 6 (R1) Guideline for Good Clinical Practice. CPMP/ICH/135/95, 2002.

<sup>265</sup> Ibid, ICH Topic E 6 (3.3.8).

<sup>266</sup> Ibid, ICH Topic E 6 (4.11.1).

<sup>267</sup> Ibid, ICH Topic E 6, article 11, 1.

<sup>268</sup> Directive 2004/23/EC, op.cit. (4).

<sup>269</sup> ICH Topic E 6, op.cit. article 11, 2.

## 12.2 ***Safety in biobanking guidelines***

For most guidelines safety means the protection of human biological materials and data and the protection of people operating in a biobank. For example, it is stated that a biobank should be established, managed, governed, and operated in such a way as to prevent inappropriate or unauthorised access to or use of participants' human biological materials and personal data and/or information.<sup>270</sup> For ISBER safety is concerned with issues related to the safe operation of a repository and with the particular activities of the repository. Regulations governing safety may be covered by national, regional or local statutes.<sup>271</sup> It distinguishes among others between biological safety, chemical safety, electrical safety, fire safety and physical safety.<sup>272</sup> In summary, the recommendations of most biobank guidelines concerning safety are of importance to biobank owners and play little role for the p-medicine research projects.

---

<sup>270</sup> OECD: OECD Guidelines on Human Biobanks and Genetic Research Databases. 2009.

<sup>271</sup> ISBER: 2012 Best Practices for Repositories Collection, Storage, Retrieval, and Distribution of Biological Materials for Research.

<sup>272</sup> Ibid. E6.000.

## 13 Quality aspects assigned to the metabiobank framework of p-medicine

The p-medicine biobank access framework will provide access to different kind of human biomaterials and associated data for research purposes. For this purpose the data are harmonised according to a standard biobank data set. The main component of the framework is p-BioSPRE, the Biomaterial Search and Project Request Engine, which is a metabiobank to enable the sharing of biomaterial between researchers and biobanks. Additionally Biobank Wrappers comprise the local component, allowing biobank owners to offer their biomaterial. Because p-BioSPRE is not a biobank but a reference and search system, that is a metabiobank which provides researchers with a possibility to search for and request biomaterial under the usage conditions stated in the p-medicine security framework. All biomaterial data that is provided in p-BioSPRE is anonymized.

The four formal use cases for biobank access in p-medicine were used to assign quality requirements derived from in guidelines and regulations (Table 1). The table does not list processes or tasks conducted in p-medicine to increase biobanking quality. It suggests, factors that p-medicine could consider for the biobank access framework to support the harmonisation of biosample quality aspects for research. In these use cases following stakeholders are involved: biobank operators holding the human tissue and associated data, researchers searching for human biological samples and associated data for their research project, the metabiobank operator who gathers data on the availability of human samples stored in the different biobanks. He makes these data available to researchers. Three different formal agreements regulate interactions between these three stakeholders.

Use case	Processes	Suggestions for supporting the harmonisation of quality aspects
<b>Integration of biomaterial data repositories</b>	User wants to link his own biomaterial data repository to the p-medicine biobank access framework in order to share biomaterial	Quality of samples and data and standards are supported by the contacted biobank.  Ideally, the user's data repository was created compliant with Good Practice guidelines; a quality assurance system is available (e.g. SOPs).  Precondition: the quality of biomaterial data repository is known (metadata).
<b>Managing biomaterial data in ObTiMA</b>	User collects biomaterial in a clinical trial, conducted with ObTiMA and wants to manage biomaterial and related data with ObTiMA (link the biomaterial data directly to the clinical data of the patients)	Quality of samples and data in a clinical trial and supported standards.  In general, biosampling in clinical trials is subject to requirements stated in the trial protocol and in trial SOPs guaranteeing a similar

		high degree of quality and similarity for all participating sites. Clinical trials audits and monitoring are conducted to control quality. A high degree of data quality is one of the aims of GCP.
<b>Offering human biomaterial to a closed and/or open clinical research community for research</b>	User within a research community wants to offer biomaterial for research. The search engine includes an indicator whether and how much material is available for research	Availability of indicators that indicate the quality of samples and data.  Ideally, the biomaterial repository and the associated data were created compliant with Good Practice guidelines; a quality assurance system is available (e.g. SOPs, validated protocols).  Precondition: sample collection and sample handling are according to Best Practices. Data quality is confirmed.
<b>Requesting specific human biomaterial within a closed and/or open clinical research community</b>	User within a research community needs specific biomaterial for research. After selection of required biomaterial, the user provides details about the planned research with the material. His request will then be forwarded by the system to the corresponding biomaterial owners. Biomaterial owners will get in contact with the “customer” and agree on the details for the material provision	Availability of indicators that indicate the quality of samples and data.  Ideally, biomaterial owners / providers offer biosamples created compliant with Good Practice guidelines and a quality assurance system is available (e.g. SOPs, validated protocols). Precondition: sample collection and sample handling are according to Best Practices.

*Table 2: Formal use cases for biobank access in p-medicine and their quality aspects*

Ideally, information about the quality that is about the authenticity, purity and stability of samples should be provided by the database owner to be included in the p-medicine biobank access system. Table1 shows that in three use cases the exchange of information about compliance with Good Practice guidelines, the existence of a quality assurance system, the use of SOPs (validated protocols) would profit the biobank querying process giving the researcher some information about the quality of biosampling. Knowledge about storage and, processing requirements, length of storage and application are necessary when assessing the biobank’s safety and security requirements<sup>273</sup>. For biosampling in clinical trials, it may be the case that there is some conflict of interest (COI) in terms of access to samples and some samples may not be eligible for biobanking due to other usages in a pharmaceutical

<sup>273</sup> ISBER 2008 Best Practices for Repositories.

company acting as trial sponsor. As outlined by ISBER Best Practices<sup>274</sup>, it is essential that systems are in place to track all events in relation to a sample and to confirm that samples are handled correctly at all times.

Requirements exist for the sample data management<sup>275</sup>:

Best practices for data coding, classification, storage and protection should be followed

1. All relevant data associated with samples should be collected
2. Uniform vocabulary and CDEs
3. Data should be coded, and a secure link to the patient should be maintained
4. The data management system must be able to track all aspects of data/sample collection, processing, and distribution
5. Roles and their permissions must be defined
6. Procedures regarding patient follow-up must be defined
7. Data collection, including collection of follow-up data, should be co-ordinated between centres
8. A minimum clinical dataset should be defined

Sample collection, handling and storage procedures should adhere to ISBER 2008 Best Practices for Repositories. These would include the following:

1. Pilot studies/feasibility studies should be carried out to identify any problems associated with the collection and processing of different sample types
2. Appropriate inventory systems and SOPs for sample inventory and tracking

Recommendations for safety, security and back-up as outlined in ISBER guidelines include following requirements:

1. Security systems should be in place and monitored 24 hours a day
2. Access systems should prevent unauthorised entry
3. A back-up power supply is required.
4. Back-up system for data / sample storage is required.
5. An appropriate safety programme should be developed; a safety officer should be designated, and a training procedure should be implemented

It should be considered that although the information attached to a biosample is of highest importance for the use of samples for research, the complete information available about a sample may be critical to evaluate:

1. inconsistency of information between different biobanks (important for exchange)
2. undocumented differences in quality of data and samples that were collected
3. differences in the estimation of the potential of the information to be suitable to investigate a specific research question

For example, information may need to have been collected according to a specific SOP to be used to perform some specific analysis (e.g. DNA sequence analysis).

---

<sup>274</sup> Ibid, 23–30.

<sup>275</sup> National Cancer Institute Best Practices for Biospecimen Resources: 7.6.

## 14 Discussion

Biobanking services must improve rapidly to serve the needs of personalized medicine and biospecimen research should be encouraged and supported at all levels from project funding to publication of results. Biobanks need to be run to high professional standards and the importance of adequate funding; training and certification must be emphasized.

The importance of standardizing processes for processing and storing biological samples is becoming increasingly obvious<sup>276</sup>. The use of standards and quality control across the field are imperative for the use of biobanks in research. Especially, in cancer research, there is an increased focus on documenting and improving the quality of biospecimen prior to the downstream analysis. It is important to know how the samples were collected, processed, and stored. It is also important to document that biospecimen are managed in the same way. Specimen collection and storage conditions performed by different laboratories create variations in specimen quality. These differences in specimen quality, even the minor ones, have consequence and can be detected. They may have effects on test results when the samples are used for research. An important challenge is to ship and prepare samples in controlled environments within short time periods. Another challenge is the storage of biological samples under low-temperature conditions and avoidance of unnecessary thawing.

Several challenges play the most important role. First, managing the increasing number of biospecimen generated during clinical discovery, clinical trials, and in patient registries is becoming more and more complex. Second, the costs to collect and maintain these collections are continually growing. In addition, biobanks are under pressure to meet heightened regulatory and privacy compliance. With personalized medicine starting to take a research approach, integrating discovery and development has become important and requiring a link between samples, treatments, case histories, and outcome results. To address some of these uncertainties, the Institute for Prospective Technological Studies (IPTS) of the European Commission's Joint Research Centre, in collaboration with the European Science and Technology Observatory (ESTO), launched an examination of the situation of biobanking in Europe<sup>277</sup>. The results show that access to biobanks is, in most cases, either entirely free or restricted to a part of the repository. Fees for granting access to samples were found in about a third of the cases. Collaborations based on the use of biobank samples are prominent. Eighty-five per cent of the survey respondents reported at least two collaborations with other researchers and 45% reported more than 10. Moreover, 52% of the biobanks surveyed are involved in international collaborations<sup>278</sup>. Significant variability was detected in privacy and data protection requirements among biobanks in Europe. The majority of biobanks have at least one type of consent form that allows tissue (63.5%) and data (69%) sharing. Yet, a significant proportion of them utilise more than one type of consent depending on the type of sample. The use of samples defined in the consent form is also highly varied, ranging from research on specific diseases to blanket (e.g. in UK biobanks). Altogether thirteen biobanks indicated that they do not apply consent at all (mainly from Eastern European Countries)<sup>279</sup>.

---

<sup>276</sup> Elizabeth Lipp: Biobanking Needs More Standardized Procedures. Personalized Medicine Brings Unique Requirements for Managing Specimens. GenEngNews Jan 15, 2008 (Vol. 28, No. 2).

<sup>277</sup> Ieni Zika, Daniele Paci, Tobias Schulte in den Bäumen, Anette Braun, Sylvie Rijkers-Defrasne, Mylène Deschânes, Isabel Fortier, Jens Laage-Hellman, Christian A. Scerri, Dolores Ibarreta: Biobanks in Europe: Prospects for Harmonisation and Networking. European Commission Joint Research Centre, JRC EUR 24361 EN, 2010.

<sup>278</sup> See above.

<sup>279</sup> See above.



The FP7 BioSHaRE-EU<sup>280</sup> (Biobank Standardisation and Harmonisation for Research Excellence in the European Union) project goes on from 2011-2016. The mission of BioSHaRE is to develop harmonized measures and standardized computing infrastructures. Sixteen research institutes from Europe and Canada participate in the project which works on the coordination and sharing of data and biological samples from different biobanks for the purpose of studying the causes of disease, especially the causal architecture of common chronic diseases. Biobank base analysis will only be possible if we are able to harmonise and standardise the collection, storage and management of data and bio-samples across biobanking studies. Biobanking in Europe has made major steps towards harmonization and shared standards for the collection and processing of data and samples stored in biobanks<sup>281</sup>. The access and the exchange of biomaterial are regulated by policies and rules and the existence of an adverse events reporting system that consider patient safety. What is missing is a harmonisation on a more technical level. For international research it must be guaranteed that all samples have a similar level of quality. Examinations of samples that were treated differently suggest that these samples may result in different research results. Small aliquots of samples, deep-freezing and only one-time thawing, the use of always the same small number of preservatives and other additives may create a good basis for the comparability of samples and the research results that are based on them. This approach may reduce the necessary harmonisation efforts focused on different and varied practices and protocols and may serve as an example how to support sample harmonisation for p-medicine.

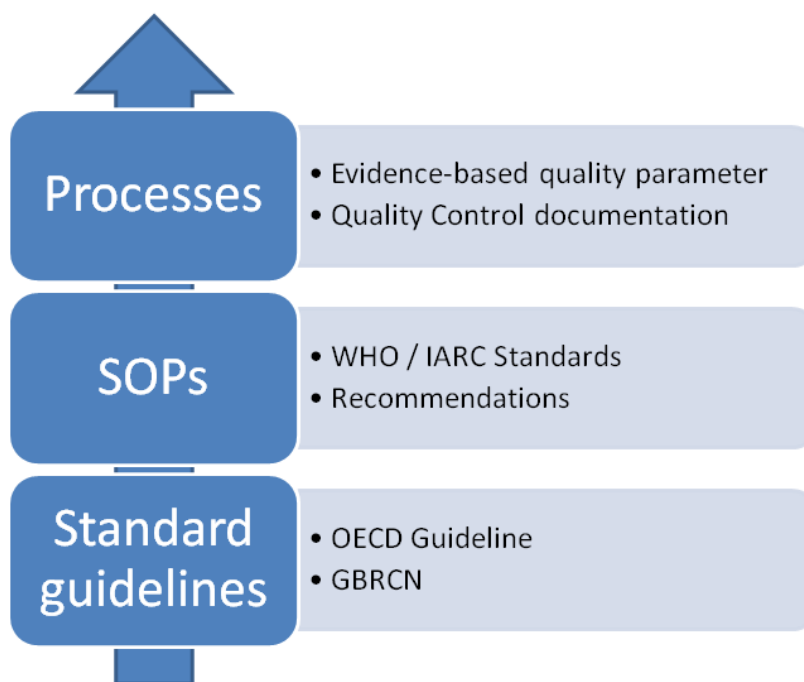
BBMRI uses a different approach trying to achieve a global integration of biobanks resources by implementation of the OECD GBRCN concept in Europe<sup>282</sup>. This includes the adoption of all Best Practices (Guidelines for all BRCs, biosecurity for BRCs, micro-organism domain, and human-derived material) (Figure 10). The strength of using OECD Guidelines lies in their global scope that may foster harmonization efforts. Their weakness lies in the complex consensus finding process and that they constitute only a minimal compromise. The aim is to move the biobank from a sole storage facility to an interdisciplinary research infrastructure. This requires the integration of different sample types and their corresponding data, the consequent use of harmonization / standardization, and the employment of an harmonized informed consent procedure, e.g. with only one informed consent for an whole university. Because the development of biobanks for research in personalized medicine requires large biosamples collections, issues of harmonisation and a consistent quality in internationally distributed locations plays an important basis. For Personalized medicine a harmonisation on the SOP level should be aimed for (Figure 10).

---

<sup>280</sup> <http://www.bioshare.eu/>.

<sup>281</sup> Schulte in den Bäumen T., Paci D., Ibarreta D.: Data Protection and Sample Management in Biobanking – A legal dichotomy. *Genomics, Society and Policy*, 2010, Vol.6, No.1 pp.33-46.

<sup>282</sup> Kurt Zatloukal: Biobanking in Biomedical Research Part 4. Biobank quality management and harmonization: current guidelines, evidence-based standards. Presentation in Siena, Italy, June 2009.



*Figure 10: The 3-step standardisation and interoperability approach of BBMRI (IARC: International Agency for Research on Cancer)*

The quality problem for biobanks is based on the fact that most biomolecules are unstable. It is the opinion of BBMRI that no common quality standard will be feasible for all biomolecules and for all biobanks. To enable a high quality of biosamples and support standardization and Interoperability, and at the same time limit the transport of samples, BBMRI plans to develop “Expert Centres” that support standardisation of processes and data, enabling data sharing and effective resource management<sup>283</sup>. These Expert Centres will use the latest technologies for biobanking, implement a common quality management, use common standards and will be certified. They guarantee a high quality of sample processing avoiding any transnational sample shipments. Nonetheless, still in the planning the “Expert Centres” cannot be a solution for p-medicine. p-medicine has to achieve harmonisation of sample management and support of high-quality practices for its associated biobanks in another way (see below).

<sup>283</sup> K. Zatloukal: Transborder flows of samples and accompanying data. Presentation Council Europe, 04.07.2012.

## 15 Suggestions to improve quality in p-medicine biobanking

p-medicine employs a metabiobank, but will develop no own biobanks. Associated biobanks can be searched using BioSPRE. Because most regulations and guidelines apply to the development and maintenance of a biobank, they to a large degree do not apply to the p-medicine platform. Nonetheless, because the biobank access framework of p-medicine will connect researchers and biobanks, p-medicine can play a role in promoting the harmonisation of biobanking quality standards that are presented in the guidelines. Novel therapies especially in the area of personalised medicine require access to well-structured collections of large numbers of biospecimen, with sufficient metadata describing clinical status and measurements of clinical phenotypes that characterize these samples. Thus, the availability of a high quality of samples, data and metadata in biobanks is an important concern for p-medicine. Thus, based on the analysis in this deliverable, we suggest that associated member biobanks of p-medicine should use best practices for biobanking to ensure the preservation of sample integrity even for long time periods. Especially for DNA sequencing, intact nucleic acids from high-quality human tissue samples are essential and may even influence the accuracy of clinical diagnosis. Thus, p-medicine should require from associated projects to use validated biobanking protocols to acquire and process suitable samples for sequencing.

All associated biobanks offering cells and tissues for human clinical use should comply with Directive 2004/23/EC (and Directive 2002/98/EC for blood samples) for the quality and safety of the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. This Directive applies to a broad range of so-called “tissues establishments”, including collections and laboratory processing facilities that might be involved in p-medicine projects. Compliance with this Directive means that certain requirements must be met for the accreditation, designation, authorisation or licensing of associated biobanks and laboratories. Requirements for the procurement of human tissues and cells, a quality system, including training, laboratory tests required for donors, cell and/or tissue procurement procedures and reception at the tissue establishment and requirements for the tissue and cell preparation process exist. Not all biobanks associated with p-medicine will have all requirements in place, or will use SOPs or validated protocols. Nonetheless, information about the quality system at a biobank should be included in the p-medicine metabiobank to enable researchers to evaluate the quality and suitability of samples. About the evaluation of biobank quality systems, the Directive is very general in requiring that biobanks and laboratories must have in place standard operating procedures, guidelines, training and reference manuals, reporting forms, donor records and information on the final destination of tissues or cells.

Biobank Best Practices Guidelines and Standards that apply to all kind of research done with tissues and cells are more specific. p-medicine should encourage the use of harmonised Guidelines and Standards to ensure that all samples although collected at different places have the same quality. For example, the OECD: Best Practice Guidelines for Biological Resource Centers (2007) gives recommendations for maintaining a biobank, including the aspects responsibilities of management, qualifications and training, safety, documentation management, data processing, quality checks on biologic material, traceability and confidentiality. Data processing and confidentiality requirements are met already by the p-medicine privacy framework. Whereas BBMRI focus on the development of Biobanking Centres of Excellence to further harmonisation of sample processing, p-medicine could evaluate the employment of Good Practices in associated biobanks and input information about the quality standard in biobanks in p-medicine’s biobank access framework. p-

medicine may collaborate with BioSHaRE (Biobank Standardisation and Harmonisation for Research Excellence in the European Union)<sup>284</sup> to develop harmonized measures and standardized computing infrastructures to ease the coordination and sharing of data and biological samples from different biobanks. For international research it must be guaranteed that all samples have a similar level of quality.

Based on the analysis of the p-medicine use cases we suggest the inclusion of metadata about quality and clinical status. An annotation describing clinical status and metadata of measurements of clinical phenotype that characterizes the sample has been suggested earlier<sup>285</sup>. But we would like to extend this amendment, by suggesting to include information about, for example freezing temperature, aliquot size, error prevention, and existence of SOPs. The idea is that it would be useful for the researcher who searches the p-medicine metabiobank for a suitable sample to receive these data in addition to the other results (names of biobanks who provide a specific sample). In this way, the research may receive some information about the suitability of the sample for DNA sequencing or other techniques. This approach requires the agreement of associated biobanks to provide these data. For many biobanks this seems not to be a problem. The SIOP Nephroblastoma biobank in Würzburg that is a member of the p-medicine clinical use case has own SOP available and is subject to review by an external advisory board.<sup>286</sup>

A growing need for standardisation of sample processing has been identified in this paper. The question is how the importance of standardizing processes for processing and storing of biological samples can be supported by p-medicine. In summary, p-medicine should encourage the use of standards and normalization across all biobanks and laboratories involved in it's projects. Metadata about how the samples were collected, processed, and stored should be provided in the metabiobank. It is important to document how biospecimen are managed, for example freezing temperature, sample size, thawing, etc. and this information may benefit the researcher.

---

<sup>284</sup> <http://www.bioshare.eu/>.

<sup>285</sup> Marko-Varga G, Végvári A, Welinder C, Lindberg H, et.al.: Standardization and Utilization of Biobank Resources in Clinical Protein Science with Examples of Emerging Applications. *J. Proteome Res.* 2012, 11, pp. 5124–5134.

<sup>286</sup> Information provided by N. Graf.

## 16 Conclusion

Research on biomaterial and related data is seen as one of the keys to enable personalized medicine. Although the demand for access to biobanks is increasing, there are, as we have noted, many factors that pose obstacles to the exchange of resources stored in biobanks: reaching from the heterogeneity in the applicable legal frameworks to the access policies of biobanks and the lack of harmonisation and standardisation.

It is generally acknowledged that researchers need more and easier access opportunities, while protecting donor's confidentiality and safety. To achieve this aim, collaboration between research facilities and biobanks needs to be improved, e.g. by enabling a better exchange of information. This is where the p-medicine metabiobank (P-BioSPRE) will step in. Participating biobanks will be able to provide information about their storages of biomaterial and pertaining data. Authorized researchers can use the metabiobank search engine to seek for suitable samples and will in addition be able to send requests to the biobanks in case of a successful search.

This metabiobank concept enables p-medicine to reflect the various interests of biobanks, researchers and patients. Researchers are able to receive information about the availability of appropriate biospecimen and data. The participating biobanks are still autonomous and can decide independently if they want to share their biomaterial with the researcher who requested them. Patients' privacy will be respected through a refined system of de-identification processes and a sophisticated access system. To increase the security level an access policy has been developed that will have to be observed by the users of the metabiobank. In addition, data transfer agreements will contribute to ensure the security of the data.

Nonetheless, a waterproof privacy protection framework does not solve another problem that has been identified: the lack of harmonisation in the quality of sample handling. We suggest that p-medicine should encourage the use of standards and quality procedures in all associated biobanks and laboratories. Metadata with information about the collection, processing, and storage of samples, for example freezing temperature, sample size, and thawing, in addition to metadata about quality aspects (e.g. validated protocol), should be included in the metabiobank to provide researchers with quality information.

## Appendix 1 - Abbreviations and acronyms

<i>ALL</i>	Acute lymphoblastic leukemia
<i>BBMRI</i>	Biobanking and Biomolecular Resources Research Infrastructure
<i>BRA</i>	Biomedical Research Act (Spain)
<i>BRC</i>	Biological Resource Centre
<i>BioSHaRE</i>	Biobank Standardisation and Harmonisation for Research Excellence
<i>BioSPRE</i>	Biomaterial Search and Project Request Engine
<i>CDE</i>	Common Data Element
<i>COI</i>	Conflict of Interest
<i>CRIP</i>	Central Research Infrastructure for molecular Pathology
<i>ECR</i>	European Court Reports
<i>ECJ</i>	European Court of Justice
<i>EHR</i>	Electronic Health Record
<i>ESF</i>	European Science Foundation
<i>ESTO</i>	European Science and Technology Observatory
<i>EU</i>	European Union
<i>GBRCN</i>	Global Biological Resource Centre Network
<i>GCP</i>	Good Clinical Practice
<i>GMC</i>	Good Manufactural Practice
<i>HUGO</i>	Human Genome Organization
<i>IARC</i>	International Agency for Research on Cancer
<i>ICT</i>	Information and communications technology
<i>ISBER</i>	International Society for Biological and Environmental Repositories
<i>MRC</i>	Medical Research Council
<i>MTA</i>	Material Transfer Agreement
<i>NCI</i>	National Cancer Institute
<i>OECD</i>	Organization for Economic Co-operation and Development
<i>P3G</i>	Population Project in Genomics
<i>PHOEBE</i>	Promoting Harmonization of Epidemiological Biobanks in Europe
<i>PRIVELEGED</i>	Determining the Ethical and Legal Interests in Privacy and Data Protection for Research Involving the Use of Genetic Databases and Biobanks
<i>QA</i>	Quality Assurance
<i>QMS</i>	Quality Management System
<i>SOA</i>	Service Oriented Architecture
<i>SNOWMED</i>	Systematized Nomenclature Of Medicine Clinical Terms

<i>SOP</i>	Standard Operating Procedure
<i>TEC</i>	Treaty Establishing the European Community
<i>TFEU</i>	Treaty on the Functioning of the European Union
<i>TMG</i>	Telemediengesetz
<i>TKG</i>	Telekommunikationsgesetz
<i>UNESCO</i>	United Nations Educational, Scientific and Cultural Organization
<i>UK</i>	United Kingdom

Annex 1

# Biobank Data Transfer Agreement

Contracting parties:

Data exporter/Biobank provider  
hereinafter “Biobank Partner”

–

Metabiobank provider  
hereinafter “Metabiobank Provider”

## Preamble

To contribute knowledge for new VPH simulation tools, it is essential to find biomaterials where clinical and other data are already available and can be used to run new experiments in postgenomic trials. In particular for rare diseases such as childhood cancer it is of crucial importance that distributed biomaterial stocks are merged virtually and presented to the research community through one homogenous search and project request interface. However, to acquire sample cohorts for VPH models and retrospective clinical studies, technical solutions are needed to index, annotate, browse, integrate and access such complex heterogeneous content from diverse human biomaterial repositories. Such interface has to provide a clear legal and ethical policy for getting access to biomaterial samples and associated data, safeguarding biobank autonomy, as well as implement patients' consent preferences.

One of the goals of p-medicine therefore is to enable through its ICT infrastructure the searching for and sharing of high quality biological material in order to conduct clinical research and advance personalised medicine. The project shall provide an access tool to facilitate access to existing clinically annotated biobanks and biomaterial repositories in the cancer domain. This shall be done by a query interface that allows users to search for cases and materials in various bio-repositories according to their selection criteria. This tool shall serve as a meta search engine for biomaterial or a “metabiobank”.

By means of this metabiobank researchers of the participating research organisations can search whether there are bio-samples available in the affiliated biobanks that might be suited for their research requirements. The result will reveal the number of suiting cases available at the different biobanks. Accordingly, only anonymized and statistical data will be revealed to the researchers via the metabiobank access tool. Researchers will then have the possibility



to contact the respective biobank operators holding samples that are suitable for their envisaged research project. In order to facilitate the communication, biobank operators have to reply to these requests within reasonable time, indicating whether they are interested in a possible cooperation or not. The p-medicine metabiobank access tool, however, will not oblige Biobank Partners to grant access to their biobank. The terms and conditions for material transfer or access to data, on the contrary, will be subject to bilateral agreements between the research organisations/researchers and the Biobank Partner.

The following clauses shall be the terms and conditions for this agreement:

## 1. Scope

- (1) This agreement shall regulate
  - a. the transfer of data regarding human biomaterial and associated data, available at the Biobank Partner, to the Metabiobank; and
  - b. purposes and functionalities of the Metabiobank.
- (2) This agreement shall not regulate the exchange of biomaterial between the Biobank Partner and the research organisation/researcher. The terms and conditions for the access to the biomaterials and related data shall be subject to bilateral agreements between the respective research organisation/researcher and the Biobank Partner.

## 2. Definitions

For the purposes of the Clauses in this agreement:

- (1) “Biobank” shall mean structured resource that can be used for the purpose of medical research and which include:
  - a. human biological materials and/or information generated from the analysis of the same; and
  - b. extensive associated information.<sup>287</sup>
- (2) “Biobank Partner” shall mean the legal person (e.g. a hospital, research institute) that establishes and maintains a biobank.
- (3) “Metabiobank” shall mean the database containing information about bio-materials and related data available at the participating biobanks., and the infrastructure to make such information available within the p-medicine framework.
- (4) “Metabiobank Provider” shall mean the legal person that establishes, maintains, hosts and manages the Metabiobank for p-medicine.
- (5) “Metabiobank access tool” shall mean a software/web-application that

---

<sup>287</sup> See similar definition in the OECD Guidelines on Human Biobanks and Genetic Research Databases, <http://www.oecd.org/dataoecd/41/47/44054609.pdf>.

- a. enables the transfer of relevant data from a Biobank Partner to the Metabiobank; and
  - b. facilitates the web-based interactive query of researchers for biomaterials and associated data available at the participating biobanks.
- (6) “Research organisation” shall mean the entity, e.g. healthcare organisation/hospital, which has signed the p-medicine biobank registration form
  - (7) “Metabiobank user” shall mean a natural person, e.g. investigator/researcher, who is working for a research organisation defined in paragraph 6 of this clause.
  - (8) “Donor” shall mean the individual from whom bio(logical) materials, data and information are obtained.
  - (9) “Ethics committee” shall mean the competent ethical committee within the organisation of the biobank partner.
  - (10) “Biomaterials” shall mean specimens, samples and aliquots of the original human materials and their fractionated components stored at the biobank.
  - (11) “Associated data” or “associated information” shall mean personal clinical, biochemical and phenotypic information about the donor.
  - (12) “Clauses” shall mean the contractual clauses in this agreement.

### **3. Warrants by the Biobank Partner**

The Biobank Partner warrants and ensures that:

- (1) the transfer of data concerning biomaterial and associated information available at its biobank to the Metabiobank is compliant with applicable national data protection law, dealing with such transfer, in particular the implementing provision of Article 14 of Directive 2004/23/EC;
- (2) it has in particular, the ethical approval of its competent ethics committee for the transfer of respective data to the Metabiobank;
- (3) it shall only transfer data of biomaterials that are correct and available in its biobank;
- (4) it ensures that only authorised staff will upload data to the Metabiobank;
- (5) the biobank complies with the standards and guidelines set out by the OECD, in particular the OECD Guidelines on Human Biobanks and Genetic Research Databases issued in 2009.<sup>288</sup>.

### **4. Warrants by the Metabiobank Provider**

The Metabiobank Provider warrants and ensures that:

- (1) it shall provide adequate technical and organisational measures in order to ensure the security of the data transmitted to the Metabiobank against any accidental or

---

<sup>288</sup> <http://www.oecd.org/dataoecd/41/47/44054609.pdf> .

unlawful destruction or accidental loss, alteration, unauthorized disclosure or access. In particular where the processing involves the transmission of data over the internet it shall be operated through communication channels only with state of the art security mechanisms (such as HTTPS protocol) and shall be protected against all unlawful forms of processing;

- (2) it shall provide data about the biomaterials and associated data available at the Biobank Partners to research organisations only in anonymized, aggregated, and statistical form. Accordingly, the research organisation will not receive any data of a specific donor via the research interface;
- (3) it shall import anonymized data only and shall not take any measures to reidentify a donor;
- (4) it shall grant access to the Metabiobank only to research organisations that have signed the p-medicine Metabiobank access registration form and have identified themselves in the foreseen identification and authentication procedure .

## **5. Intellectual property rights relating to the data**

- (1) Any rights with respect to biomaterials and associated data, as well as rights relating to the database from which such data originate exclusively belong to the Biobank Partner.
- (2) The Biobank Partner shall grant the Metabiobank Provider the right to use the transferred data and to provide such data to research organisations/Metabiobank users according to the procedure described in Clause 7 of this agreement.
- (3) Subject to paragraphs 1 and 2 of this clause, any other intellectual property accruing from the metabiobank infrastructure will be resolved in accordance with the p-medicine Consortium Agreement, FP7 Grant Agreement – Annex II - General Conditions, as well as Regulation No 1906/2006.

## **6. Provision relating to technical infrastructure**

- (1) The Biobank Partner shall use the p-medicine biobank software/web-application for the transmission of only the necessary data to the Metabiobank. The usage of this application shall be in accordance to these clauses.
- (2) The Biobank Partner shall adhere to the technical description that comes with the software as annexed to this contract, which also in addition to these clauses forms an integrated part of this agreement.
- (3) The Metabiobank Provider will take the necessary steps to ensure that the Metabiobank is accessible to the Metabiobank user. A guarantee of accessibility to a given moment or for a given period of time can however not be given.

## **7. Cooperation procedure**

- (1) The p-medicine biobank access tool shall provide a platform that allows researchers to search for availability of appropriate biospecimens relevant for their field of research in different biobanks.
- (2) If a researcher identifies samples that potentially meet the requirements for the envisaged research project, he/she can send a project request to the Metabiobank. This access request will be forwarded to the Biobank Partner via the access tool platform.
- (3) The Biobank Partner shall answer the access request in reasonable time, not later than 10 (ten) working days after receiving the request.
- (4) The Biobank Partner's body/committee responsible for sample allocation is free in its decision, whether the samples will be provided or not. The conditions under which the Biobank Partner might provide samples are subject to a bilateral project agreement between such Biobank Partner and the research organisation/Metabiobank user.

## **8. Enforcement, termination and obligations of the parties after the termination**

- (1) This agreement shall come into force upon signature of both parties and remain effective for an unlimited period until terminated in accordance with this clause.
- (2) In case of violation of Clauses 3 to 6 of this contract by one of the parties, the other party is entitled to terminate this contract immediately.
- (3) Without prejudice to the foregoing provisions, any party may terminate this contract for good cause such as where it becomes legally impossible to fulfil the obligations under this agreement.
- (4) Each party may terminate this contract after giving a written notice of six weeks to the end of the quarter. At the earliest, termination becomes effective when the other party receiving the notice confirms in writing that termination should take effect at an earlier date before the end of the quarter.
- (5) In the case of termination of this agreement, the metabiobank provider shall erase from the Metabiobank database all data of the Biobank Partner transferred in the course of this transaction.

## **9. Liability**

Each party shall be liable to the other parties for damages it causes by any negligent or wilful breach of this agreement. Liability between the parties is limited to actual damage suffered.

## 10. Governing law and Jurisdiction, miscellaneous

- (1) This contract shall be governed by German law. The courts of Munich shall have exclusive jurisdiction. This shall also apply to disputes on the validity of this Clause.
- (2) Changes and amendments to this contract and all of its components, including any assurances by one of the parties, require written agreement and an explicit statement that they represent a change or amendment to these conditions. The same applies to the waiving of this formal requirement.
- (3) If any provision of this contract shall be entirely or partly invalid or unenforceable, this shall not affect the validity and enforceability of all other provisions of this contract. An invalid or unenforceable provision shall be regarded as replaced by such a valid and enforceable provision that as closely as possible reflects the privacy, security and/or economical purpose that the parties hereto had purposed with the invalid or unenforceable provision.

Made in.....signed copies, each party having received its own signed copy.

Dated: \_\_\_\_\_

---

–  
for the Meta Biobank 1. Person who is authorized to sign

\_\_\_\_\_  
2. contact person

---

for the Biobank Partner 1. Person who is authorized to sign

\_\_\_\_\_  
2. contact person