Deliverable No. 10.2

Initial Implementation of the Components of the *p-medicine* Biobank Access Framework

Grant Agreement No.:	270089
Deliverable No.:	D10.2
Deliverable Name:	Initial Implementation of the Components of the *p-medicine* Biobank Access Framework
Contractual Submission Date:	31/01/2013
Actual Submission Date:	31/01/2013

Dissemination Level		
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)	X
CO	Confidential, only for members of the consortium (including the Commission Services)	

COVER AND CONTROL PAGE OF DOCUMENT	
Project Acronym:	***p-medicine***
Project Full Name:	From data sharing and integration via VPH models to personalized medicine
Deliverable No.:	D 10.2
Document name:	Initial Implementation of the Components of the Biobank Access Framework
Nature (R, P, D, O)[1]	P
DisseminationLevel (PU, PP, RE, CO)[2]	RE
Version:	1
Actual Submission Date:	31/01/2013
Editor: Institution: E-Mail:	Gabriele Weiler Fraunhofer Institute for Biomedical Engineering Gabriele.Weiler@ibmt.fraunhofer.de

ABSTRACT:

Biobanks represent key resources for clinico-genomic research and advances in personalized medicine. With its ICT infrastructure and contractual framework, p-medicine will support researchers' growing demand to access and share high quality biomaterial and related data for their research projects. For this purpose a Biobank Access Framework called p-BioSPRE has been developed within the p-medicine platform to enable and simplify access to existing biobanks but also to offer own biomaterial collections to research communities and manage biobank specimens over the ObTiMA Trial Biomaterial Manager. p-BioSPRE is being developed along two underlying user scenarios. This deliverable describes these user scenarios, and its software modules implemented so far.

KEYWORD LIST: Biobank Access, specimen, p-BioSPRE, ObTiMA Trial Biomaterial Manager, IDB, p-Biobank Wrapper

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.

[1] **R**=Report, **P**=Prototype, **D**=Demonstrator, **O**=Other

[2] **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)

MODIFICATION CONTROL			
Version	Date	Status	Author
0.1	14/01/13	Draft	Gabriele Weiler, Fatima Schera
0.2	15/01/13	Draft	Matthias Dobkowicz, Christina Schröder
0.3	18/01/13	Draft	Gabriele Weiler
0.5	24/01/13	Draft for Review	Gabriele Weiler, Christina Schröder
1.0	31/01/13	Final	Gabriele Weiler, Norbert Graf

List of contributors

- Gabriele Weiler, Fraunhofer IBMT
- Fatima Schera, Fraunhofer IBMT
- Dr. Christina Schröder, Fraunhofer IBMT, Branch Potsdam-Golm
- Matthias Dobkowicz, Fraunhofer IBMT, Branch Potsdam-Golm
- Prof. Norbert Graf, Universität des Saarlandes

Contents

1 EXECUTIVE SUMMARY 7
2 INTRODUCTION 8
3 USER SCENARIOS 9
3.1 SIOP WILMSTUMOR BIOBANKING SCENARIO 9
3.2 ACUTE LYMPHOBLASTIC LEUKAEMIA BIOBANKING SCENARIO 11
4 MAIN FUNCTIONALITY AND BASIC ARCHITECTURE 13
4.1 MAIN FUNCTIONALITY 13
4.2 BASIC ARCHITECTURE 13
5 P-BIOSPRE AND ITS COMPONENTS 15
5.1 P-BIOSPRE 15
5.2 IN-HOUSE DATABASE / P-BIOBANK WRAPPERS 18
6 OBTIMA TRIAL BIOMATERIAL MANAGER 21
6.1 MANAGING BIOBANKS 21
6.2 CREATING SPECIMENS AND BIOBANKING SPECIMEN CRF 25
6.3 SHIPPING BIOMATERIAL 33
6.4 IMPORT FUNCTIONALITY FOR SIOP SCENARIO 33
6.5 INTERFACE TO P-BIOSPRE 34
7 CONCLUSION 35
7.1 EVALUATION 35
7.2 FUTURE WORK 35
APPENDIX 1 - ABBREVIATIONS AND ACRONYMS 37
APPENDIX 2 - IMPORT DATA SET WILMSTUMOR SCENARIO 38
APPENDIX 3: ALL DATA SET 47

1 Executive Summary

Biobanks represent key resources for clinico-genomic research and advances in personalized medicine. With its ICT infrastructure and contractual framework, p-medicine will support researchers' growing demand to access and share high quality biomaterial and related data for their research projects. For this purpose a Biobank Access Framework called p-BioSPRE has been developed within the p-medicine platform to enable and simplify access to existing biobanks, but also to offer own biomaterial collections to research communities and manage biobank specimens over the ObTiMA Trial Biomaterial Manager. p-BioSPRE is being developed along two underlying user scenarios on acute lymphoblastic leukemia (ALL) and Wilmstumor. This deliverable describes these user scenarios and their requirements, the correspondent functionalities of the p-medicine Biobank Access Framework, and its software modules implemented so far.

2 Introduction

P-medicine's mission is to foster and support the advent of personalized medicine for patients, and an integrated biobanking solution is critical to its success. The explosion of molecular medicine and molecular imaging in cancer has led to an exponential increase in the possibilities for individualised cancer care. But the accompanying complexity of the resulting cellular biomarkers, their application in radiotherapy planning and targeted drug choice has made the knowledge base too great for physicians to retain, and certainly too complex for patients to understand. Many more new molecules will be designed in the time course of this project and their validation as useful biomarker driven treatments will require fast reference to the global collection of carefully, (and molecularly) characterised stored tissue samples. Therefore, a Biobank Access Framework called p-BioSPRE has been developed in p-medicine, with the aim to shorten the time between bench to bedside including drug development.

Within its overall ICT and contractual architecture, the Biobank Access Framework and the p-medicine Data Warehouse are foreseen to complement and synergise with each other to generate and contribute critical VPH knowledge.

The aim of p-BioSPRE is to provide access to different kinds of human biomaterials and related data for research purposes. A biomaterial owner is supported in offering his biomaterial and related data to research communities according to legal aspects. A researcher is enabled to search the biomaterial that is offered within his communities. It is furthermore possible for him to request biomaterial for a research project and his request is forwarded to the biomaterial owner.

Furthermore, within p-BioSPRE the ObTiMA Trial Biomaterial Manager is developed that enables users of ObTiMA, the *p-medicine*'s ontology based trial management system, to manage their biomaterial data within clinical trials. For this purpose a pre-defined but adjustable case report form for patient's biomaterial according to a standard biobank dataset is provided in ObTiMA. The biomaterial data can be integrated with clinical data.

In this deliverable we describe the functionality of the p-medicine Biobank Access Framework. The deliverable is structured as follows:

Chapter 3 describes the two user scenarios provided by the *p-medicine* partners Universität des Saarlandes (USAAR) in the context of the SIOP Wilmstumor trials and Christian-Albrecht-Universität zu Kiel (CAU) in the context of clinical research and trials related to acute lymphoblastic leukaemia. These scenarios mainly drive the technical development of the biobank access framework.

In chapter 4 an overview of the main functionality based on the user scenarios and the basic architecture of the biobank access framework is given.

Chapter 5 describes two of the main components of the Biobank Access Framework, the p-BioSPRE metabiobank, and the associated biobanks' local software and database, namely the Inhouse Database (IDB) / p-Biobank Wrappers. P-BioSPRE provides researchers the possibility to search for and request biomaterial that fits their research purposes. P-Biobank Wrappers enable biobank owners to share their biomaterial and related data in p-BioSPRE.

Chapter 6 describes the functionality of the ObTiMA Trial Biomaterial Manager that enables management of biobanks and associated specimen data in clinical trials and sharing selected specimen data.

Chapter 7 concludes the deliverable by outlining the future work.

3 User Scenarios

The technical development of the biobank access framework is mainly driven by two user scenarios provided by the *p-medicine* partners Universität des Saarlandes (USAAR) in the context of the SIOP Wilmstumor trials and Christian-Albrecht-Universität zu Kiel (CAU) in the context of clinical research and trials related to acute lymphoblastic leukaemia (ALL). The two scenarios constitute typical use cases for biobanking. The scenarios have already been described in D10.1 and are summarized in the following. Based on these scenarios four general use cases for the *p-medicine*'s biobank access framework have been defined and contributed to Deliverable D2.2 "Definition of scenarios and use cases and report on scenario based user needs and requirements".

3.1 SIOP Wilmstumor biobanking scenario

During the runtime of the SIOP Wilmstumor trials biological material (tumour, normal kidney and blood samples) is collected by the participating centres. Fresh tumour material and normal kidney is shock frozen and also fixated and embedded in paraffin. From some tumours vital material is preserved for cell culture. All the biomaterial is sent to central labs in the participating country for further processing and analysis and for long-term preservation. The Biocenter of the University Würzburg is the central facility in Germany to preserve this biomaterial analyzed and made available for further research to SIOP partners. Standardized procedures and ethical approval are in place how requests to material are handled. A committee of the SIOP Wilmstumor study group decides about material requests. Among others, the approval of the committee depends on the research that the requester wants to conduct with the biomaterial, whether similar research has already been conducted or not, the availability of material and so on. Childhood Wilmstumor is a rare disease. Around 100 cases in Germany are reported annually (for paediatric leukaemia 550 cases) and, as almost all of the patients are treated in the prospective SIOP trial, their biomaterial is stored in the Wilmstumor repository by the Biocenter. The tumour tissue received from the different pathology institutes of the clinical partners is shipped on dry ice and varies in quality on arrival. A quality control system based on SOPs with observable quality variables is not implemented yet (i.e. time from surgery to asservation; cooling chain observation, etc) beside the visual test whether dry ice can still be found in the shipping box on arrival.

Data about the material is captured in several Excel files, which fulfil the needs of researchers regarding flexibility (i.e. new data fields) and further data analysis options (i.e. data export). Additional data is created in further experiments using tumour material, which include microarray analysis, LOH (loss of heterozygosity) and others. The data are of particular interest for the clinical researchers, and are not only relevant for retrospective studies but also in some cases in routine clinical care. A so-called SIOP number is the identifier of the biomaterial that also links the material to the clinical data of a patient in the SIOP trial. LOH analysis data is captured in a simple Excel file, while micro array data are more complex. There standardization is important and depends on the platform used and the SOPs of the lab.

The primary goal of the clinicians involved in SIOP Wilmstumor research is to combine the clinical data of the patient with molecular data in order to find new biomarkers or stratification markers for upcoming trials. This will allow applying better treatments with fewer side effects to patients. In summary there are four important issues of this biobank scenario:

Through the Biobank Access Framework developed in *p-medicine* researchers of the German Wilmstumor study group want:

1. to access data from the central Wilmstumor repository in Würzburg and link them with clinical data.

2. to check if there is biomaterial available for further research, after getting such a request from any researcher. This needs approval by the respective SIOP committee. The approval will depend on the experience of the researcher, the scientific question, the ethical approval, the availability of material, the knowledge that this kind of research will generate, and financial issues.
3. to share data and biomaterial cross borders. Prof. Norbert Graf and Prof. Manfred Gessler, responsible for the German Wilmstumor repository at the Biocenter Würzburg, consider this as relevant. As trials in North America follow a different treatment approach (primary surgery), comparison of biomaterial between these approaches would add significantly to the knowledge about Wilmstumor.
4. to collect through the *p-medicine* biobank access framework information about the planned research with samples and to link this information to the remaining aliquots on stock. Ultimately, information of the outcome of such research should be linked to the remaining stock of aliquots as well. According to resource limitations of *p-medicine* this is out of the scope of WP10.

The strategy for access to the biobank in p-medicine regarding the SIOP Wilmstumor biobank scenario is

- To demonstrate the feasibility and advantage of legally integrating biomaterial data with clinical data and sharing data and biomaterial within the German SIOP study group through the p-medicine infrastructure and its biobank access framework to be developed in WP10,
- To establish this technical approach as the standard in the SIOP Wilmstumor community,
- To transfer this approach to other SIOP countries. There is a close cooperation with ENCCA (European Network for Cancer Research in Children and Adolescents[3])

Through the Biobank Access Framework researchers of the German Wilmstumor study group and the operator of the German Wilmstumor repository want:

1. To upload/export existing Excel based specimen data sheets to the p-medicine infrastructure for further searching and processing by SIOP researchers
2. To upload/export also the analytical/research data, in particular LOH data and microarray data
3. To flexibly manage the German biomaterial repository through the WP10 Biobank access components instead of filling and exporting Excel tables.
4. To search and view all biomaterial data and
5. To combine the biomaterial data with clinical data from ObTiMA, the data warehouse, or from any other external data base in particular the KEGG Pathway Database,
6. To request the availability of Wilmstumor material for a certain research question

Regarding aspects of pseudonymization/anonymization the Biobank Access Framework has to follow the privacy policy of the p-medicine infrastructure in all aspects.

[3] http://www.encca.eu/Pages/home.aspx

3.2 Acute Lymphoblastic Leukaemia biobanking scenario

Around 80% of minor Acute Lymphoblastic Leukaemia (ALL) patients in Germany are treated according to ALL-BFM studies, which are coordinated by the University Hospital Schleswig-Holstein of the Christian-Albrecht-Universität zu Kiel (CAU). Annually, there are about 500-550 new cases of minor ALL patients reported in Germany.

Clinical data, biobanking data, and samples for German ALL-BFM patients are collected and processed in the study centre in Kiel. The data has previously been stored in a home-grown data base management system (Postgres, Access) and has been transferred to Scopeland and Marvin in 2012.

Local clinics document ALL-BFM cases paper-based. The CRFs summarize approximately 600 parameters per patient. The completed document is sent to the study centre in Kiel, where all data is entered manually into the data base management system.

When minor ALL patients, which were treated in an ALL-BFM study, have a relapse, they are usually treated according to ALL-REZ BFM studies, which are coordinated by the university hospital of Charité Universitätsmedizin in Berlin. Annually, around 60 relapses occur in Germany. Biobanking data and samples for German relapse patients are collected in the Charité study centre in Berlin. The data is collected in a web-based biobanking management system that was tailored for the Charité based on the universal database application platform Scopeland[4]. Clinical data will be collected for the next trial (IntReALL 2010) in the trial management system Marvin. The ALL-BFM and ALL-REZ BFM study groups collaborate with several other study groups in Europe. Each study group has own solutions to store clinical and biobanking data. The trial IntReALL 2010 has started in the beginning of 2012. It is intended that all partners, who don't possess qualified solutions for biobanking, can use the customized Scopeland system.

Currently, ALL partners can only access clinical data and biomaterial data of their own patients that are stored in their own databases. In particular, it is not possible for the ALL-REZ BMF study centre in Berlin to get automated access for their patients with relapses to biomaterial and relevant analytical and clinical data from the acute phase in the study centre in Kiel. Regarding European and world wide collaborations of CAU for research on ALL it is desired to access and share biomaterial and related analytical data within the respective international research collaboration. Relevant collaborations are the study AIEOP-BFM ALL 2009 with biobanks from Austria, Australia, Czech Republic, Germany, Israel, Italy and Switzerland as well as the EC funded relapse study IntReALL 2010 with partners from UK, Germany, Australia, Austria, Czechia, France, Israel, Italy, Japan, Netherlands, Sweden, Switzerland and Poland.

The strategy for biobank access in p-medicine regarding the ALL biobanking scenario is

- To demonstrate feasibility of simultaneous access to patients' biomaterial and related data from their acute and recurrent phase, collected in different trials at the study centres Kiel and Berlin,
- To show advantage of integrating and accessing biomaterial data provided by collaborating international partners for international research collaborations on lymphoblastic leukaemia. For this purpose, initially one or two biobanks of international ALL research partners of CAU shall be integrated under p-medicine's biobank access framework.

[4]Scopeland is a universal database application platform of the German SME Scopeland Technology GmbH, Berlin, http://www.scopeland.de

- To demonstrate location of and access to such samples under a model based legal framework which ensures legally correct data transfer and safeguards biobank autonomy.

4 Main Functionality and Basic Architecture

In this section we summarize the technical solution for the *p-medicine* Biobank Access Framework according to the use cases described in Deliverable 10.1. We will firstly summarize the main functionality based on the use cases and then describe the basic architecture of the biobank access framework.

4.1 Main Functionality

The aim of *p-medicine*'s biobank access framework is to provide access to different kind of human biomaterials and related data for research purposes. Based on a minimum data set, the framework will harmonize the data and enable flexibility of data import through its metadata repository. In particular the p-medicine biobank framework will support the following main functionalities:

1. **Offering Biomaterial for Research**

   A biomaterial owner is supported in offering his biomaterial and related data to open or closed research communities, according to legal aspects. The offered data can be stored in and extracted from any arbitrary biobank management system. The owner has the possibility to select which of his biomaterial he wants to offer to which research communities, and he will in any case keep control of his material and data.

2. **Searching and Requesting Biomaterial for Research**

   A researcher is enabled to search the biomaterial that is offered within his communities. He can get information about the data that is related to the material and the number of available cases. It is furthermore possible for him to request biomaterial for a research project on-line. For this purpose he will need to describe the project in some detail. The biobank access framework will automatically forward his request to the biomaterial owner.

3. **Managing Biomaterial Data in ObTiMA**

   Users of ObTiMA, the *p-medicine*'s ontology based trial management system, can manage their biomaterial data within clinical trials. For this purpose a pre-defined but adjustable case report form for patient's biomaterial is provided in ObTiMA. The biomaterial data can be integrated with clinical data within a trial or across several trials for further analysis. Legacy biomaterial data can be imported into ObTiMA from excel files that comply with the standard biobank dataset.

4.2 Basic Architecture

We have designed the biobank access framework as a set of coupled components, which are depicted in Figure 1. The main component of the framework is ***p-BioSPRE***, the *p-medicine* Biomaterial Search and Project Request Engine, which is a metabiobank to share biomaterial for research purposes. Furthermore, the framework comprises the ***p-Biobank Wrappers,*** which are tools to support biobank owners to offer their biomaterial and related data, (regardless which biobank information system they are running on-site), in p-BioSPRE and manage associated requests. Core of each p-Biobank Wrapper is the In-house Database (IDB), a database structure and software drawing upon components of the CRIP Toolbox[5]. In order to enable users of the *p-medicine* trial management system ObTiMA to

[5] 1. Nationales Biobanken-Symposium, Berlin 2012 (Ref. To be completed)

integrate biomaterial data in clinical trials and offer it in p-BioSPRE a ***Trial Biomaterial Manager*** is provided.

In the following chapters we will describe the functionality of the different components in more detail.

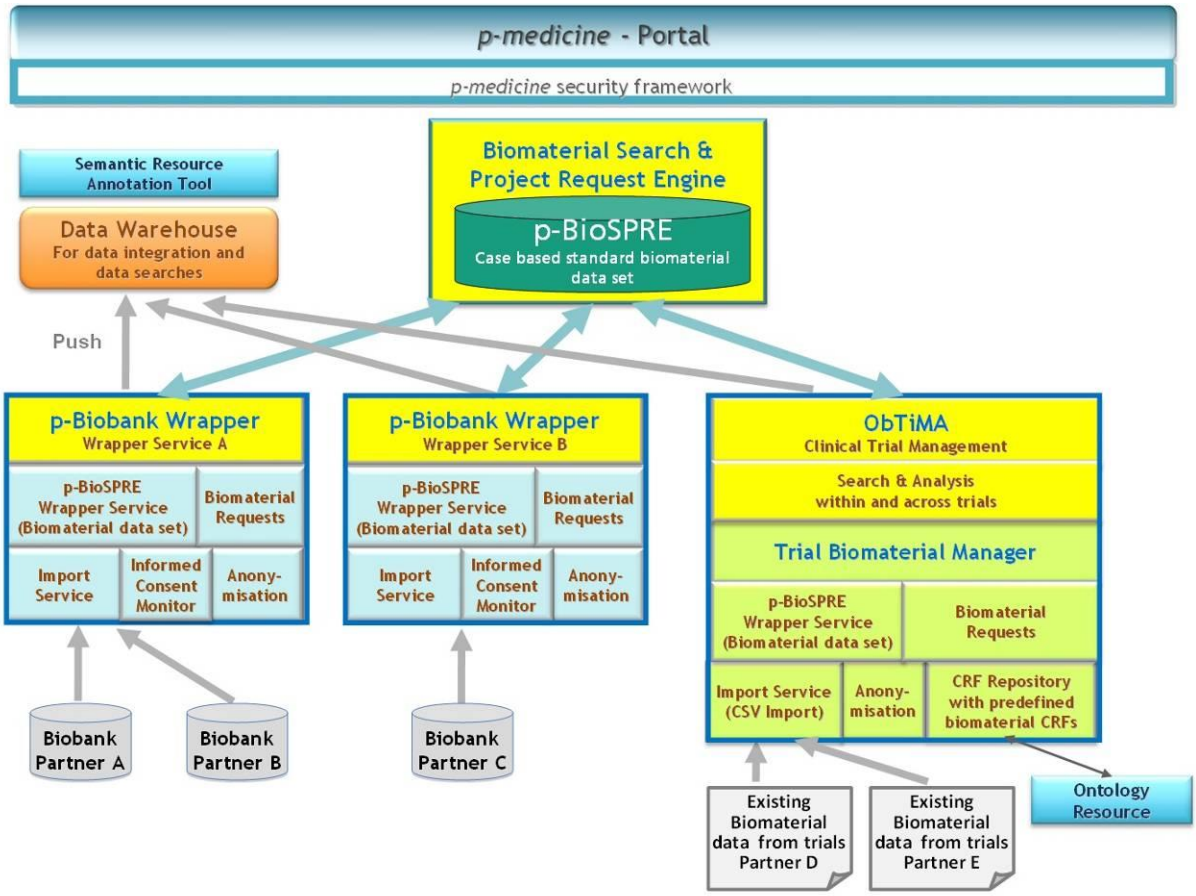

Figure 1: Basic Architecture of the p-medicine Biobank Framework:
p-BioSPRE Wrapper Services are provided by an In-house Database (IDB) and software harmonizing and anonymizing data extracted from the biobank information management system (BIMS)

5 P-BioSPRE and its components

5.1 p-BioSPRE - The *p-medicine* Biomaterial Search and Project Request Engine

P-BioSPRE is a metabiobank that provides researchers the possibility to search for and request biomaterial that fits their research purposes. Technically, p-BioSPRE bases on the CRIP metabiobank[6]. It is a web application and database architecture and can be accessed via the p-medicine portal. The application's management of user roles and rights is compliant with the p-medicine security framework being established by work package 5.

Figure 2: p-BioSPRE Search Tool:
The p-BioSPRE Search Tool covers all disease areas, classified according to ICD-10 ("Localization") and ICD-O ("Disease"), and all types of specimens ("Specimen"). Patient's annotation (e.g. age, sex, genetic subtype, etc.) will be complemented by an additional tab/category on "Consent" (see Fig. 5 / text below).

P-BioSPRE provides a search interface that enables authorized users to search for biomaterial. After authentication, users access an interactive search tool (Figure 2) allowing for selection of

- **localization** (organ or organ system from which biomaterial is derived)

[6] http://crip.fraunhofer.de

- **disease** (ICD-classified)
- **specimen** (type of specimen, e.g. whole blood, serum, tissue (FFPE or cryo-preserved), DNA, RNA, etc.)
- **annotation** (patient data (age, sex) including clinical information and genetic subtypes)
- **consent** (information on patient's informed consent given for the underlying biobank/trial according to the CONTRACT[7] framework)

or entering free text. Although in *p-medicine* only cases of Wilmstumor and ALL will be processed initially, we deem it necessary to provide a system covering the entire ICD, which will be flexible enough to include also secondary diagnoses, and to be extended to further disease entities later on.

As a first-step search result, users will retrieve the number of cases/specimens matching their request, enabling them to decide if further query will make sense. If the user wants to go for further information on the retrieved material and data, he may enter a Project Request on-line. For this purpose, an xls-file is made up from the search criteria / set of parameters the user has collated when browsing p-BioSPRE. This file is attached to the request form the user might submit (Figure 3), and transferred to the biobank for handling as agreed in the Biobank Transfer Agreement (see WP 5, Del. 5.3).

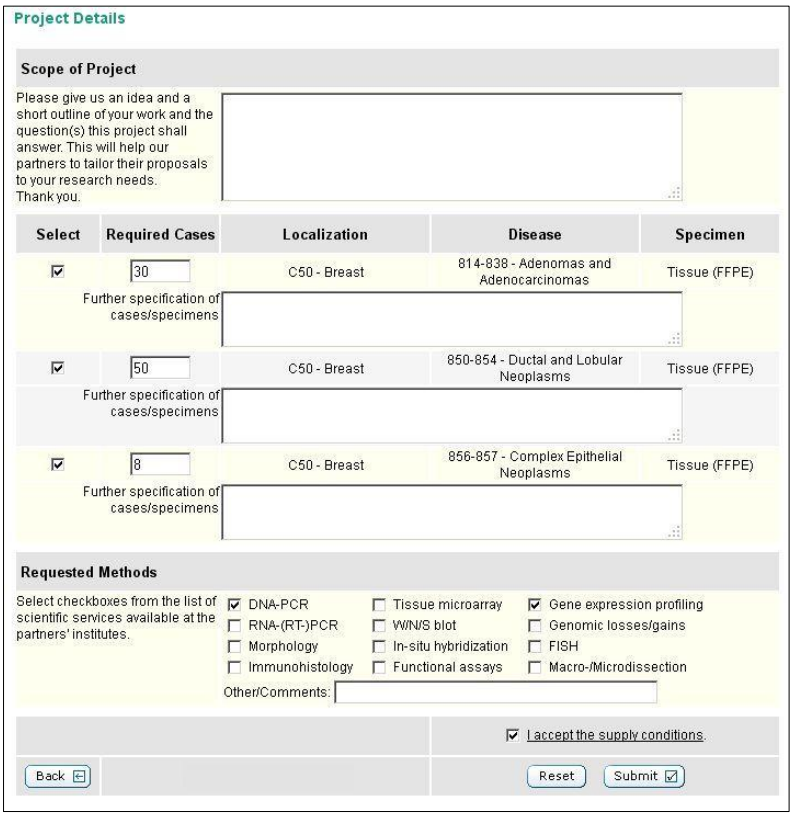

Figure 3: p-BioSPRE Search Tool:
The requested biobank will run this „input file" on their In-house Database (IDB; see Figure 4) and retrieve the pool list of pseudonymized cases matching the project request (see Del. 5.3).

[7] http://www.contract-fp7.eu/site/

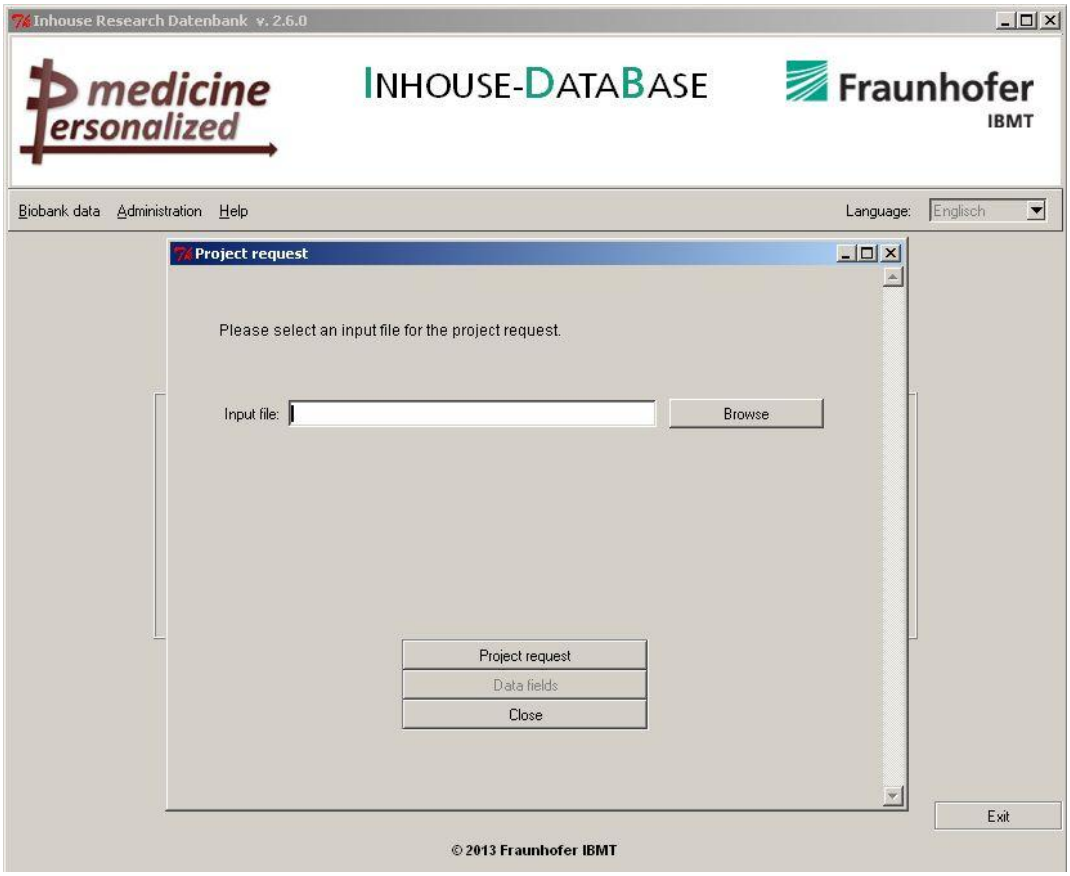

Figure 4: Entering a Project Request into the IDB

To enforce patients' decision on the research use of their specimens, and to prepare for existing privacy regulations[8] and upcoming "Privacy-by-Design" approaches[9] as well, p-BioSPRE will be equipped to record tiered informed consent and provide this information, if available, for the metabiobank query (Figure 5).

[8]Forgo N, Kollek R, Arning M, Kruegel T, Petersen I: Ethical and Legal Requirements for Transnational Genetic Research, C.H. Beck oHG, München 2010.

[9]http://www.coe.int/t/dg3/healthbioethic/Activities/10_Biobanks/biobanks_for_Europe.pdf

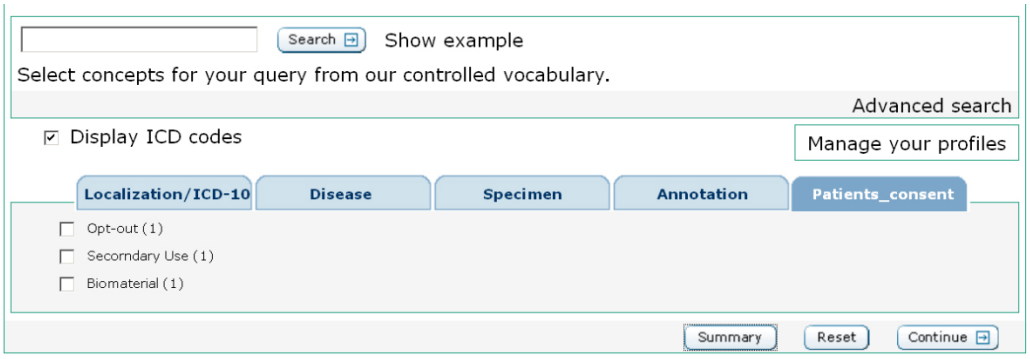

Figure 5: Search Tool Tab allowing for specification of patient's informed consent

5.2 In-house Database / p-BioBank Wrappers

Biomaterial data is uploaded into p-BioSPRE from so called p-Biobank Wrappers (Fig. 1). A p-Biobank Wrapper enables a biobank to share their biomaterial and related data in p-BioSPRE within an open or closed research community. Technically a p-Biobank Wrapper is based on the IDB, a local server installed at the site of a biomaterial owner and configured to link one or more of his biobank management systems, in which data is stored that he wants to share. Running an IDB does not require specific ICT expertise on the biobank owner's side (Figs. 4, 6 and 7). As a precondition to link a biobank information management system (BIMS) to a p-Biobank Wrapper, this system however needs to implement an export interface that allows exporting pseudonymized biomaterial data to the IDB.

Upon import into the IDB, pseudonymized data is harmonized and de-identified further, e.g. by converting a patient's exact age into full years. (In addition, in p-BioSPRE only 5-years intervals will be displayed.) Further features of the IDB are

- elements of k-anonymization[10]
- calculation of values (e.g. age of patient from dates of birth and sample preservation, or of body mass index from patient's height and weight)
- controlled vocabulary
- metadata repository

This software has already been implemented and, based on information from CAU on the ALL data structure, equipped with an import interface for this use case.

Due to the metadata repository (MDR) implemented in the IDB, its adaptation to different biobank datasets is flexible and feasible without any programming efforts. Before export to the p-BioSPRE metabiobank, the IDB software will strip off any pseudonyms thus generating anonymized data for on-line queries. As a next step, the MDR will be adopted to the ALL and SIOP data structure, as soon as data will be exported from both biobanks.

[10]El Emam K, Kamal Dakar F (2008) Protecting Privacy Using k-Anonymity. J Am Med Informatics Association 15:627-637

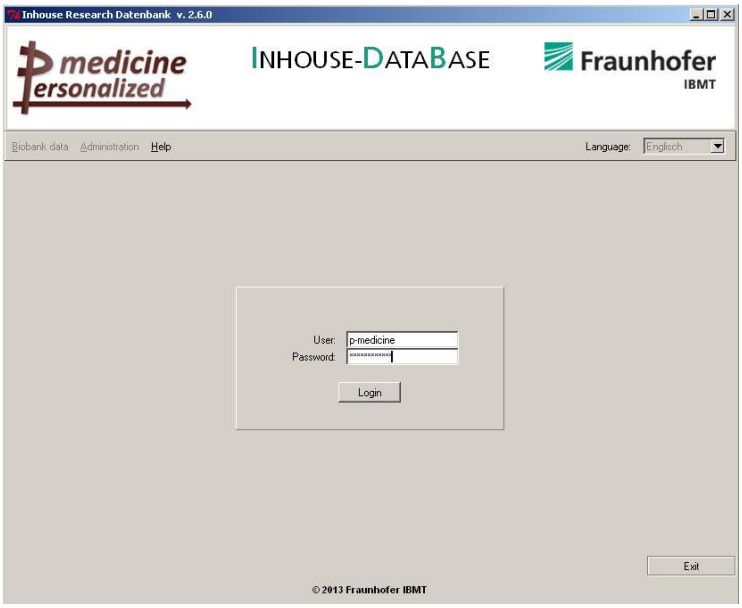

Figure 6: Log-in to IDB

The role model of the IDB includes the roles of

- a biobank/user (import / export / search data)
- an administrator (delete data from database / add IDB users / add biobanks).

In addition to performing project requests (Fig. 2 and button “Project Request”, Fig. 7), the IDB allows the biobank owner to select the imported data that he wants to share with certain research communities (“Insert biobank data”, Figure 7), anonymize, and upload the data to p-BioSPRE.

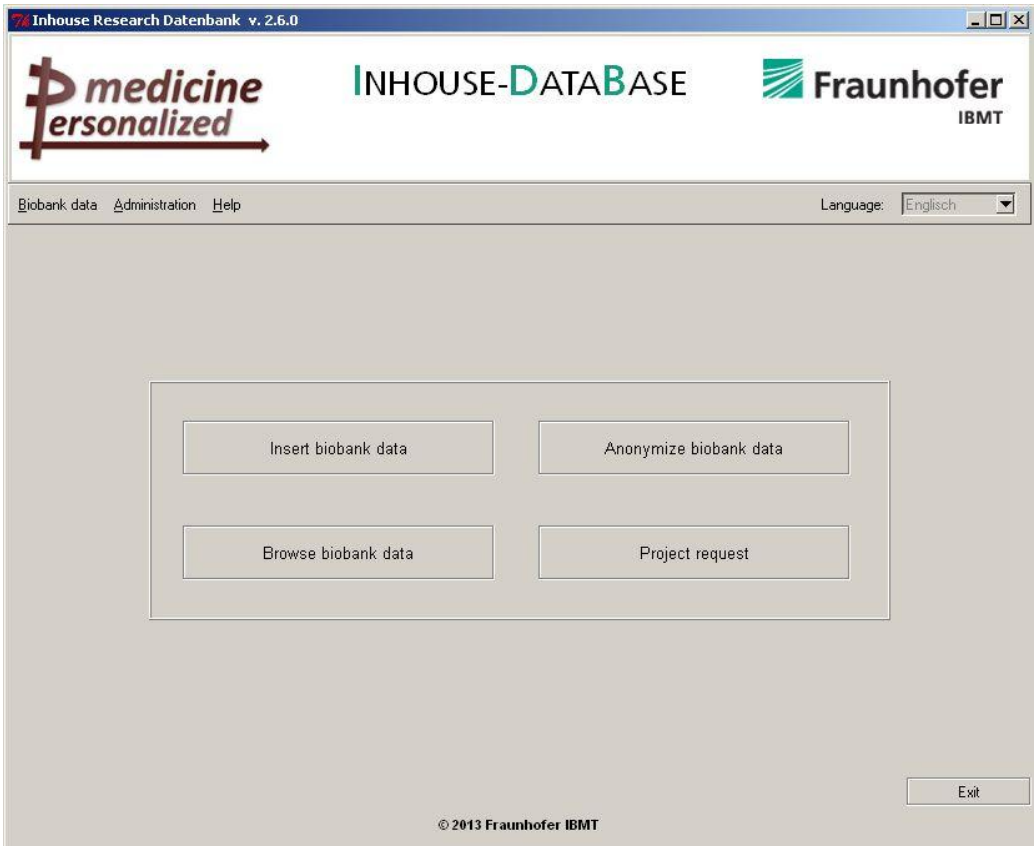

Figure 7: IDB User Interface

Data is being anonymized before the upload process. It has to be noted, that if biomaterial data for the same patient is imported from different BIMS into a p-Biobank Wrapper, the data is still linked, since for a patient always the same pseudonym is used. The information that the data belongs to the same patient is preserved when the data is anonymized locally over the IDB and uploaded into p-BioSPRE. This information is lost, when the data is uploaded from different p-Biobank Wrappers to the central database.

6 ObTiMA Trial Biomaterial Manager

The Trial Biomaterial Manager is developed as a component of the web based trial management system of the p-medicine infrastructure ObTiMA. It enables management of biobanks and associated specimen data in clinical trials and sharing selected specimen data.

The Trial Biomaterial Manager provides users an interface to manage specimen data in clinical trials according to the standard SIOP biomaterial data set. For this purpose a predefined biobanking specimen CRF is provided that can be adjusted to the user's needs. This CRF is stored in the ObTiMA CRF repository.

Furthermore, the Trial Biomaterial Manager enables users to upload their legacy biomaterial data into ObTiMA. Therefore, it provides an import service that enables users to import excel files with existing biomaterial data.

An interface is provided to get an overview about the available biomaterial. Furthermore, it is possible to link clinical data and biomaterial data within clinical trials.

Furthermore, it is possible to select the biomaterial data that the biobank wants to share, and upload the data to p-BioSPRE. In the following the current functionality of the Trial Biomaterial Manger is described in more detail.

6.1 Managing Biobanks

The Trial Biomaterial Manager provides biobank owners the possibility to create biobanks, edit and view the biobank metadata and manage the samples of the biobanks. Furthermore, biobank owners can assign trials to the biobank and specify and control, which users may access the data of the biobank.

Creating Biobank / Editing Biobank Metadata

To create a new biobank or edit the metadata of an existing biobank the biobank owner has to select the item "Manage Biobanks" from the ObTiMA main menu. After selecting this item a list of biobanks for which the user has rights is shown (2, Figure 7).

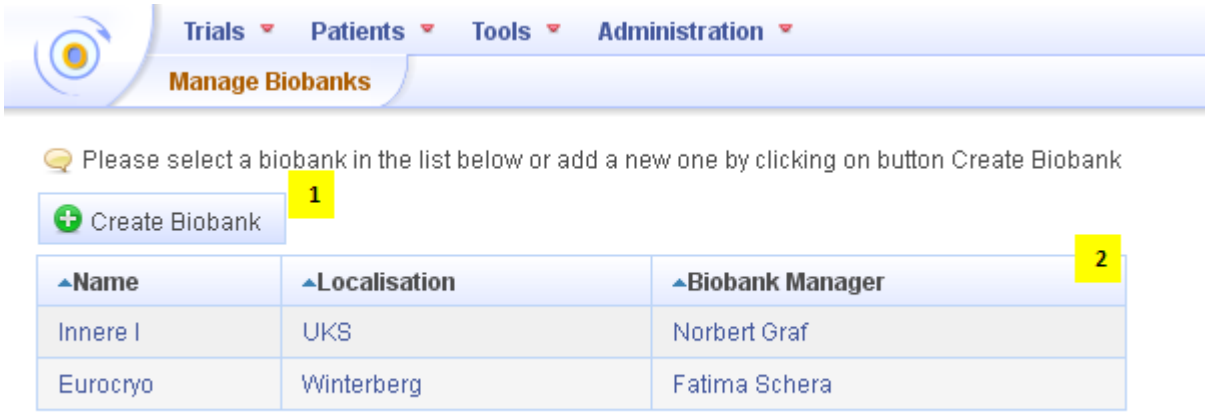

Figure 7: List of Biobanks.

The user can then create a new biobank by pressing the button "Create Biobank" (1, Figure 7) or select a biobank from the list to edit or view its metadata. The metadata of a biobank can be edited in several tabs:

In the tab "Biobank Details" (1, Figure 8) the main metadata for the biobank can be filled in by the user. The biobank details comprise:

- General Information (2, Figure 8) as the name, the biobank owner and the location of the biobank.
- Specification of the provided services as e.g. the specification of the storage cost and if the biobank is used commercially (3, Figure 8).
- Specimen Information as the number of specimens that can be stored and the number of specimens that are stored (4, Figure 8).
- Detailed information: Additional information about the biobank, as e.g. the homepage and the contact mail (5, Figure 8).
- Tissue Information: Information about the tissue types stored in the biobank (6, Figure 8).

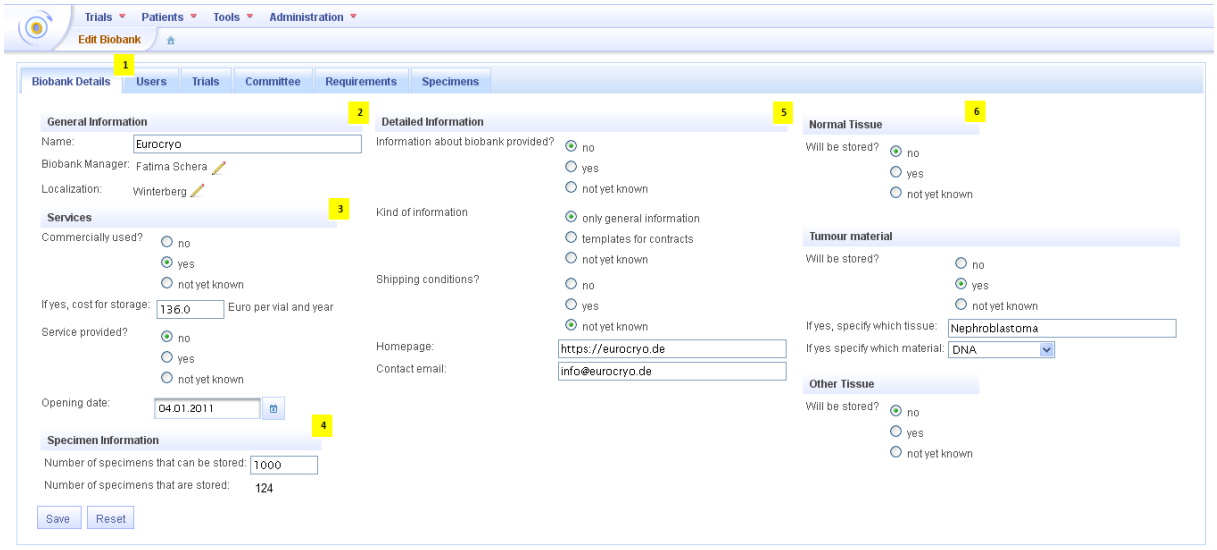

Figure 8: Biobank Details.

In the tab “Committee”, the user can list the members of the biobank committee. He can enter the name, organization, mail and phone number for each committee member (

Figure 9). The members do not need to be users of ObTiMA.

Figure 9: Biobank Committee

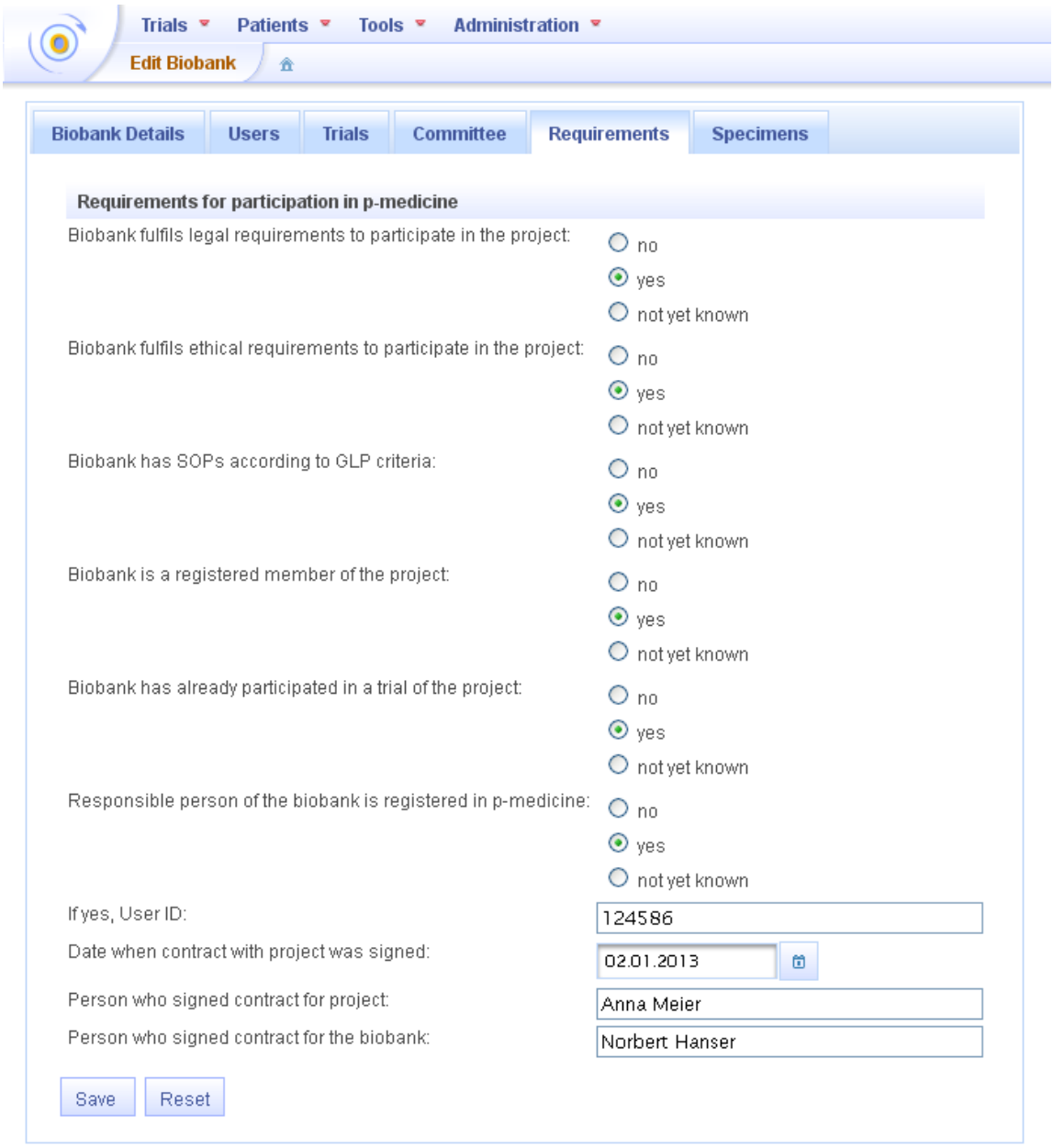

Figure 10: Biobank Requirements

In the tab “Requirements”, the requirements for the biobank to participate in the *p-medicine* project can be filled in.

Assigning Trials

It is possible to assign biobanks to trials in order to enable collection of biomaterial for the biobank in the according trial.

To this aim the biobank can be assigned to a trial in the tab “Trials” (1, Figure 11). A specimen that is created in a trial can only be assigned to a specific biobank if the biobank is assigned to the trial. For assigning a biobank to a trial the biobank owner needs to select a trial by clicking the button “Add Trial” (2, Figure 11) and select the appropriate trial from the shown list. The trial is then shown in the table “Related Trials” with status “Pending” (3, Figure 11), meaning that the biobank still needs to be confirmed by the trial chairman.

Figure 11: Trials related to a biobank

The trial chairman can confirm a biobank in the tab “Biobanks” in the trial menu after choosing the appropriate trial by pressing the 'plus'-sign (Figure 12).

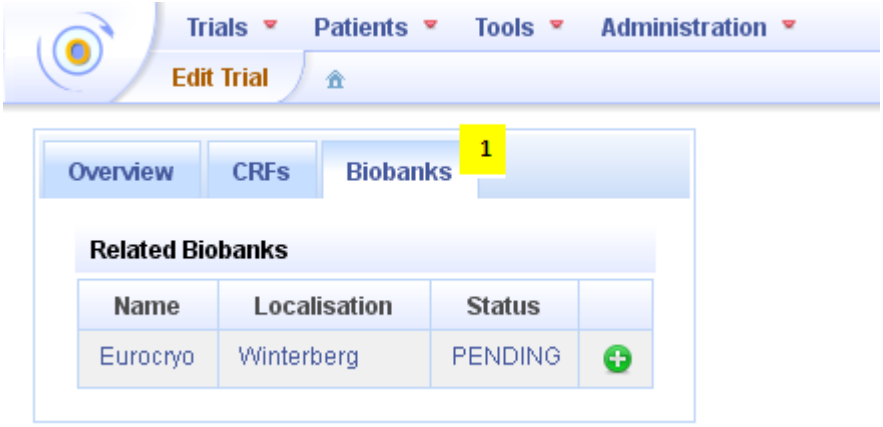

Figure 12: Biobanks related to a trial

User Rights

In the tab “Users” the biobank owner can assign rights for specific ObTiMA users to manage the biobank (1, Figure 13).Firstly the biobank owner needs to add a user by pressing the button “Add user” (2, Figure 13) and selecting the appropriate user from a list with all ObTiMA users. He can then assign the following rights to the user:

- Add specimens: The user can add a specimen to a biobank in a trial. The user can only add the specimen if he has the appropriate rights in the trial.
- View specimens: The user can see the list of specimens that is added to the trial.
- Metadata: The user can change the metadata of the biobank.

Figure 13: Biobank Users

View Specimens

In the tab “Specimens” a user with the appropriate rights can view all specimens that are stored in the biobank (s. Figure 14). By clicking on a specimen the user is directed to the CRF in the appropriate trial, where the specimen has been created and can view the clinical as well as the specimen data of the patient.

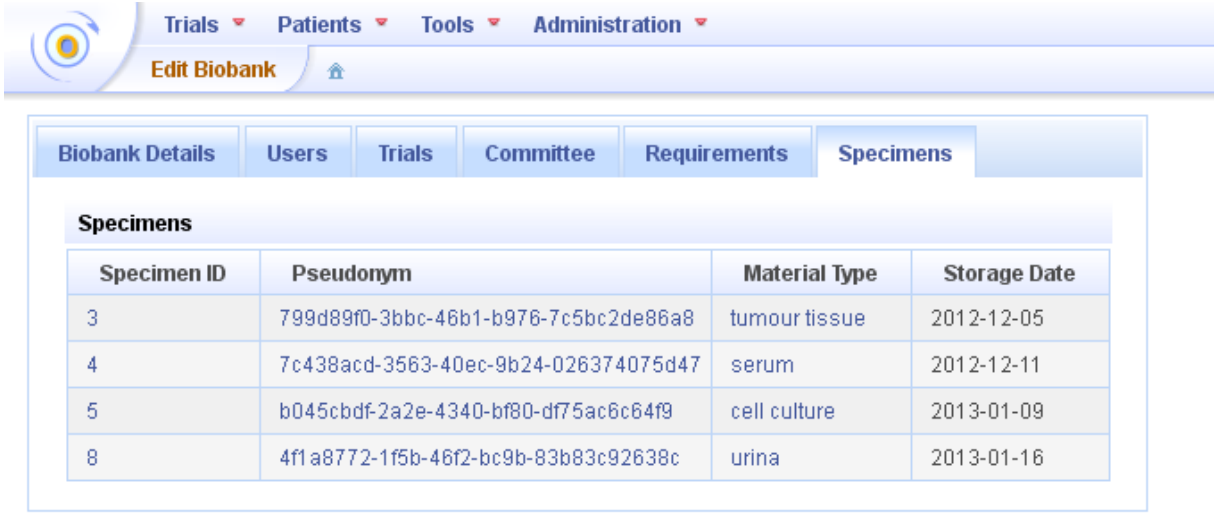

Figure 14: Biobank Specimens

6.2 Creating Specimens and Biobanking Specimen CRF

A specimen can be created by assigning the biobanking specimen CRF to a patient. This CRF can be found in the ObTiMA CRF Repository.

A precondition to create a specimen in a trial is that the biobanking specimen CRF is added to the trial in the design phase from the CRF Repository and adopted to the trial’s needs. It is possible to add, change and delete items on the biobanking specimen CRF; however, the items specimen id and biobank id are not allowed to be deleted.

When creating a specimen for a patient a specimen id is automatically assigned and filled in the according item. The specimen is associated to a biobank by selecting the according biobank id. In the according item all biobank ids are shown for which the user has rights to add specimen.

The Biobanking Specimen CRF is created for collecting specimen data in ObTiMA. The items on the CRF where the biomaterial data will be stored are structured in logical sections and subsections.

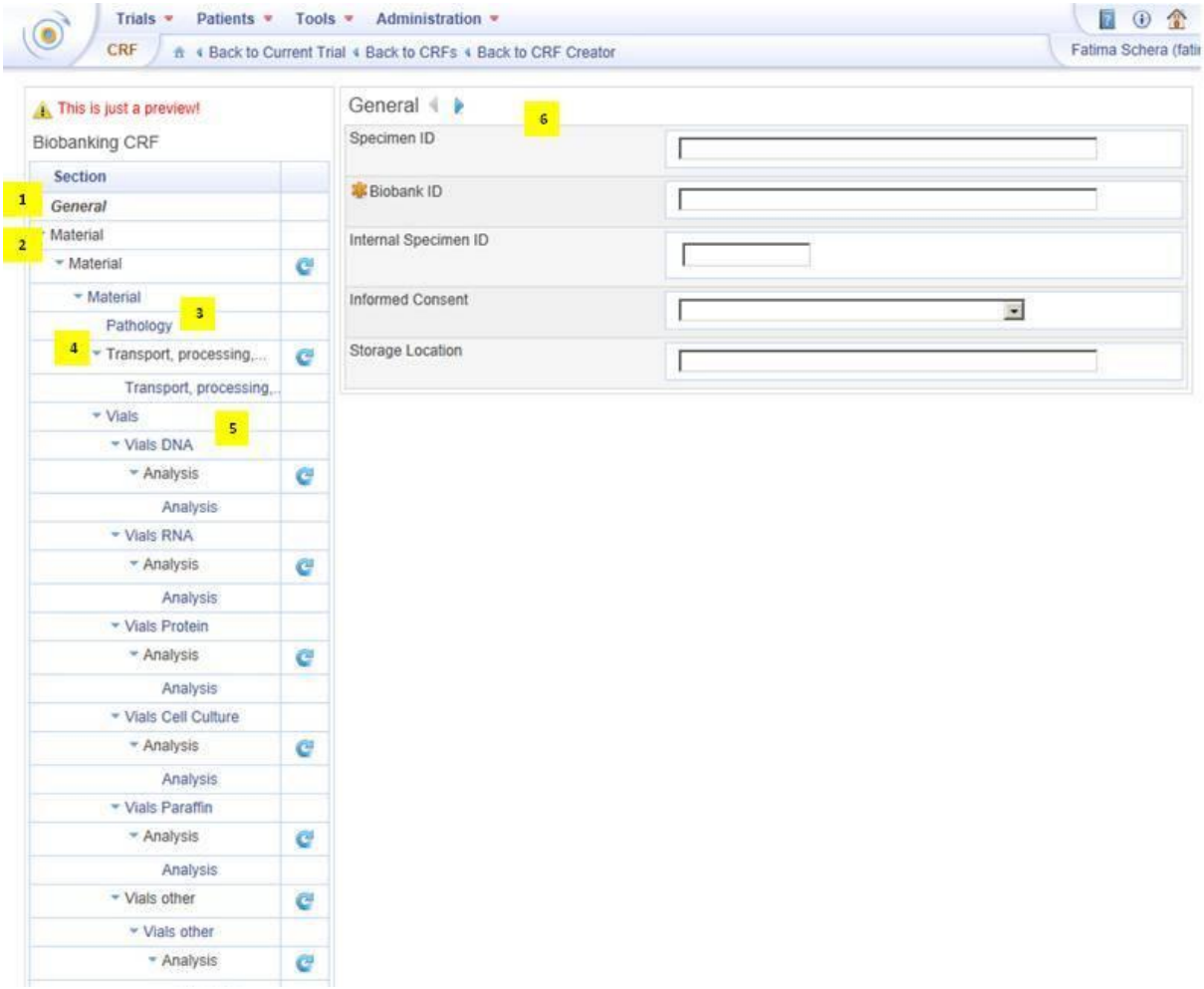

Figure 15: Biobanking CRF preview

Some of the sections have an attribute "repeatable" which is marked with the icon (Figure 15). It means that these sections can be filled in for a patient in a running trial multiple times. The main sections are "General" (1, Figure 15) and "Material" (2, Figure 15). The section "General" contains items with common information for all sample data collected on the CRF (6, Figure 15). The section "Material" is labelled as repeatable because one specimen CRF can collect information about multiple samples if they are obtained from this specimen or if they belong together according to any other criteria, e.g. the samples have been taken from the patient in the same time.

The section "Material" contains an own set of items (Figure 16) and the sub-sections "Pathology" (3, Figure 15), "Transport, Processing, Storage" (4, Figure 15, repeatable) and "Vials" (5, Figure 15). The sub-section "Vials" is specified for different types of vials (DNA, RNA, protein, cell culture, paraffin and other).

The items of the section "Material" are presented on the following picture (Figure 16):

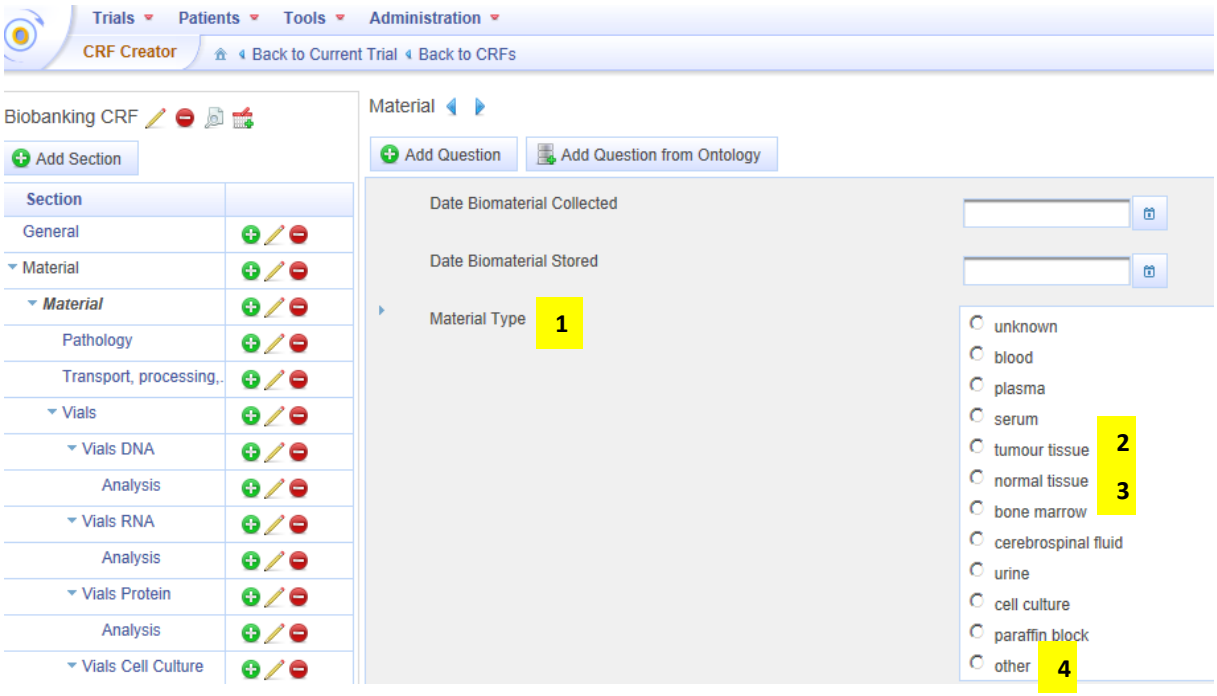

Figure 16: Biobanking CRF, section "Material"

When selecting the "normal tissue" (3, Figure 16) or "other" (4, Figure 16) options for the question "Material Type" (1, Figure 16) in the running trial, the sub-questions for specifying of the material type will be shown. When selecting the "tumour tissue" (2, Figure 16) option, the large set of embedded sub-questions appears (Figure 17):

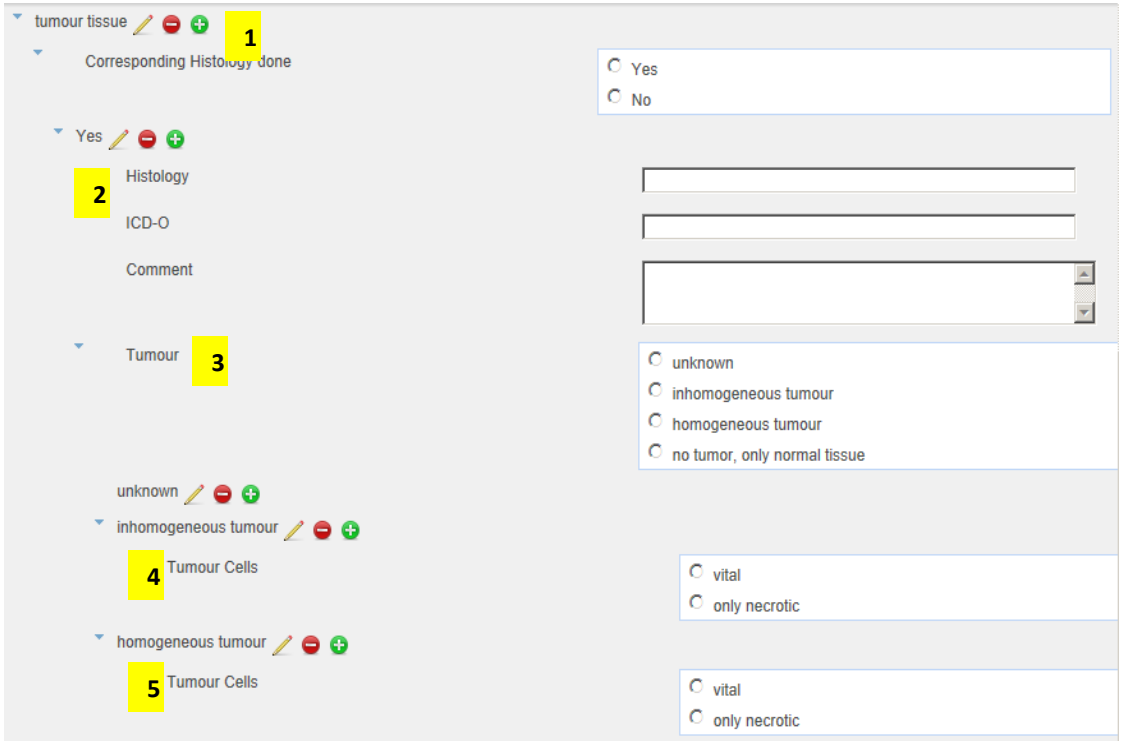

Figure 17: Biobanking CRF, section "Material", "tumour tissue" material type

If histology of a tumour tissue for a patient is done (1, Figure 17), the fields 2 and 3 (Figure 17) will be displayed. If for the question "Tumour" (3, Figure 17) the options "inhomogeneous

tumour" or "homogeneous tumour" will be selected, the fields 4 or 5 (Figure 17) will be shown.

On the following picture the section "Pathology" is shown (Figure 18):

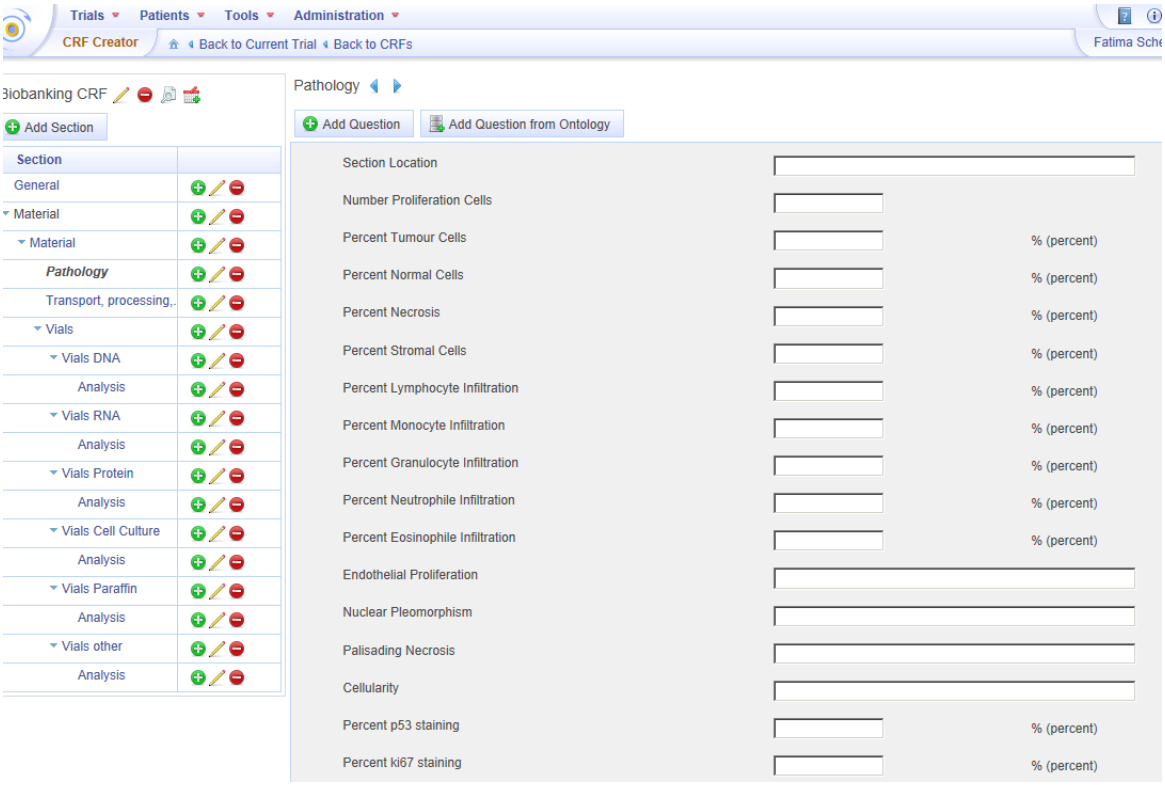

Figure 18: Biobanking CRF, section "Pathology"

The items 1-4 of the section "Transport, Processing, Storage" (Figure 19) contain some embedded sub-questions.

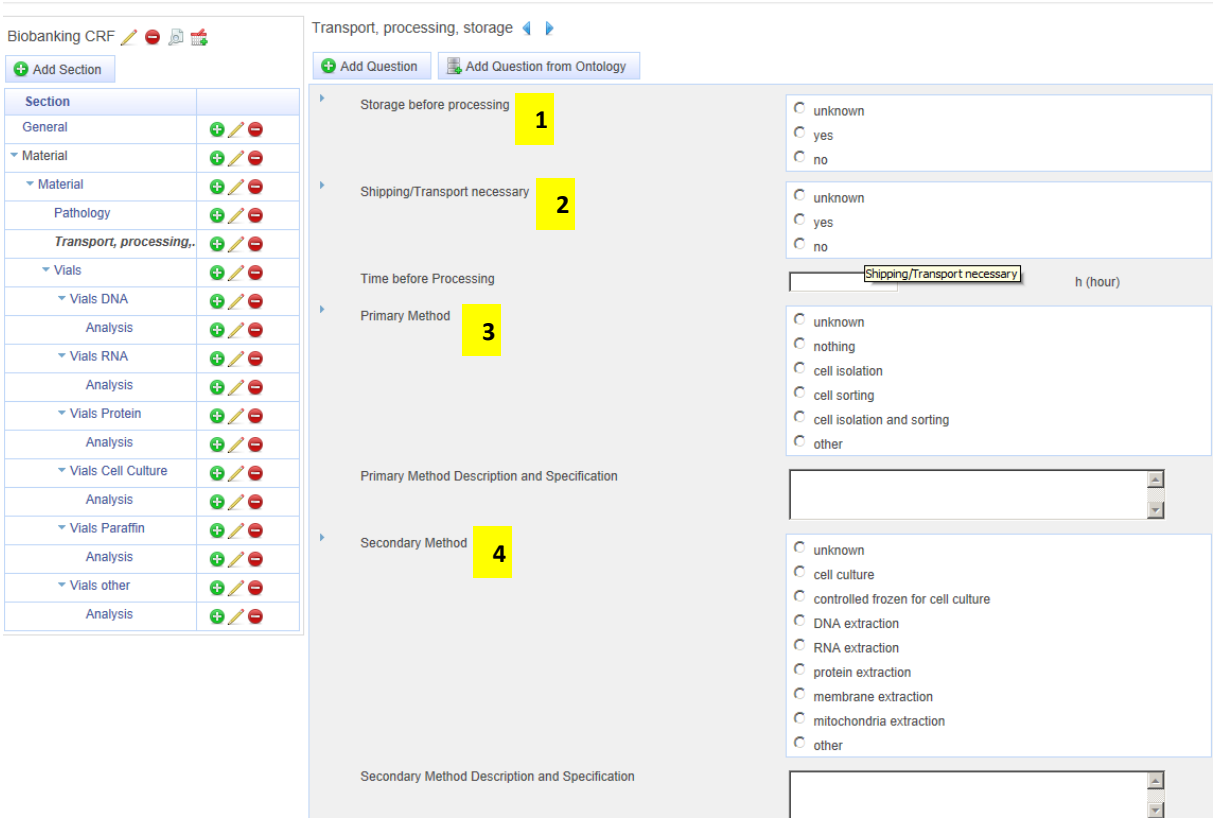

Figure 19: Biobanking CRF, section "Transport, Processing, Storage"

When the option "yes" for the question "Storage before processing" (1, Figure 19) is selected, the sub-question "Kind of Storage" will be shown (1, Figure 20):

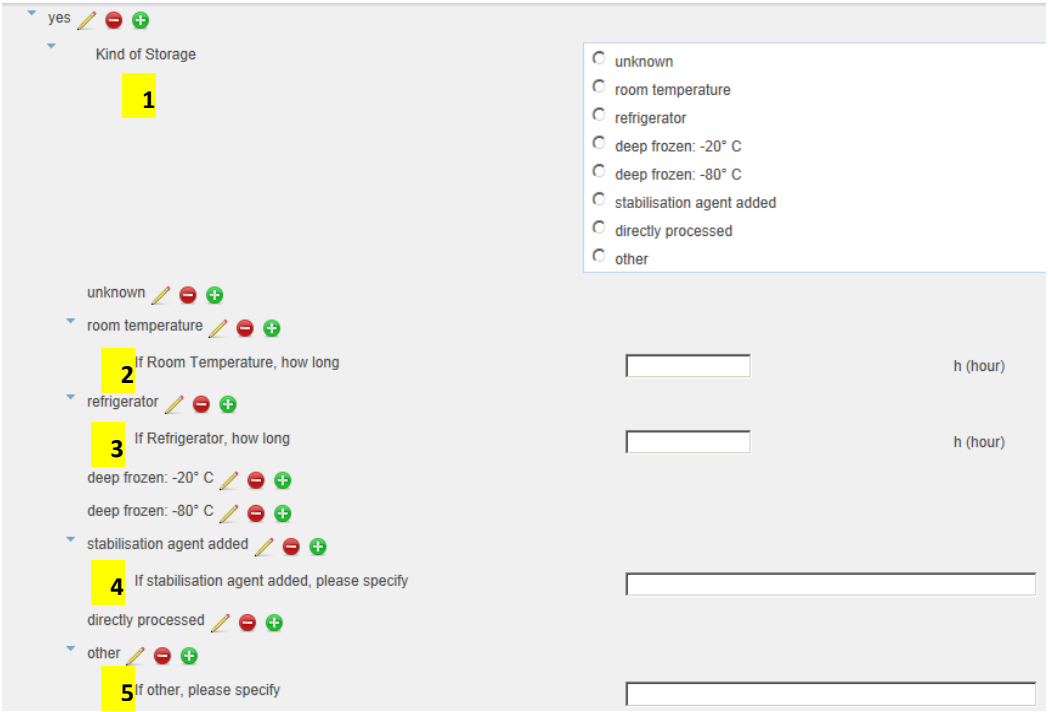

Figure 20: Biobanking CRF, section "Transport, Processing, Storage", kind of storage

For the answers "room temperature", "refrigerator", "stabilisation agent added" and "other" the fields for the following specifications will be displayed (2 - 5).

If the answer "DNA extraction" for the question "Secondary Method" or "other" (1, Figure 21) is selected, the sub-question(s) 2 or 3 (Figure 21) will be shown.

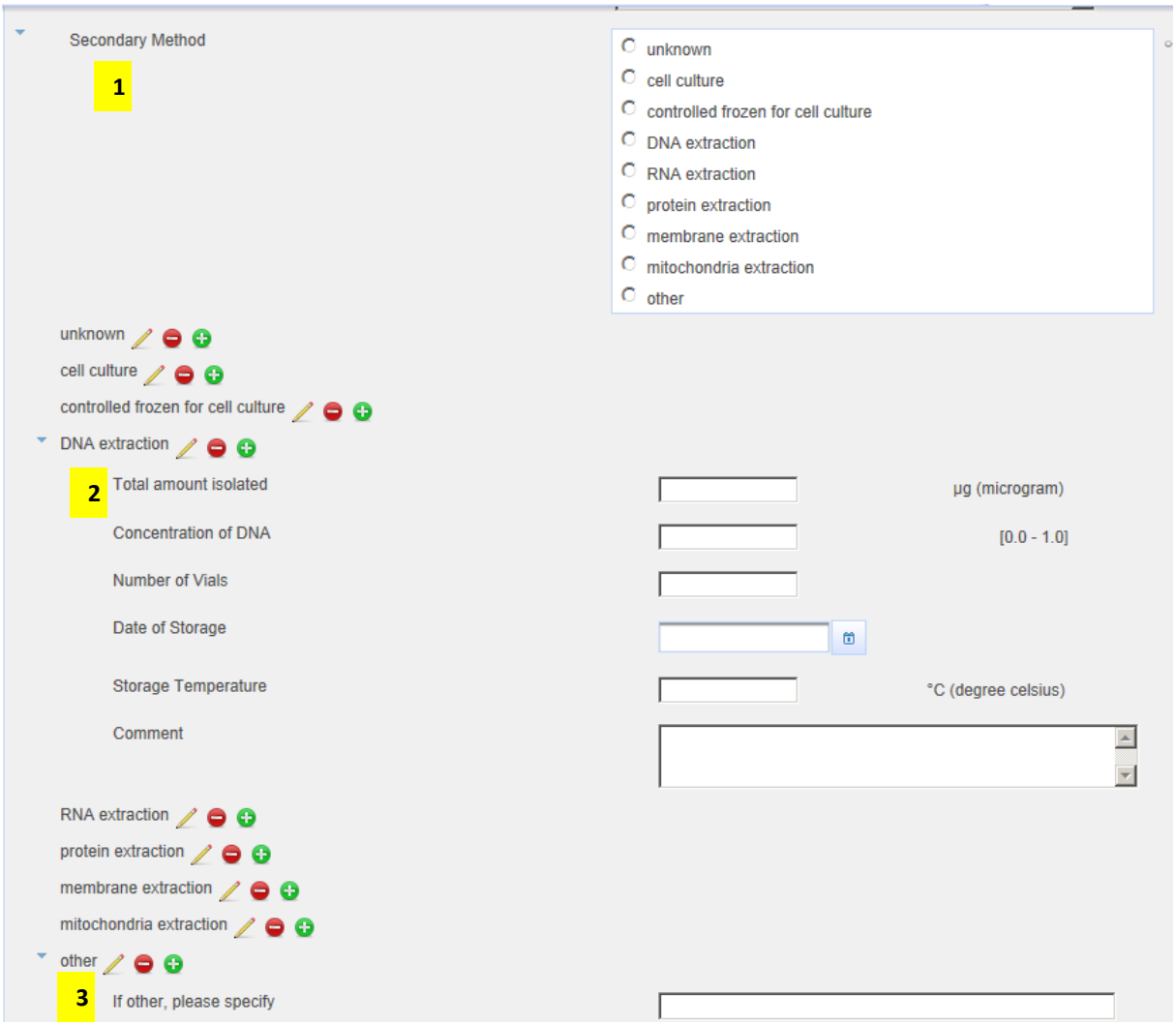

Figure 21: Biobanking CRF, section "Transport, Processing, Storage", DNA extraction as the secondary method

The sub-section under "Vials" contains questions for a corresponding vial type and a repeatable subsection "Analysis ".

Questions for the DNA vials are shown below (Figure 22):

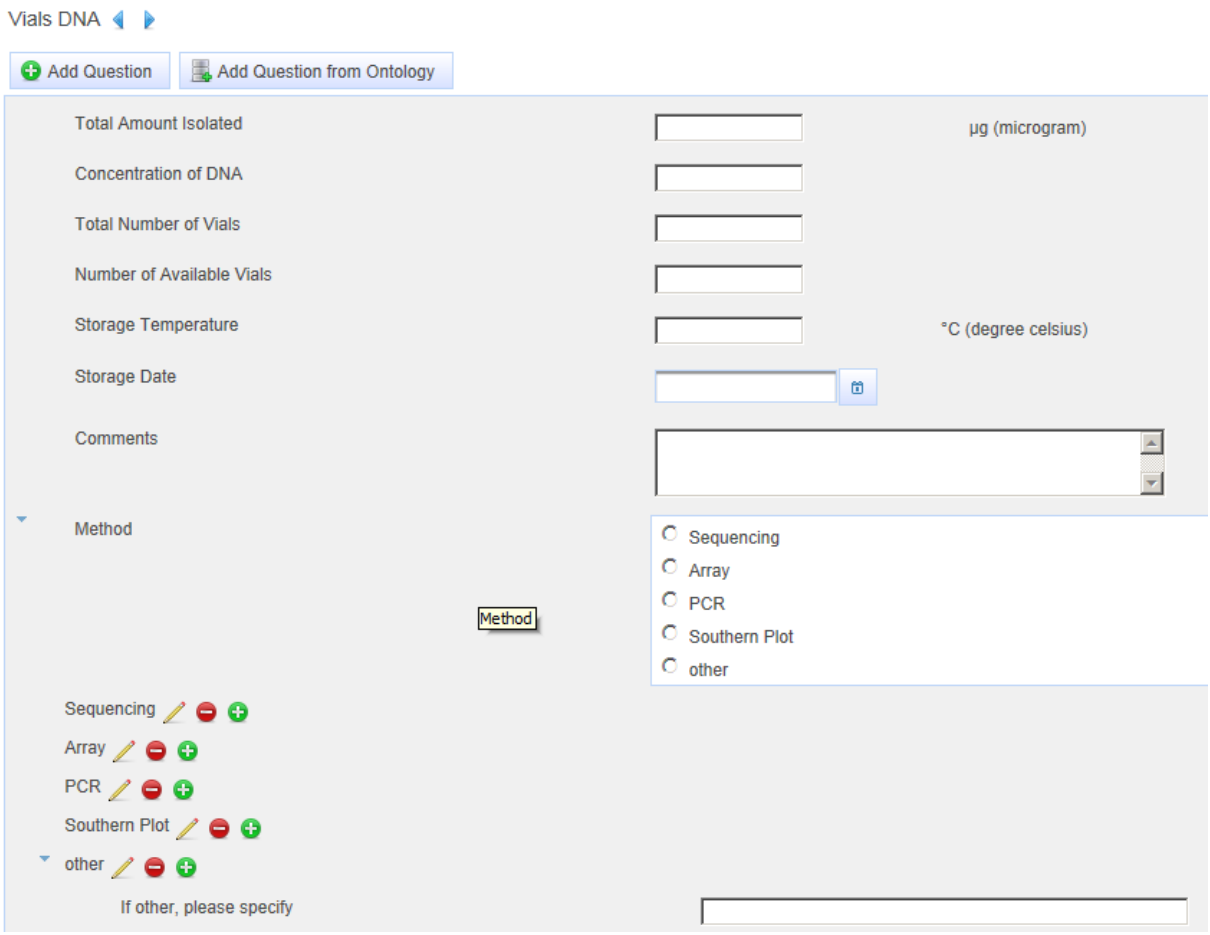

Figure 22: Biobanking CRF, section "Vials DNA"

Questions for the RNA vials are shown below (Figure 23):

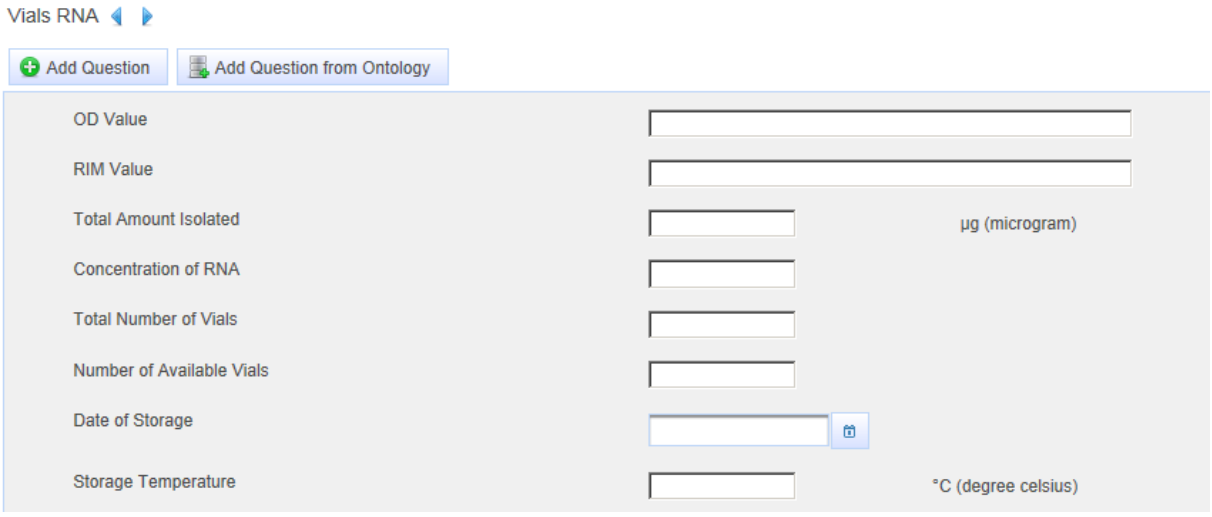

Figure 23: Biobanking CRF, section "Vials RNA"

Questions for protein, cell culture, paraffin and other vials are shown below (Figure 24):

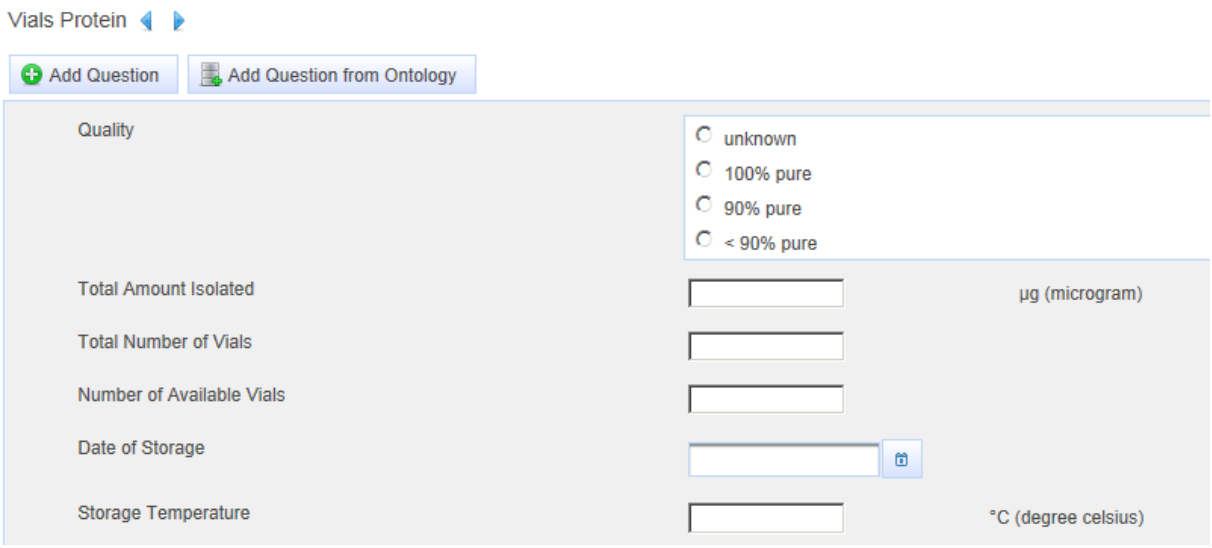

Figure 24: Biobanking CRF, sections "Vials Protein", "Vials Cell culture", "Vials Paraffin" and "Vials other"

Questions of the repeatable sub-section for vials are shown below (Figure 25):

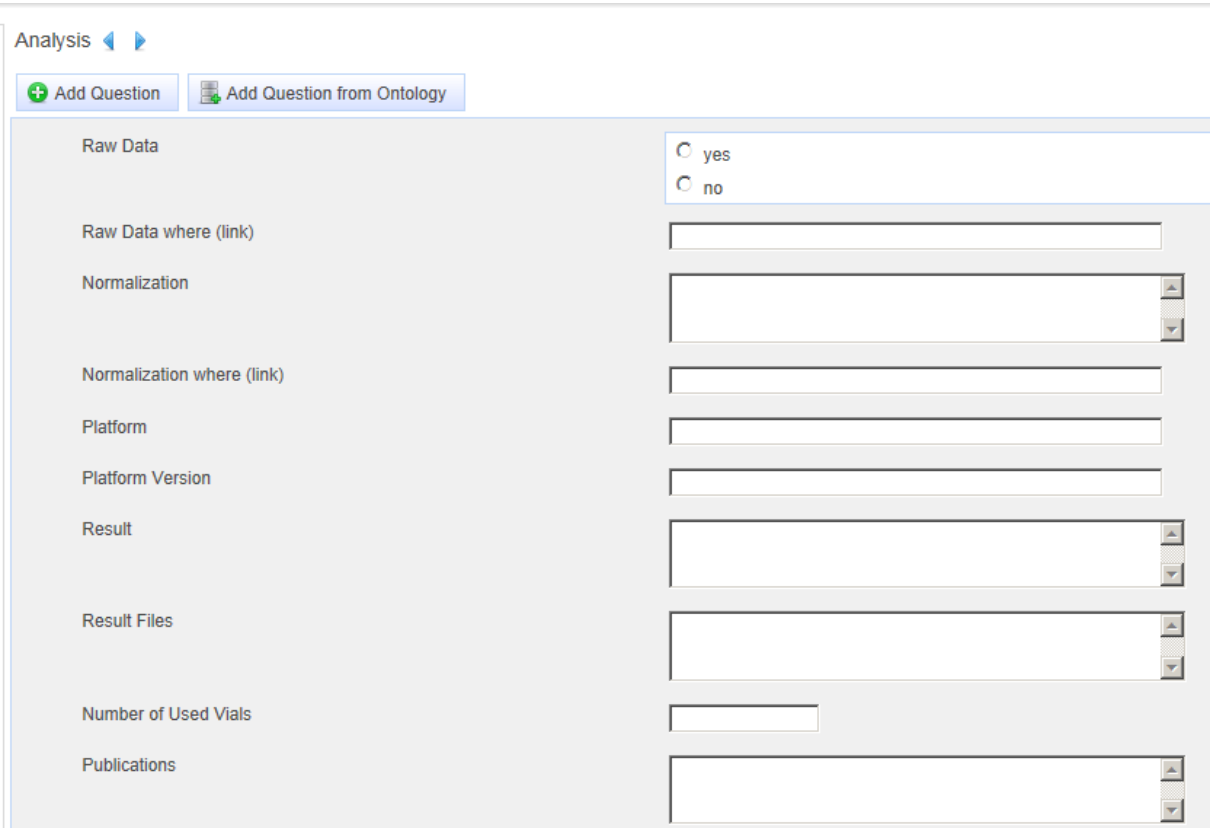

Figure 25: Biobanking CRF, repeatable sub-section for vials

The structure and the set of questions on the Biobanking Specimen CRF will be evaluated iteratively during the project progress.

6.3 Shipping Biomaterial

During trial conduction a trial chairman needs to ship biomaterial samples to a biobank owner. The biobank owner must not know the personal data of the patient. Therefore, when shipping the biomaterial the trial chairman needs to send the pseudonym to the biobank owner in order that he is able to find the according pseudonymized patient in ObTiMA. Since pseudonyms are very long, an according barcode is send.

For this purpose a trial chairman is able to print a barcode for the patient to ship it with the sample to the biobank owner on the page "Patient Details" (1, Figure 26). Additionally, the biobank owner can find the patient by scanning the barcode (Figure 27).

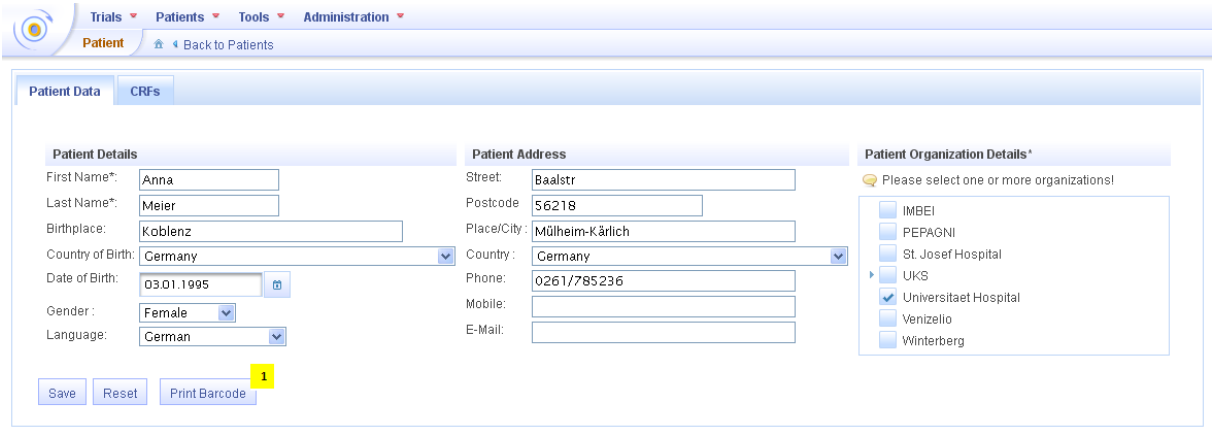

Figure 26: Patient Details

Figure 27: Patient's Barcode

6.4 Import Functionality for SIOP Scenario

For biobank owners, who have already collected biomaterial data an import interface is provided, where biobank owners can import data according to the SIOP biobanking data set.

Therefore, we have defined a set of Excel tables (or csv files) with corresponding linked files with analysis results. The format and the data types of the biomaterial data for importing are defined in Appendix 2. The format and data types are based on the SIOP biobanking data set which was also used for designing the Biobanking Specimen CRF.

6.5 Interface to p-BioSPRE

A trial chairman or biobank owner can export the specimen data of a trial to provide it in p-BioSPRE. For this purpose the data firstly needs to be loaded into his p-Biobank Wrapper installation. To this end the user can select a trial and all specimen data stored in the trial and the data is exported pseudonymized into a file in the CDISC ODM format. The user can upload the exported file into his p-Biobank Wrapper installation.

7 Conclusion

P-medicines biobank access framework p-BioSPRE enables and simplifies trans-institutional access to existing biobanks, but also to offer own biomaterial collections to research communities and manage biobank specimens over the ObTiMA Trial Biomaterial Manager. Along with biobank data, information on patients' informed consent is also processed and displayed if available.

The development of p-BioSPRE is driven by two user scenarios. In this deliverable we have described the development, functionality, and initial implementation of the basic components. In the next months it will be evaluated if p-BioSPRE fulfils the needs of the two scenarios. Components of the framework will then be further adopted to biobank requirements and fully implemented. In the following we will describe the evaluation backed by the two scenarios, and future work.

7.1 Evaluation

In the ALL biobanking scenario the study centres in Kiel and Berlin will evaluate the functionalities of the IDB, regarding user-friendly performance as well as data retrieval (see Appendix 3).

In the German SIOP group the ObTiMA Trial Biomaterial Manager will be tested and evaluated. The aim is to flexibly manage the German biomaterial repository through the Trial Biomaterial Manager instead of filling and exporting Excel tables. This allows combining the biomaterial data with clinical SIOP data in ObTiMA. Furthermore, analytical and research data can be uploaded into the Trial Biomaterial Manager, in particular LOH data and microarray data.

Therefore, firstly the biobanking specimen CRF and the different components of the ObTiMA Trial Biomaterial Manager will be evaluated on its practicability for the German SIOP group with test data. Then the existing SIOP group biomaterial Excel sheets will be imported into ObTiMA. In the last step the SIOP group will evaluate and test the ObTiMA Trial Biomaterial Manager for their daily work. Furthermore, p-BioSPRE and the p-BioBank Wrappers will be evaluated for sharing biomaterial in the German SIOP group.

7.2 Future Work

In the future p-BioSPRE will be fully integrated into the p-medicine environment, and the current web application will be accessible via the p-medicine portal. The application's management of user roles and rights will then be compliant with the p-medicine security framework being established by work package 5.

In the ALL biobanking scenario the study centres in Kiel and Berlin will start regular data export over the planned database architecture (Figure 28) as soon as the export interface for the Scopeland database will be available.

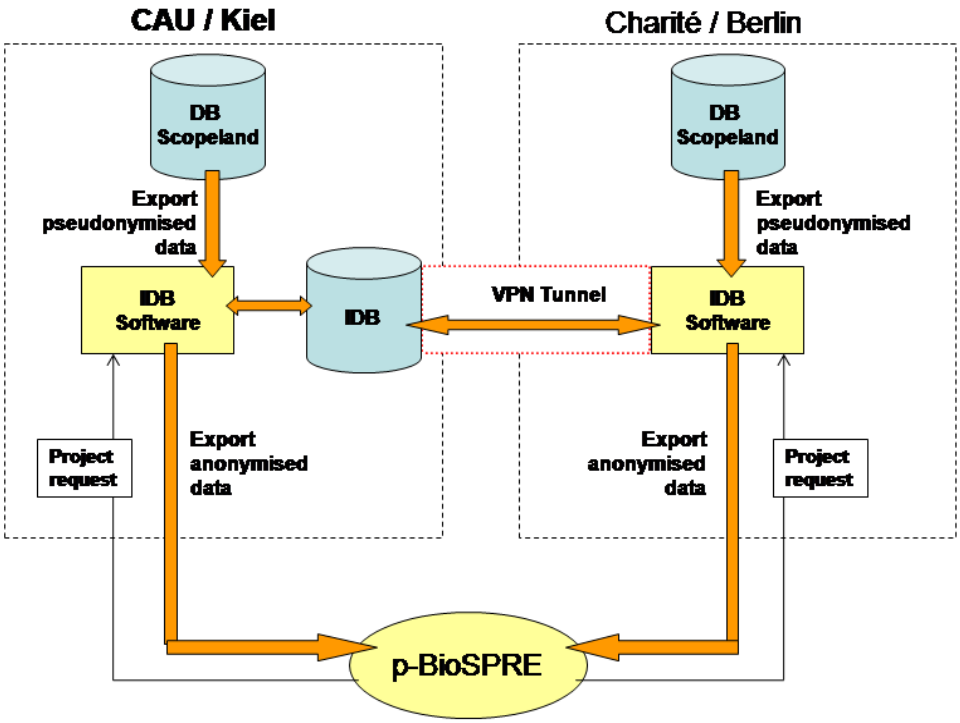

Figure 28: Trans-institutional database architecture for ALL use case.
(DB = Database; IDB = In-house Database, cf. chapter 5.2)

After final adoption of the IDB, ALL biobank data will be integrated into the search and request engine, together with Wilmstumor data.

In the future, an extended search interface will be developed for the Trial Biomaterial Manager to get an overview about the available biomaterial. The search interface allows to link clinical data and biomaterial data within clinical trials and across trials for further analysis. For linking the data across trials the search interface will exploit the HDOT ontology. Furthermore, push services that are able to push selected data from the Trial Biomaterial Manager into the data warehouse will be developed.

The process “Shipping Biomaterial” will be improved. With this functionality the trial chairman will be supported to ship biomaterial. He will be enabled to add a biobank sample CRF to the patient, where the trial chairman can specify sample details and select the biobank to which the sample will be shipped. From this data a letter for the receiving biomaterial owner including the patient’s barcode is generated automatically and can be printed from the trial chairman. The biobank owner, who receives the sample, can then find the according patient by scanning the barcode and fill in more details into the biobank sample CRF that was already created by the trial chairman.

A reporting functionality will be developed for the Trial Biomaterial Manager. That means a biobank owner may generate a report about the movements in his biobank. The report will show administrative data as e.g. which samples were stored or removed or which samples were send to whom, for which research purpose.

Appendix 1 - Abbreviations and acronyms

IDB	In-house Database
ObTiMA	Ontology based Trial Management Application
p-BioSPRE	p-medicine Biomaterial Search and Project Request Engine

Appendix 2 - Import Data Set Wilmstumor scenario

Table "general"

Nr.	Column name	Data type	Possible values	Format, comment
1	ExternalId	text		[ExternaId description]: [value], [dateOfBirth]: [value] Example: *SiopId: 9481*
2	DateOfBirth	text		
3	InternalSampleID	text		
4	InformedConsent	text	• not yet known • donated material, every analysis possible • analysis restricted • new informed consent for each analysis needed	
5	StorageLocation	text		

Table "material"

Nr.	Column name	Data type	Possible values	Format, comment
1	MaterialId	number		
2	InternalSampleID	text		
3	DateBiomaterialCollected	text		yyyy-MM-dd
4	DateBiomaterialStored	text		yyyy-MM-dd

5	MaterialType	text	• unknown • blood • plasma • serum • tumour tissue • normal tissue • bone marrow • cerebrospinal fluid • urine • cell culture • paraffin block • other	
6	NormalTissueSpec	text		Specification of a normal tissue: fill in only if 'normal tissue' is entered in column 5
7	OtherMaterialSpec	text		Specification of another tissue: fill in only if 'other' is entered in column 5
8	HistologyDone	text	• Unknown • Yes • No	
9	Histology	text		Fill in only if 'yes' is entered in column 8
10	ICDO	text		Fill in only if 'yes' is entered in column 8
11	Comment	text		Fill in only if 'yes' is entered in column 8
12	Tumour	text	• unknown • inhomogeneous tumour • homogeneous tumour • no tumor, only normal tissue	Fill in only if 'yes' is entered in column 8
13	InhomogeneousTumourCells		• vital • only necrotic	Fill in only if 'inhomogeneous tumour' is entered in column 12

14	HomogeneousTumourCells		• vital • only necrotic	Fill in only if 'homogeneous tumour' is entered in column 12

Table "transportprocessingstorage"

Nr.	Column name	Data type	Possible values	Format, comment
1	MaterialId	number		
2	StorageBeforeProcessing		• Unknown • Yes • No	
3	Kind of Storage		• unknown • room temperature • refrigerator • deep frozen: -20° C • deep frozen: -80° C • stabilization agent added • directly processed • other	Specify of other storage if 'other' is entered in column 3
4	RoomTemperatureDuration	Number (hours)		Fill in only if 'room temperature' is entered in column 3
5	RefrigeratorDuration	Number (hours)		Fill in only if 'refrigerator' is entered in column 3
6	StabilisationAgentSpec	text		Fill in only if 'stabilization agent added' is entered in column 3
7	ShippingTransportNecessary	text	• Unknown • Yes • No	
8	TransportKind	text	• unknown • without cooling • with cooling • deeply frozen	Fill in only if 'yes' is entered in column 7
9	TransportDuration	Number (hours)		Fill in only if 'yes' is entered in column 7
10	MaterialLabeledForTemperatureMeasurement	text	• Unknown • Yes • No	Fill in only if 'yes' is entered in column 7

11	MaterialConditionAfterTransport	text	• unknown • good • defrosted • deeply frozen during whole transport • cold chain interrupted	Fill in only if 'yes' is entered in column 7
12	TimeBeforeProcessing	Number (hours)		
13	PrimaryMethod	text	• unknown • nothing • cell isolation • cell sorting • cell isolation and sorting • other	Specify of other primaty method if 'other' is entered in column 13
14	PrimaryMethodDescription	text		
15	SecondaryMethod	text	• unknown • cell culture • controlled frozen for cell culture • DNA extraction • RNA extraction • protein extraction • membrane extraction • mitochondria extraction • other	Specify of other secondary method if 'other' is entered in column 15
16	TotalAmountIsolated	number, mg		Fill in only if ' DNA extraction' is entered in column 16
17	DnaConcentration	number, 0-1		Fill in only if ' DNA extraction' is entered in column 16
18	VialsNumber	number		
19	StorageDate	text, date		yyyy-MM-dd
20	StorageTemperature	number,°C		
21	SecondaryMethodDescription	text		

Table "pathology"

Nr.	Column name	Data type	Possible values	Format, comment
1	MaterialId	number		
2	SectionLocation	text		
3	NumberProliferationCells	number, %		
4	PercentTumourCells	number, %		
5	PercentNormalCells	number, %		
6	PercentNecrosis	number, %		
7	PercentStromalCells	number, %		
8	PercentLymphocyte	number, %		
9	PercentMonocyte	number, %		
10	PercentGranulocyte	number, %		
11	PercentNeutrophile	number, %		
12	PercentEosinophile	number, %		
13	EndothelialProliferation	text		
14	NuclearPleomorphism	text		
15	PalisadingNecrosis	text		
16	Cellularity	text		
17	PercentP53Staining	text		
18	PercentKi67Staining	text		

Table "dnavials"

Nr.	Column name	Data type	Possible values	Format, comment
1	MaterialId	number		
2	VialId	number		
3	TotalAmountIsolated	number, microgram		
4	DnaConcentration	number, 0-1		
5	VialsTotalNumber	number		
6	VialsAvailableNumber	number		
7	StorageDate	text, date		yyyy-MM-dd
8	StorageTemperature	number,°C		
9	Comment	text		
10	Method	text	• Sequencing • Array • PCR • Southern Plot • other	
11	OtherMethodSpec	text		Specification of other method: fill in only if 'other' is entered in column 9

Table "rnavials"

Nr.	Column name	Data type	Possible values	Format, comment
1	MaterialId	number		
2	VialId	number		
3	OdValue	text		
4	RimValue	text		
5	TotalAmountIsolated	number, microgram		

6	RnaConcentration	number, 0-1		
7	VialsTotalNumber	number		
8	VialsAvailableNumber	number		
9	StorageDate	text, date		yyyy-MM-dd
10	StorageTemperature	number,°C		

Table "dnarnaanalysis" + attached file(s) with results

Nr.	Column name	Data type	Possible values	Format, comment
1	AnalysisId	number		
2	VialId	number		
3	RowData	text	• Yes • No	
4	RowDataWhere	text (link)		
5	Normalization	text		
6	NormalizationWhere	text (link)		
7	Platform	text		
8	PlatformVersion	text		
9	Result	text		
10	ResultFile	text		
11	VialsUsedNumber	number		
12	Publications	text (link)		

Table "vials"

Nr.	Column name	Data type	Possible values	Format, comment
1	MaterialId	number		
2	VialType	text	• protein • cell culture • paraffin • other	

3	Quality	text	• unknown • 100% pure • 90% pure • < 90% pure	
4	TotalAmountIsolated	number, microgram		
5	VialsTotalNumber	number		
6	VialsAvailableNumber	number		
7	StorageDate	text, date		yyyy-MM-dd
8	StorageTemperature	number,°C		

Table "analysis" + attached file(s) with results

Nr.	Column name	Data type	Possible values	Format, comment
1	AnalysisId	number		
2	VialId	number	•	
3	Substances	text	• Peptide • Protein • Lipid • Carbohydrate • Element	
4	MoleculesMarker	text		
5	Method	text	• Electrophoresis • Chromatography • Centrifugation • Spectroscopy • Mass-Spectroscopy • Hybridisation • other	
6	ElectrophoresisSubmethod	text	• Discontinous Electrophoresis • Agarrosegel Electrophoresis • Capillar Electrophoresis • Gradient Electrophoresis • Pulsed-field Electrophoresis • Density Gradient Electrophoresis • Electrofocussing	Fill in only if 'Electrophores' is entered in column 10

			• Lipid Electrophoresis • Serum Electrophoresis • Twodimensional Electrophoresis • Freeflow Electrophoresis • Electroosmosis • Isoelectric Focussing • Monitoring Electrophoresis • SDS-PAGE	
7	HybridisationPlot	text	• Western Plot (Protein) • Nothern Plot (DNA) • Southern Plot (RNA) • other	Fill in only if 'Hybridisation' is entered in column 10
8	OtherMethodSpec	text		Specification of other analysis method: fill in only if 'other' is entered in column 10
9	RowData	text	• Yes • No	
10	RowDataWhere	text (link)		
11	Normalization	text		
12	NormalizationWhere	text (link)		
13	Platform	text		
14	PlatformVersion	text		
15	Result	text		
16	ResultFile	text		
17	VialsUsedNumber	number		
18	Publications	text (link)		

Appendix 3: ALL data set

Description	Variable Name	Format	Example
Patient ID	patient_id	varchar(8)	7T9KN8HR
Trial Name	trial	varchar(50)	IntReALL 2010
Trial ID	trial_id	varchar(20)	KI9890
Treatmant arm / Stratification / Risk group	stratification	varchar(10)	z.B. S1, -1, HR, SR, MR
	Stage	varchar	primary disease, 1st relapse
Immunphenotype	immunophenotype	varchar(50)	z.B. pre, pro, common
Sex	sex		male, female, unknown
	age	decimal, 1NKS	1,3 2,5
Trial Follow-Up	trial_follow_up	integer	
	leukocytes	integer	5000 7000 9000 0
	blasts_pb	varchar	char(5)
	blasts_bm	varchar	char(5)
	extramedullary_compartment	varchar (20)	CNS, Testis, other, …
	genetic_subtype	varchar(50)	BCR-ABL1; TCF3..
	ikzf1	varchar	amplification, normal, deletion, unknown,…
	CRLF2	varchar	
	NOTCH1	varchar	

	TP53_diagnose	varchar	
	TP53_remission	varchar	
	TPMT	varchar	
	MLPA_screening		yes/no
	MLPA_kit	varchar	
Gene expression profiling	Gene_expression_profiling		yes/no
	Gene_expression_platform	varchar	
	SNP_diagnose		yes/no
	SNP_platform_diagnose	varchar	
	SNP_remission		yes/no
	SNP_platform_remission	varchar	
	Epigenetic_profiling		yes/no
	Epigenetic_platform	varchar	
	Whole_exome_seq		yes/no
	exom_Sequencing_platform		
	Whole_genome_seq		yes/no
	Genome_Sequencing_platform		
	Micro_RNA_profiling		yes/no
	Micro_RNA_platform		
	prednison_response	varchar	good/poor
	Cytological_response	varchar	good/poor
	mrd_response	varchar	good/intermediate/poor
	bm_cells_diagnosis		yes/no
	bm_cells_remission		yes/no
	bm_xeno_diagnosis		yes/no

	bm_xeno_remission		yes/no
	bm_dna_diagnosis		yes/no
	bm_dna_remission		yes/no
	bm_rna_diagnosis		yes/no
	bm_rna_remission		yes/no
	bm_cdna_diagnosis		yes/no
	bm_cdna_remission		yes/no
	bm_plasma_diagnosis		yes/no
	bm_plasma_remission		yes/no
	bm_smear_diagnosis		yes/no
	bm_smear_remission		yes/no
	bm_protein_diagnosis		yes/no
	bm_protein_remission		yes/no
	bm_cytospin_diagnosis		yes/no
	bm_cytospin_remission		yes/no
	pb_cells_diagnosis		yes/no
	pb_cells_remission		yes/no
	pb_xeno_diagnosis		yes/no
	pb_xeno_remission		yes/no
	pb_dna_diagnosis		yes/no
	pb_dna_remission		yes/no
	pb_rna_diagnosis		yes/no
	pb_rna_remission		yes/no
	pb_cdna_diagnosis		yes/no
	pb_cdna_remission		yes/no
	pb_plasma_diagnosis		yes/no
	pb_plasma_remission		yes/no

	pb_smear_diagnosis		yes/no
	pb_smear_remission		yes/no
	pb_protein_diagnosis		yes/no
	pb_protein_remission		yes/no
	pb_cytospin_diagnosis		yes/no
	pb_cytospin_remission		yes/no
	csf_cells_diagnosis		yes/no
	csf_cells_remission		yes/no
	csf_dna_diagnosis		yes/no
	csf_dna_remission		yes/no
	csf_rna_diagnosis		yes/no
	csf_rna_remission		yes/no
	csf_cdna_diagnosis		yes/no
	csf_dcna_remission		yes/no
	csf_supernatant_diagnosis		yes/no
	csf_supernatant_remission		yes/no
	csf_cytospin_diagnosis		yes/no
	scf_cytospin_remission		yes/no
	pl_cells_diagnosis		yes/no
	pl_cells_remission		yes/no
	pl_dna_diagnosis		yes/no
	pl_dna_remission		yes/no
	pl_rna_diagnosis		yes/no

	pl_rna_remission		yes/no
	pl_cdna_diagnosis		yes/no
	pl_dcna_remission		yes/no
	pl_supernatant_diagnosis		yes/no
	pl_supernatant_remission		yes/no
	pl_cytospin_diagnosis		yes/no
	pl_cytospin_remission		yes/no
	ti_dna_diagnosis		yes/no
	ti_dna_remission		yes/no
	ti_rna_diagnosis		yes/no
	ti_rna_remission		yes/no
	ti_cdna_diagnosis		yes/no
	ti_dcna_remission		yes/no
	ti_piece_diagnosis		yes/no
	ti_piece_remission		yes/no