PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/174452

Please be advised that this information was generated on 2019-01-03 and may be subject to change.
The Parelsnoer Institute (PSI) is a collaborative biobanking project of all eight University Medical Centers in the Netherlands which was launched in 2007. Basically, PSI consists of three dimensions: participating institutions, disease entities and a central organization. An executive board for operational management instigates collective strategic and tactic policies and a central team of PSI experts and advisors supports the researchers and the board in establishing and implementing standards and procedures. PSI offers researchers an infrastructure and standard procedures for the establishment, expansion and optimization of clinical biobanks for scientific research. To ensure patient privacy clinical data is pseudonymized and carefully stored in a central database. Human biomaterials are collected according to nationally agreed standards.

Currently PSI covers fifteen large disease specific cohorts (the so-called ‘Parels’ or ‘Pearls’) and new ‘Pearls’ are being developed. The Parelsnoer Institute currently (December 2016) has stored more than 538,000 biospecimens with annotated clinical data of more than 30,000 patients. All these materials and data are available for anyone with a bona fide research proposal.

Keywords: Harmonized standards; clinical biobanking; translational medical research; health innovation; generic information architecture; international security and privacy standards

Funding statement: PSI started in 2007 with a five year initial grant from the Dutch Government. From 2011 onwards PSI is supported and facilitated by the Netherlands Federation of University Medical Centers (NFU) and its member institutions. This means that sustainability of PSI as core infrastructure for applied clinical research in the Netherlands is not dependent on external funds. Additional funds from charities, governmental sources and industrial sponsors are used to expand PSI with new disease groups and for the analyses of the collections in actual research projects.
Each UMC stores biomaterials in their own certified biobank(s) according to the PSI biobanking protocol, which was developed by biobank coordinators from all UMCs together and covers all phases of biobanking. Each Pearl provides a different variety of biomaterials such as serum, plasma, DNA, faeces, urine, cerebrospinal fluid, pancreatic cyst fluid, viable cells, fresh frozen tissues and/or FFPE tissues. Metadata (e.g., type of material) from biomaterials and the unique sample code are registered in the central database together with the clinical data [18].

For each Pearl a specific information model is defined for the detailed clinical dataset including personal data and clinical data pertaining the specific disease [19]. The data are collected both via electronic and manual methods and are hosted in a validated web based application (ProMISe) that fulfills international standards for data management, quality assurance, and privacy protection using a Trusted Third Party [20, 21].

**Classification (1)**

Human.

**Classification (2)**

Biological samples and associated clinical data.

**Context**

**Spatial coverage**

Description:

All eight University Medical Centers across the Netherlands: Academic Medical Center (Amsterdam), Erasmus Medical Center (Rotterdam), Leiden University Medical Center, Maastricht University Medical Center, Radboud University Medical Center (Nijmegen), University Medical Center Groningen, University Medical Center Utrecht, VU University Medical Center (Amsterdam).

Northern boundary: +53.4647366.

Southern boundary: +50.757197.

Eastern boundary: +7.222824.

Western boundary: +3.364563.

**Temporal coverage**

Eight disease-specific bioresources started their collection in 2009. Five others started later and new collections will start in the (near) future. The end date might differ between the collections, however, so far no expected end date has been determined for any collection.

**Temporal coverage for accessibility**

The bioresources are available for use in bona fide research projects; no end date determined.
(2) Methods

Steps
For each Pearl a specific information model is defined, called PRISMA: Parelsnoer Repository for Information Specification, Modelling and Architecture. PSI adheres to the principle of reusing electronic health record (EHR) information for scientific purposes ("registration at the source", [1]). Therefore, PRISMA is developed with reuse of information and with minimization of registration burden as prime directives, while also taking routine care procedures into account. The architecture is in compliance with (inter-)national classifications such as International Classification of Diseases and Related Health Problems (ICD-10), SNOMED CT and the Logical Observation Identifiers Names and Codes (LOINC®).

Each Pearl defines its own set of biosamples to be collected and stored in the biobank. Biomaterials are preferably collected during routine clinical procedures. Samples are stored in certified UMC biobanking facilities which collectively constitute the federative PSI biobank. The biobanking protocol of PSI is implemented in all the participating institutions and covers all phases of biobanking; from collection to storage of

<table>
<thead>
<tr>
<th>Sample</th>
<th>Volume/number</th>
<th>Processing</th>
<th>Time</th>
<th>Aliquoting</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>10 ml clotted blood</td>
<td>2000 × g at room temperature or 4°C for 10 minutes</td>
<td>Within 2–4 hours</td>
<td>≥ 5 × 0.5 ml</td>
<td>–80°C</td>
</tr>
<tr>
<td>EDTA plasma</td>
<td>10 ml</td>
<td>2000 × g at room temperature or 4°C for 10 minutes</td>
<td>Within 2–4 hours</td>
<td>≥ 5 × 0.5 ml</td>
<td>–80°C</td>
</tr>
<tr>
<td>Citrate plasma</td>
<td>9 ml</td>
<td>2000 × g at room temperature for 10 minutes</td>
<td>Within 2–4 hours</td>
<td>≥ 5 × 0.5 ml</td>
<td>–80°C</td>
</tr>
<tr>
<td>DNA (blood)</td>
<td>10 ml EDTA blood</td>
<td>Whole blood or cell pellet, to UMC specifications</td>
<td>Within 4 weeks (4°C or 3 months (&lt; –20°C))</td>
<td>≥ 2 stock aliquots</td>
<td>4°C or lower</td>
</tr>
<tr>
<td>Faeces</td>
<td>Not specified</td>
<td>Direct storage or after homogenization</td>
<td>Within 12 hours</td>
<td>≥ 5 × 5 gr</td>
<td>–80°C</td>
</tr>
<tr>
<td>Urine +/− antioxidants (AO)</td>
<td>Not specified, midstream</td>
<td>2000 × g at room temperature or 4°C (AO) for 10 minutes</td>
<td>Within 4 hours</td>
<td>6 aliquots 0.9 ml</td>
<td>–80°C</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>3–20 ml</td>
<td>2000 × g at room temperature or 4°C for 10 minutes</td>
<td>Within 2 hours</td>
<td>≥ 6 × 0.5 ml</td>
<td>–80°C in polypropylene tubes</td>
</tr>
<tr>
<td>Biopsy FFPE</td>
<td>n* per location#</td>
<td>Formalin fixation and paraffin embedding</td>
<td>Immediate fixation</td>
<td>Per set</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Biopsy frozen</td>
<td>n* per location#</td>
<td>Snap frozen in isopentane</td>
<td>Immediate</td>
<td>Per set</td>
<td>–80°C</td>
</tr>
<tr>
<td>Resection specimen FFPE</td>
<td>n* per location#</td>
<td>Snap frozen in isopentane</td>
<td>At pathology</td>
<td>0.5 cm³ samples</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Resection specimen frozen</td>
<td>n* per location#</td>
<td>Snap frozen in isopentane</td>
<td>At pathology</td>
<td>0.5 cm³ samples</td>
<td>–80°C</td>
</tr>
<tr>
<td>Pancreatic cyst fluid</td>
<td>≥ 0.5 ml</td>
<td>None</td>
<td>Within 2–4 hours</td>
<td>0.5 ml portions</td>
<td>–80°C</td>
</tr>
<tr>
<td>Viable cells (PBMCs or bone marrow)</td>
<td>20–40 ml heparinized sample</td>
<td>Density centrifugation at room temperature</td>
<td>Within 24 hours</td>
<td>10 × 10^6 cells per cryovial</td>
<td>–130°C</td>
</tr>
</tbody>
</table>

Table 1: Summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.†

† Deviations to be registered: hemolytic, lipemic, icteric, wrong tube, volume incorrect, storage temperature deviation, longer storage time, mixing/homogenization incorrect, centrifugation process different, storage problem, other deviation as free text.

* as specified by Pearl.
# for instance normal or affected or inflamed or tumor in intestinal tract or skin.

PBMCs: peripheral blood mononuclear cells.
the samples. Metadata (e.g., type of material) from biomaterials and the unique sample code are registered in the central database together with the clinical data. The detailed clinical dataset includes personal data (e.g., age, gender, education level, ethnic origin, weight, height) and clinical data pertaining the specific disease (e.g., diagnosis, lab results, complications, physical examination, (medical) treatment, questionnaires). The data are collected both via electronic and manual methods and are hosted in a validated web based application (ProMISe) [20].

PSI also provides an infrastructure and procedures to uniformly collect and store images, for instance MRI images. Standardized source images are safely stored in the local Picture Archive and Communication System (PACS) in the UMCs. After anonymization, the images are subsequently uploaded in the TraIT Bio-Medical Imaging Archive (BMIA), which is a safe and sustainable online archive [22].

**Stabilization/preservation**

Table 1 gives a summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.

**Type of long-term preservation**

See Table 1.

**Storage temperature**

See Table 1.

**Shipping temperature from patient/source to preservation or research use**

See Table 1.

**Shipping temperature from storage to research use**

–80°C (on dry ice).

**Quality assurance measures**

Quality of data and quality of stored biomaterials are by no means self-evident. In PSI, the two most important critical success factors for adequate data quality are: to limit the number of elements in the information model to what is necessary for future research and to fully integrate the collection of data in the routine of the EHR. Other essential elements for adequate quality are: use international standards (Detailed Clinical Models), develop simple and logical instructions for data collection and registration, mandate and authorize dedicated research employees, and perform regular quality checks.

For biomaterials there is no possibility to improve quality afterwards. Only a strict adherence to the biobank protocol and related SOPs can assure quality of material available for research. This is under the assumption that SOPs describe (either evidence or consensus based) what is optimal for integrity of the biomaterials. In PSI, biobank coordinators from all UMCs together have developed the PSI biobanking protocol and revise them every two years. This involvement of all biobank coordinators in establishing the protocol enhances adherence to the described procedures. The PSI biobanking protocol covers all phases of biobanking: collection, pre-analysis, registration, processing and storage of the samples (Table 1).

**Source of associated data**

The associated data are mainly coming from electronic health records, laboratory reports, and questionnaires. Each UMC has its own research IT infrastructure that

---

**Figure 2:** IT Infrastructure of PSI.
delivers the data to their local database in ProMISe, which is a web based application. In some UMCs data are entered manually into the local database (mostly by research nurses and/or clinicians) while other UMCs benefit from automatic data capture directly from the EHR resources. The information supplied by each UMC is periodically uploaded, after validation, to the central database in ProMISe (one database per Pearl, which is the combination of the 8 local UMC Pearl databases) for storage on a national level (Figure 2). During upload of data to the local and central databases, identifying data are encrypted by special software of a Trusted Third Party (Trusted Reversible Encryption Service®, Houten, Utrecht, The Netherlands). As to further protect the privacy of the patients, the identifying data are encrypted again when exported from the central database for delivery to the researchers. In specific situations, e.g., in case of incidental findings that need feedback to the patient or necessary data-linkage, depseudonymization is possible by authorized personnel only. The PSI IT infrastructure is compliant with international security and privacy standards.

(3) Bioresource description

Object name
The Parelsnoer Institute.

Bioresource name
The Parelsnoer Institute (PSI).

Bioresource location
All eight University Medical Centers across the Netherlands participate in PSI:

1. Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
2. Erasmus Medical Center, ’s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
3. Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
4. Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands
5. Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, The Netherlands
6. University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
7. University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
8. VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Bioresource contact
Parelsnoer Institute, Jaarbeursplein 6, 3521 Al Utrecht, The Netherlands.
Email: info@parelsnoer.org

Bioresource URL

Identifier used
N/A.

Bioresource type
PSI is a collaborative clinical biobank, comprising a number of disease specific national bioresources (the Pearls). All types of pathology and disease samples are stored (see Table 1). To date (October 2016) the following fifteen disease categories are included:

- Abdominal aortic aneurysm
- Congenital heart disease
- Cerebrovascular accident
- Diabetes
- Hereditary colorectal cancer
- Inflammatory bowel disease
- Ischemic heart disease
- Leukemia, myeloma and lymphoma
- Multiple endocrine neoplasia
- Neurodegenerative diseases
- Oesophageal and gastric cancer
- Pancreatic cancer and pancreatitis
- Renal failure
- Rheumatoid arthritis and arthrosis
- Parkinson’s disease

Type of sampling
PSI consists of disease based cohorts with longitudinal collections, sampled in clinical care.

Anatomical site
The fifteen Pearls cover several anatomical sites of the human body.

Disease status of patients/source
See the fifteen Pearls/diseases mentioned above.

Clinical characteristics of patients/source
A full clinical characterization, including extensive diagnostics, demographics, therapeutics and clinical follow-up is specified for each disease specific bioresource.

Vital state of patients/source
All patients are alive at inclusion.

Clinical diagnosis of patients/source
PSI covers several significant diseases, presently fifteen: Abdominal aortic aneurysm, Congenital heart disease, Cerebrovascular accident, Diabetes, Hereditary colorectal cancer, Inflammatory bowel disease, Ischemic heart disease, Leukemia, myeloma and lymphoma, Multiple endocrine neoplasia, Neurodegenerative diseases, Oesophageal and gastric cancer, Pancreatic cancer and pancreatitis, Renal failure, Rheumatoid arthritis and arthrosis, Parkinson’s disease.

Pathology diagnosis
The architecture is in compliance with (inter-)national classifications such as International Classification of Diseases and Related Health Problems (ICD-10), SNOMED...
CT and the Logical Observation Identifiers Names and Codes (LOINC®).

Control samples
The Parelsnoer Institute does not collect control samples from healthy individuals. If needed controls can be obtained from LifeLines, a national longitudinal population biobank in the Netherlands [24].

Biospecimen type
Each Pearl provides a different variety of biomaterials such as serum, plasma, DNA, RNA, faeces, urine, cerebrospinal fluid, pancreatic cyst fluid, viable cells, fresh frozen tissues and/or FFPE tissues. Table 1 gives a summary of procedures on collection, processing and storage of samples defined in the biobanking protocol of PSI.

Size of the bioresource
In total, clinical data of more than 32,000 patients and 538,000 biospecimens of more than 30,000 patients are available. PSI has no end date. The current number of included patients per Pearl is shown in Table 2.

Release date
Data and samples are currently available. PSI releases data and samples to research projects on a regular basis. Thus far, the research projects have led to many scientific publications [3–17].

Access criteria
A catalogue, i.e., an open access searchable database on the internet, provides up-to-date information about the content of all PSI collections [18]. This gives researchers the opportunity to discover for what type of patients which type and amount of data and biomaterials are available. Every researcher worldwide may submit a study proposal to the Pearl and request data, biomaterials and/or images. A scientific committee of the Pearl (consisting of representatives of the Pearl and independent scientific experts) judges whether the proposed study is relevant, compliant with the scientific aims of the Pearl, methodologically sound, compliant with privacy protection rules and feasible in relation to the amount of biomaterial requested. In addition, permission from the Research Ethical Committee of the coordinating UMC has to be obtained and from some other participating centers according to local policy. When permissions have been granted and request forms are completed, the PSI data manager will deliver the data (and images if needed) from the central PSI facilities to the researcher. The biobank coordinators of the UMCs will deliver the requested biomaterials. If scientific analyses in research projects yield new data, PSI demands these newly acquired (individual) data to be made available for future research purposes.

Costs vary depending on the type and amount of samples. An economic quotation is sent covering shipping costs and partially costs for biobanking-related services (sample handling, consumables).

(4) Reuse potential
Samples from the same donor may be used in several different projects. As a condition of supply of material, the recipient of samples and/or data must agree to return findings to PSI on conclusion of the research purpose. These newly acquired (individual) data are then available for future research purposes. Besides, the applicant must

<table>
<thead>
<tr>
<th>Pearl</th>
<th>Number of patients with clinical data</th>
<th>Number of patients with biomaterials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>5400</td>
<td>5400</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5815</td>
<td>5374</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6673</td>
<td>6226</td>
</tr>
<tr>
<td>Hereditary colorectal cancer</td>
<td>1853</td>
<td>1534</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>4642</td>
<td>4139</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>632</td>
<td>412</td>
</tr>
<tr>
<td>Leukemia, myeloma and lymphoma</td>
<td>1755</td>
<td>1596</td>
</tr>
<tr>
<td>Neurodegenerative disease</td>
<td>1213</td>
<td>1122</td>
</tr>
<tr>
<td>Esophageal and gastric cancer</td>
<td>122</td>
<td>93</td>
</tr>
<tr>
<td>Pancreatic cancer and pancreatitis</td>
<td>318</td>
<td>282</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1991</td>
<td>1963</td>
</tr>
<tr>
<td>Rheumatoid arthritis and arthrosis</td>
<td>2277</td>
<td>2190</td>
</tr>
</tbody>
</table>

Table 2: The number of included patients per Pearl.*
* dd December 12, 2016.
† Three Pearls (i.e., Multiple Endocrine Neoplasia, Abdominal Aortic Aneurysm and Parkinson’s Disease) started recently and to date (December 2016) have not yet included patients.
acknowledge PSI in all publications resulting from the use of these data and samples and provide a copy of the published paper to PSI.

**Ethics Statement**

PSI provides a regulatory framework in which ethical guidelines, in accordance with (inter-)national legislation and rules, are described [23]. Supported by a member of the PSI Central Team, each Pearl composes a patient information brochure, a consent form and regulations. These documents together with the strategic plan of the Pearl are reviewed by the Medical Ethical Committee of the coordinating UMC. Subsequently, Medical Ethical Committees and Board of Directors of the remaining participating UMCs have to approve local implementation of the Pearl’s biobanking activities. Patients included in the Pearl give written informed consent prior to inclusion.

**Constraints**

Only patients who provided written informed consent are included, no healthy controls. Participants may withdraw their consent at all times. The patient can express the wish to withdraw to his/her doctor, in which case the doctor will ensure that data and materials are destroyed unless needed for validation of earlier issuance.

**Competing Interests**

The authors have no competing interests to declare.

**Author Roles**

Judith Manniën: PSI Data Manager
Tessa Ledderhof: PSI Operational Manager
Hein Verspaget: PSI Bioresource Manager
Roger Snijder: PSI Information Architect
Erik Flikkenschild: PSI ICT Coordinator and Privacy-Security Officer
Nicole van Scherrenburg: PSI Management Assistant
Ronald Stolk: member of PSI Board
Gerhard Zielhuis: PSI Managing Director

**References**

2. Boeckhout, M, Reuzel, R and Zielhuis, G 2014 The donor as partner. How to involve patients and the public in the governance of biobanks and registries. Leiden: BBMRI-NL.