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Primary Studies

Radboud Biobank: a central facility for prospective clinical biobanking in the Radboud university medical center, Nijmegen

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Abstract

Introduction

There is a growing need for large-scale data and biobanks for biomedical research. Therefore, a central biobank facility at the Radboud university medical center, Nijmegen, the Netherlands, was established to contribute to biomedical research and innovation by creating an infrastructure for collecting, storing and managing biomaterial and associated clinical data. The Radboud Biobank was conceived from the standards that were laid down in the String of Pearls Initiative (PSI), a unique partnership between the eight University Medical Centers (UMCs) in the Netherlands, that contributes to innovation in health care by facilitating biomedical research. The aim of the Radboud Biobank is to offer researchers an infrastructure wherein sub-collections are professionally secured for the long-term according to high quality standards.

Conclusion

The Radboud Biobank has set procedures for handling, storage and release of samples and data. These procedures are generic and established with a view on standardization, quality and efficiency, transcending the interests of single departments. Furthermore, (quality) standards are set in the field of ICT, legal and ethical aspects, communication and distribution. The establishment of the RadboudBiobank creates an efficient and high quality facility for scientific research and medical innovation.

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Introduction

A decade ago authoritative experts demonstrated that most pharmaceuticals/drugs are ineffective in at least half of the treated patients[1]. In this context, it is often observed that some patients respond well and show substantial health improvement, while an identical treatment has no or limited effect on other patients with the same disease. What could be the cause of this variation? Is it the differences in the genetic makeup between patients, as a result of which some patients lack enzyme activity that is needed to metabolize the drug into the active compound? And if so, what are the biomarkers that can predict which patient will profit from therapy and which will not?

To answer such relevant biomedical questions, access to DNA, serum or other biomaterial from a large cohort of well characterized patients is essential. However, this material would easily take a decade to prospectively collect. Therefore, large pre-existing collections of biomaterial from well characterized patients, would enable the investigator to carefully select those patients with associated clinical data and stored material that are indispensable for answering their specific research question. That is the idea of a biobank.
And how about biobanks and healthy aging? We all want to stay in good health, also in the final years of our lives. We do not just want to grow old, we want to age healthily. But which factors determine our health status at a later age? Are these factors genetic or related to nutrition, to the amount of physical exercise taken, or to other environmental aspects? Are immune, hormonal or metabolic pathways responsible for good health at an advanced age? Again, to study these kind of questions, we need large biomaterial collections of large, well characterized groups of patients as well as of age-matched healthy individuals.
Hospital integrated biobanks are crucial for science-based health care solutions in the 21st century[2,3]. In order to improve the diagnosis, prevention and treatment of complex, multi-factorial diseases a better understanding is needed of genetic and environmental factors causing these disorders and diseases. Ideally hospital integrated biobanks focus on specific disease categories, enabling efficient case-control studies (e.g. for investigating gene-environment interactions) as well as prognostic studies (e.g. for investigating gene-treatment interactions).
Hospital integrated biobanks form a bridge between patient care and research. Patients are motivated to donate samples and give access to clinical data4. They are willing to contribute to research and development that may bring prevention, cure, or management of their disease closer; if not for their own sake, then for the sake of future patients and their relatives. Clinical investigators have similar ambitions using their patients' biomaterial for studies on the pathogenesis of diseases and their treatments.

For university hospitals, biobanks belong to the core facilities bridging health care and research. To this end, after several years of preparation, the Radboud Biobank officially launched its activities in 2012. The ultimate goal of the Radboud Biobank is to facilitate personalized medicine, i.e. clinical decisions and practices that are tailored to the individual patient by use of

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genetic or other information obtained from the patient's biomaterial.

In this article, the organizational, financial, legal and ethical aspects of the Radboud Biobank are described. Furthermore, the current paper gives insight into the procedures of the Radboud Biobank regarding collection and storage of biomaterial and associated clinical data.

Discussion

Basic principles along the lines of the String of Pearls Initiative

The basic principles of the Radboud Biobank are: 1) Hospital wide activities, i.e. all disease groups and clinical departments are represented, 2) Patient inclusion is integrated in daily clinical practice, 3) Adherence to international quality standards, 4) Cooperation with other clinical biobanks to accomplish large collections, 5) Standardized and transparent procedures within the Radboud Biobank and connected biobanks, 6) Sustainability: independent of outside grants or sponsors and guaranteed for at least 15 years, 7) Open for every researcher with a good scientific idea within or outside the hospital, and 8) Patient representatives in the driver's seat.

In the execution of many of these basic principles the Radboud Biobank follows the guidelines, procedures and standards developed within the String of Pearls Initiative (PSI), a unique partnership between the eight University Medical Centers (UMCs) in the Netherlands. Since 2007, the eight UMCs based in the Netherlands have joined forces in PSI. This initiative aims to develop tools for high quality biobanking, hence a national cooperative infrastructure for collecting, storing and managing biomaterial and associated clinical data, where strictly defined procedures are established[5].

Types of Clinical Biobanks within the Radboud Biobank

Clinical ('hospital integrated') biobanks, defined as the systematic collection, storage and retrieval of biomaterial of well characterized patients, form the essential source for high quality clinical research. The Radboud Biobank comprises all types of collections, thus defined:

De novo biobanks: after careful appraisal of the scientific ambitions and the consequences for the choice of specific patient categories, prospective inclusion of new patients with explicit consent to donate additional biomaterial and associated data, on top of that obtained for diagnostics, for future research purposes;

Secondary use biobanks: left over material obtained in the diagnostic or therapeutic process, for which the patients did not object to secondary use for purposes of future research;

Clinical trials and non-experimental follow-up studies: material of patients participating with full informed consent in studies with a specific research purpose; after closure of the trial, consent may be requested to keep the remaining material for future research.

Organizational Model

The Radboud Biobank is installed by the Board of Governors of the Radboud university medical center (Radboudumc) as part of the research infrastructure. It is a central facility for the Radboudumc, with guaranteed central support for at least 15 years. The Department of Laboratory Medicine hosts the Radboud Biobank, as a separate entity, servicing all departments of the UMC. All material and data is available for (local, national and international) research groups with good scientific ideas. All procedures and collections are published on the website6. A board of stakeholders (chaired by a patient representative) sets biobank policy and monitors the performance of the Radboud Biobank. This organizational model of the Radboud Biobank is depicted in figure 1.

Business model

The Radboud Biobank is established as an infrastructure to stimulate scientific medical research by contributors to the biobank and other researchers. The underlying business model is that research will profit much from the availability of a biobank, that meets the highest quality standards. Clinical departments cover all costs for the inclusion of patients (i.e. obtaining informed consent, biomaterial and associated clinical data), but the costs for organization, sample handling and (prolonged) storage are paid by the Radboud Biobank. Research groups using the samples and data pay a fee per sample, depending on the nature and quantity of the requested samples, and on the affiliation of the applicants (i.e. internal vs. external / non-commercial vs. commercial). In addition, a fixed administrative fee is charged for each delivery. All revenues are used as return of investment. With a 30% utilization rate (of all samples) after five years, the total income is estimated to be in balance with the total costs of the Radboud Biobank.

Ethical and legal issues

The use of large epidemiological sample collections in genome research has raised numerous issues concerning the status of informed consent in re-using samples for purposes other than what they were originally intended for[7]. In order to deal with these issues for the Radboud Biobank the so called Research Ethics Committee-light (REC-light) was installed.

The REC-light is a formal institutional review board with senior multidisciplinary expertise to review non-experimental studies using biomaterial with associated patient data. The purpose of the REC-light is to make decisions on the formal ethical assessment for i) the establishment of a sub-collection, at the start of a new initiative to collect biomaterial and associated clinical data from clinical patients for future scientific studies, and ii) each time a specific request is made for use of the material and the accompanying data in a specific research proposal. Criteria used for approval of applications are listed in table 1.

The committee deals with this ethical assessment of biobank related issues in a way that guarantees both quality (i.e.

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principles of Good Research Practice) and efficiency (i.e. high frequency of meetings, digital procedure). A positive assessment is followed by an immediate authoritative decision and fast delivery of the material to the researcher.

In general, patients are asked to give broad consent[8,9]. The biomaterial and associated clinical data that have been stored in the Radboud Biobank are released for research purposes only after being approved by the REC-light.

Biomaterial

The Radboud Biobank encompasses biomaterial, the related description of the patient of origin (disease-specific and phenotypic data) and the data subsequently collected (genotypic and gene expression data and biomarkers). Currently, a variety of biomaterials is stored in the Radboud Biobank. DNA is sampled and stored in all instances, but the specific collection of other materials depends on the category of disease. In 2017, we anticipate to have a collection of around 120 000 DNA samples, 110 000 plasma samples and 65 000 serum samples in the Radboud Biobank. Besides these sample types other materials, among which, urine, cerebrospinal fluid and tissue samples are stored. In specific cases other human body fluids (e.g. faeces, saliva) or microbiome DNA (i.e. from skin, throat, vaginal or faeces) are also anticipated to be incorporated in the biobank. The growth of the sample collection of the Radboud Biobank, differentiated by sample type, until 2017 is showed in Table 2. The anticipated total growth of the collection of the Radboud Biobank (number of inclusions) plus the number of deliveries is depicted in figure 2.

The Radboud will launch a catalogue that provides an overview of the collections of biomaterial and associated clinical data stored in the Radboud Biobank. This catalogue will disclose what type of material for which patients groups is included in the Radboud Biobank and available

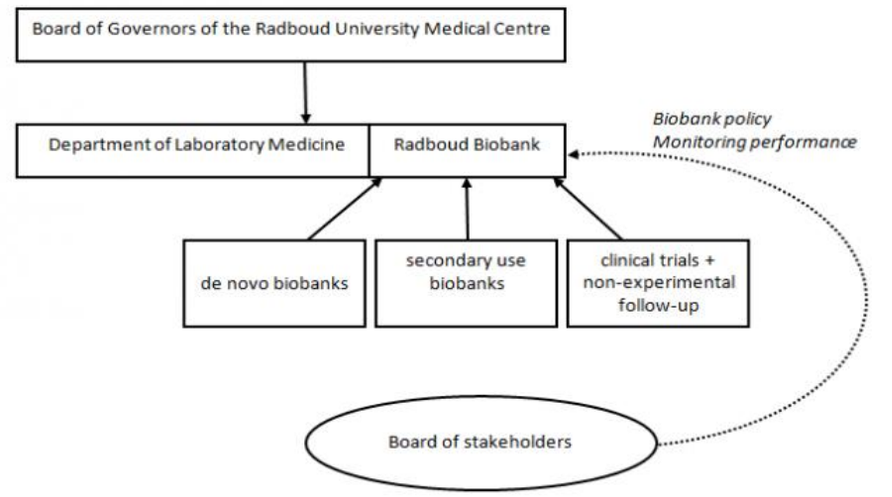

Figure 1: Organizational model of the Radboud Biobank.

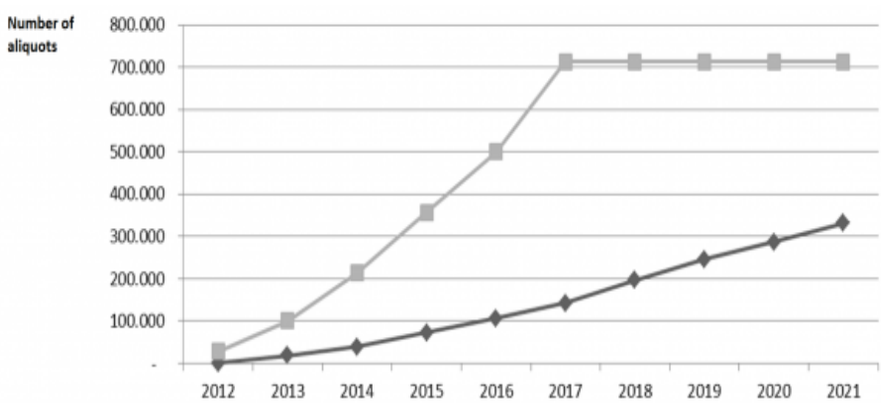

Figure 2: Increase in number of inclusions versus number of deliveries. On average there will be 5 aliquots per included sample. square: number of inclusions (aliquots per year) rhom: number of deliveries (aliquots per year).

for biomedical research in the public domain. The catalogue of the Radboud Biobank will be available in the autumn of 2013.

The Radboud Biobank guarantees the privacy of the participants. Biomaterial and associated clinical data are stored using unique codes. The key connecting these codes to patient identifiers is kept by the owner of the sub-collection. The software package for the research database produces the unique code also noted on the application form accompanying the biomaterial. The Radboud Biobank laboratory technician enters the same code in the laboratory sample management software system. Each month the Radboud Biobank functional manager synchronize the research database and the sample management system using study numbers. Pseudonymisation is considered necessary as hospital patient identifier are not considered to protect privacy sufficiently. For external use the identifiers of the Radboud Biobank are encrypted by a Trusted Third Party using TRES (Trusted Reversible Encryption Services)[10].

The collection of the samples takes place in the setting of routine clinical care. The clinical departments are responsible for this part of the biobanking process. Once a sample

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Table 1: Criteria used by the REC-light[1] to test applications
· ***Applications from departments or research groups for membership of the Radboud Biobank***
o Scientific relevance in a specified domain of medicine. Foreseen contribution of biobank samples in the reduction of the burden of disease for future patients with this type of disease[2]; o Proper procedure for informed consent; o Minimal risks of the donation; o Appropriate governance of the biobank and the delivery procedures, including adequate measures for privacy protections.
· ***Applications for use of the material and accompanying data of a biobank***
o Scientific and clinical relevance of the study; o Proposal that fits the original aim (and informed consent) of the collection; o Validity of the study design and proposed analyses; o Relevance of the requested material (type, volume, numbers) for this study; o Expertise of the applicant and the organization for this study; o Appropriate measures for privacy protection.
[1]REC-light: Research Ethics Committee-light. [2] Note that the purpose is defined necessarily broad, as no one can predict what future research questions will appear

arrives at the central sample reception of the Department of Pathology or Laboratory Medicine, responsibility for the material is transferred to the Radboud Biobank. Sample handling and storage, is performed according to standard operating procedures (SOPs) and summarized in table 3. These generic procedures are established in order to standardize sample collection and handling, and to guarantee a collection of samples of high and reproducible quality.

Note that according to these SOPs, patient plasma and serum samples are divided into 5 aliquots before storage at -80°C. For DNA, the SOP describes the storage at -20°C of both a stock solution and a normalized fraction (100 ng/µl). Figure 3 shows the flow of the biomaterial and associated clinical data of new patients with explicit consent for the Radboud Biobank. Freezers of the Radboud Biobank are located in a central facility provided with real time XiltriX data logging, monitoring and alarm system (IKS international) and emergency power.

The laboratory sample management software system "ItemTracker" (ItemTracker Software Ltd., South Nutfield, United Kingdom) is used to record all sample related data, such as storage location, sample type and characteristics. A subset of the data in this database will be made available to the applying researcher upon release of the samples.

Clinical data

To facilitate research leading to medical innovation, patient-related data are being collected. The department responsible for a specific sub-collection has defined a minimal dataset (MDS). This dataset comprises patient information collected in the context of routine daily clinical practice, among which are base-line data (history of the patient, the physical examination, diagnostic laboratories, imaging, pharmacy) as well as data obtained during the follow-up of the patient. Setting up a MDS requires a delicate balance between quality, comprehensiveness, and feasibility.

To facilitate follow-up, active connection to existing medical registries is sought. This includes, among others, connections to registries for vital status, cause of death, hospitalization, cancer diagnoses and pathology records[11].

The clinical research data management software system ProMISe (Dpt. of Medical Statistics, Section Advanced Data Management, Leiden University Medical Center, Leiden, The Netherlands) is used for storing all descriptive data in the Radboud Biobank[12]. This database has a web based interface which can be functionally customized to suit the various needs of the different sub-domains. The interface allows authorized (multi center) sub-domain contributors to collect and store data through various means of input, for example direct data entry or bulk upload of data. Extensive reporting tools and quality checks are also at the disposal of the sub-domain data manager. Upon release of samples to an applicant, a subset of the corresponding clinical data is made available to the receiver, according to a previously agreed query and format. ProMISe and the organization which maintains and develops the system (section Advanced Data Management, Leiden University Medical Center), are NEN 7510 certified.

As mentioned above, figure 3 depicts the flow of the collected biomaterial and associated clinical data of patients who gave written consent for collection of samples for the Radboud Biobank.

Donor representation

In general, a large number of samples with the associated clinical data is needed to detect associations between genetic factors and a particular disease or disorder. Thus the effectiveness of a biobank depends on the enthusiasm and motivation of patients and patient organizations to contribute. Patients are the central focus of the Radboud Biobank and without their trust and participation it is impossible to establish a good collection. Therefore, we actively involve patients in the affairs of the Radboud Biobank. The chairman of the Radboud Biobank Policy Council represents the group of patient representatives (appointed by the Patient Council of University Medical Centers (CRAZ)), disease-specific patient groups are involved in disease-specific research and a web

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Table 2: Predicted growth of sample collection of the Radboud Biobank, differentiated by sample type

Sample type[1]	Total number of samples[2]	
	2013	2017
DNA[3]	8,100	120,000
Plasma	7,200	110,000
Serum	4,500	65,000
Urine	450	6,700
Cerebrospinal fluid	450	6,700
Tissue	90	1,500
Microbiome DNA[4]	875	13,000

[1]Core collection, in time more samples types will be stored.
[2]The total collection of aliquots stored is larger than the total number of samples because there will be on average five aliquots available per included sample.
[3]Human isolated from leucocytes; for specific studies DNA will be isolated from saliva.
[4] Microbiome DNA: from skin, throat, vagina or faeces.

portal is being prepared for donors of the Radboud Biobank (ELSI application, i.e. application about ethical, legal and social issues). Patients are also represented in the REC (-light).

Historical collections

The Radboud Biobank was designed as a prospective, 'de novo' biobank for storage and dispensing of material and data from Radboud university medical center patients who explicitly give their consent for the collection of additional biomaterial for medical research and innovation.Several sub-collections, however, were already established by different departments before the commencement of the Radboud Biobank. The Radboud Biobank has taken on the management of several of these historical collections. By inclusion of existing sub-collections in the Radboud Biobank these collections will improve in quality by adhering to the standards of the Radboud Biobank. This will create added value to the material currently stored in these existing sub-collections.

The Radboud Biobank also facilitates departments that want to store DNA and other material remaining after diagnostic and surgical procedures.

Some specific examples

Within the context of the European Community (EC) 6th (Polygene) and 7th Framework (Promark and EuroTARGET) programs, the Comprehensive Center East in the Netherlands started to build a population-based biobank facility by means of the respective Polygene, Promark and EurTARGET projects. This biobank initially only included prostate and breast cancer patients but was later expanded to other types of cancer (bladder, melanoma, ovarian, kidney, lung, testicle, thyroid). This facility has already collected blood samples and data of more than 7 000 patients. The facility (blood samples only) has been used by the global research community in more than 40 high-impact publications[13,14,15].

The department of Rheumatology started systematically collecting clinical data in a central database and storing plasma and serum from patients with rheumatoid arthritis in 1985. These data improved the understanding on optimal measurement of disease activity, and on parameters that are relevant to assess the response to medication. This latter sub-collection is a real showstopper, with a still increasing number of citations[16]. However, this scientific output is only the means to the ultimate goal of the project, that is, to improve patient care.

Another example worth mentioning, is the collection 'hereditary colorectal cancer'. It started in 2008 as part of "the String of Pearls Initiative" to collect biomaterials (i.e. blood for DNA isolation, plasma and serum, intestinal biopsies and frozen and paraffin-embedded sam-ples of healthy and cancerous tissue) plus associated clinical data. This sub-collection or "pearl" has already collected samples with data of more than 1,300 patients and is a treasure chest for future research to improve prevention, treatment and the quality of care for this specific group of patients[17].
Between 2003 and 2005, the Department of Laboratory Medicine in collaboration with the Departments of

General Internal Medicine, and Epidemiology and biostatistics, and 4 additional hospitals in the Netherlands collected data and samples from ≈250 Dutch patients with clinically detected HFE-related hereditary hemochromatosis (HH) and their ≈ 970 first degree relatives. To date, this collection provided information on the morbidity rate in these families and improved our insights on the determinants of iron accumulation and HH-related diseases[18]. More recently this collection still proved valuable by contributing to our understanding of the role of the circulating iron regulatory hormone hepcidin in the pathogenesis of iron accumulation in HH patients[19].

In the year 2000 the Nijmegen Biomedical Study (NBS) was initiated among the inhabitants of the municipality of Nijmegen by the departments of Health Evidence, Clinical Chemistry, and Endocrinology of the Radboudumc in collaboration with the municipality of Nijmegen and the community health service of Nijmegen. Central research question was: 'What is the prevalence of certain risk factors, chronic diseases and genetic variations in the general population?' Goal of the study was to obtain a universal reference population

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that can be efficiently used in a variety of medical studies. The Nijmegen Biomedical Study has resulted in a number of scientific peer reviewed publications[20].

Publicity

Biobanks are a powerful tool in the study of complex diseases. Inclusion of large numbers of patients is essential to obtain a better understanding of genetic and environmental pathways causing complex, multi-factorial diseases. However, most people have never heard of biobanks[21]. For sustainable biobanks with continued donor participation, it is crucial that the general public is well informed and committed to these activities. To this end, University Medical Centers should invest time and energy in public relations and (social) media contacts. On the Radboud Biobank website[6] information for both professionals and patients is available.

Conclusion

This paper describes the design of the Radboud Biobank, unique in its provision of a large scale, hospital based comprehensive combination of high quality biomaterial and associated clinical data routinely collected in a professional and sustainable infrastructure. The aim of this biobank is to come to a large central biobanking facility, to enable scientific research which leads to medical innovations. These medical innovations comprise improved and personalized prevention, diagnostic and therapeutic strategies of both common and rare diseases.

The Radboud Biobank seeks quality at all levels, among which are clinical data, biomaterials, ICT, ELSI, logistics and procedures for delivery. Special attention is paid to quality assurance, standardization, and harmonization of the biomaterials.

The Radboud Biobank is tuned for international collaboration (international nomenclature) and biomaterials are available for good

Table 3: Material specific agreements

Sample type[1]	Summary
DNA	Concentration of the stock solution and normalized fraction100 ng/μL Storage: -20°C
Plasma	Time between sample collection and sample centrifugation: within two hours Storage: five aliquots of 0.5 ml at -80°C
Serum	Time between sample collection and sample centrifugation: within two hours Storage: five aliquots of 0.5 ml at -80°C
Urine	Time between sample collection and storage of the sample: within four hours Storage: six aliquots of 0.9 ml at -80°C
Cerebrospinal fluid	Time between sample collection and sample handling: within two hours Storage: six aliquots of 0.5 ml at -80°C
Tissue Frozen Paraffin	Immediately frozen after collecting the sample (0.5 cm^3) Storage: -80°C Immediately stored in formalin after collecting the sample (0.5 cm^3), afterwards embedded in paraffin Storage: room temperature

[1]Core collection, in time more samples types will be stored.

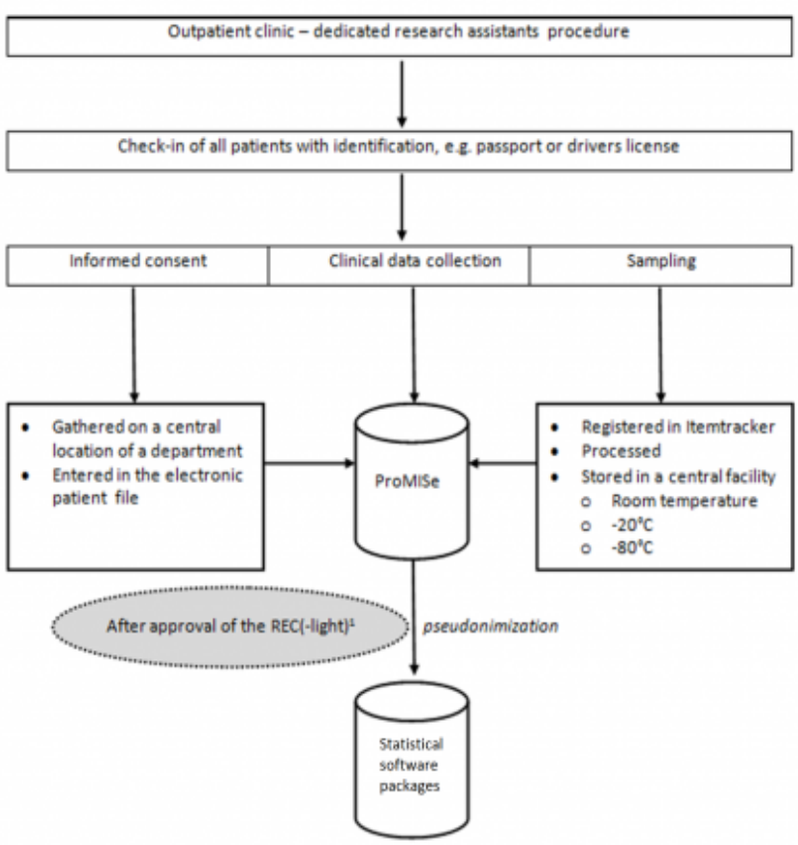

Figure 3: The flow of biomaterial and associated clinical data of new patients for the Radboud Biobank. REC, Research Ethics Committee-light; ProMISe, the clinical research data management software system. Itemtracker, the laboratory sample management software system.

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quality research proposals. Access conditions for scientific cooperation are subject to legal and ethical constraints.

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