The transition from sample storage to a biobank - A risk assessment and gap analysis in preparation for the ISO 20387 certification.

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***Abstract*—Biobanks have shown to be a valuable part of biomedical research. A broad biobank infrastructure ensures faster results in research by saving time for the sample acquisition. VASCage GmbH thereby has a sample storage of collected specimens with the perspective of getting more in the next years. To get the most impact out of the collection, VASCage GmbH needs to prove compliance with quality standards and regulations.**
Therefore, this paper provides an overview of regulations biobanks have to recognise, like the General Data Protection Regulation (GDPR). The beginning and evolution of biobanking are described, and different types of biobanks are discussed. Finally, risks that biobanks could face are identified, and measurements for reducing the risk level are presented.
Thereby, 22 risks were identified. After implementing all suggested actions, the risk of contaminated samples is the only identified risk with the risk level medium.

***Index Terms*—Biobanking, Sample storage, Sample management, Risk assessment**

I. Introduction

MOTHERN biomedical research continually generates new questions and tests both validated and invalidated hypotheses through empirical studies. A lot of time is required to collect samples from several volunteers at different points. This circumstance makes the samples a precious commodity. In order to keep the collection process as short as possible and to avoid having to collect samples from scratch for each new study, more and more extensive biobanks are being established. A biobank is a facility where biological material is stored for future research questions. [1]
VASCage GmbH is a research centre founded in 2019 focuses on vascular ageing and stroke.[2] Since then, VASCage has already created a considerable residual sample collection, which is expected to grow in the coming years. To avoid the need to store these samples in a separate facility, VASCage has aimed to build up a biobank out of their existing sample storage. Therefore, several regulations regarding data protection, participant rights, biosample handling and quality control need to be recognised. For data protection, European Union (EU) countries need to transform the General Data Protection Regulation (GDPR) into national law, and biobanks need to follow it [3][4]. To ensure the highest standards of quality control, as well as uniform specimen handling and storage, the International Organisation for Standardization (ISO) developed the standard ISO 20387 for biobanking [5].
Researchers who want to work with samples from biobanks need to trust the quality of the samples to have reliable results. The high-quality standards for biobanking are designed to maximize the reliability and effectiveness of sample outcomes. With a good biobank infrastructure and a broad sample library, the research of diseases and new treatments will be faster. [6][7]
The ISO 20387 gives guidance about the structure, risk management, equipment, facility, processes and quality management system (QMS). VASCage attempts to become certified to prove compliance with state-of-the-art biobanking. For this goal, it is necessary to know what the current state is and what is missing to be compliant with the standard. To answer this question, the master thesis, which was written in parallel with this paper, includes an analysis of VASCage's sample storage with a risk assessment and gap analysis [8]. The aim of this is to identify actions VASCage has to take for compliance with ISO 20387 and provide solutions for remaining tasks and decisions.
Because this paper will be published, details about the outcome can not be presented. This paper concentrates on the general risks a biobank could face and measures to reduce the risk level.

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II. Fundamentals

A. Definition

ÖNORM_EN_ISO_20387_2020 (hereinafter referred to as "ISO 20387"), which is the applicable standard for biobanking, defines biobanking as follows:

> Process of aquisitioning and storing, together with some or all of the activities related to collection, preparation, preservation, testing, analysing and distributing defined biological material as well as related information and data (ÖNORM EN ISO 20387, 3.6, p.2 [5])

For the VASCage biobank, the main activities are acquisition, storage and preservation. Third parties will perform collection, preparation, testing, analysis and distribution.
Biological material is defined as:

> Any substance derived or part obtained from an organic entity such as a human, animal, plant, microorganism(s) or multicellular organism(s) that is(are) neither animal nor plant (e.g. brown seaweed, fungi)(ÖNORM EN ISO 20387, 3.7, p.2 [5])

VASCage only works with human samples collected from their performed clinical trials. Due to the focus of VASCage's studies, the samples mainly relate to vascular ageing and stroke research. The preliminary definition of biobanking for VASCage is as follows:
VASCage's biobank acquires, stores and preserves human samples from studies supported by VASCage for research mainly focused on vascular ageing and strokes.

B. History of biobanking

1996 Loft and Poulsen used the word "biobank" for the first time, and since then, the amount of publications relating to biobanking has increased significantly [9][1].
Before that, however, there were already sample collections. The first was founded in 1948 by the National Institutes of Health- National Heart, Lung and Blood Institute with the "Framingham Heart Study", with the aim to find causes of heart diseases [10]. The main evolution of biobanking started with small repositories of leftovers from research projects [11]. The samples were stored in freezers with associated data records saved in laboratory notebooks [11].
The evolution process continued with technologisation, automated sample management and the invention of the internet. Biobanks became increasingly important, especially with the completion of human genome sequencing, because of the increasing demand for samples for genome analysis. Samples are needed in all kinds of -omics science like genomics, transcriptomics, proteomics or metabolomics. [1]
The beginning of biobanking started decentralised with differences in procedures like sample handling or storing. That leads to difficulties in comparing samples from different locations. In 1964, the Declaration of Helsinki guidelines declared that an internal review board should review every research project and that research with humans is always based on the results of laboratory animals and experiments. [1]
2009, the Organization for Economic Cooperation and Development (OECD) created a guideline for the establishment and management of human biobanks and genetic research databases, where the importance of an Institutional Review Board, which ensures the execution of ethical principles, was pointed out [10]. Also, the Austrian bioethics committee recognised in 2007 the lack of regulations for biobanking and described ethical problems as well as proposed solutions in a report for the Bundeskanzleramt of Austra [12].
In Europe, the aim of the Biobanking and Biomolecular Resources Research Infrastucture – European Research Infrastructure Consortium (BBMRI-ERIC), activated in 2011, is to link biobanks in Europe for better cooperation and research. They develop standards and guidelines to ensure that personal rights are respected and that health care and prevention are improving [13]. In Austria, Biobanking and Biomolecular Resources Research Infrastructure Austria (BBMRI.at) is the national biobank node for BBMRI-ERIC. In collaboration with universities and biobanks, BBMRI.at creates and enhances Austria's biobanking research infrastructure, integrating it into BBMRI-ERIC. [14]
As [15] declares, the future vision for biobank networks is that the national biobank nodes should combine national experience and become the driving power for the BBMRI-ERIC. This allows the networks to provide high-quality samples, even for rarer diseases.
The International Society for Biological and Environmental Repositories (ISBER) has been established to spread information about issues related to the management of repositories, educate and share information and tools, develop best practice guidelines, provide centralised information about existing repositories and facilitate international collaboration among members [16].

In 2018, the ISO published the standard "ISO 20387:2018 Biobanking-General requirements for biobanking", which is an essential step for harmonising biobanking procedures at an international level [1]. Researchers who want to use samples from different biobanks have to trust the quality and comparability of the samples. Together with the national biobank nodes, the BBMRI-ERIC has commented on ISO 20387 for biobanking and helps biobanks with future accreditation. [15]
Over time, the field of biobanking evolved rapidly. Nowadays, fully automated systems are available where robots manage the samples, and in case of a freezer failure directly, liquid nitrogen is injected to hold the samples frozen [17].

C. Types of biobanks

Biobanks exist around the globe. Large ones are, for example, the UK Biobank, which collects DNA samples from a random population to find connections between diseases, lifestyle, genes and risk factors, or the Biobank Japan, which aims to research the evolution of specific disease pharmacogenetics [10]. The largest biobank in Europe is located in Austria, Graz. It contains formalin-fixed paraffin-embedded (FFPE) and fresh frozen tissue samples and body fluids [18].

As shown above, biobanks can differ in terms of funders, research purpose and sample types. They can be sponsored by universities, private companies, national or regional agencies or non-profit organisations. Some biobanks follow the target to collect samples from a random population, specific demographic group, and donors with specific diseases or combinations out of them. The sample type can differ a lot as well. Starting with the fact that the samples can be from humans, animals or plants, it is important to note that even within human samples, the extraction site within the body can vary. The sample can be cells, tissue from surgery, whole blood, serum, DNA, body fluids, stool, urine, etc. or, e.g. in imaging biobanks, only data [19][1].
Depending on the sample type, the storage conditions must be adjusted accordingly, e.g., frozen at -80 °C in freezers or at -196 °C in liquid nitrogen. The size and shape of the tubes can also vary. Whole blood samples can be stored in ethylenediaminetetraacetic acid (EDTA)-coated collection tubes for, e.g. protein analysis or tubes with heparin for, e.g. metabolomic studies. Tubes for stool are bigger than cryotubes for serum, and tissue can be stored FFPE at room temperature or in tubes at -80 °C. A biobank needs to

combine these variables best to save space and resources. [1] Because VASCage only works with frozen human samples, this thesis will focus on them.

D. Requirements

For countries in the European Union, it is crucial to recognise the EU laws and regulations. One essential regulation is the GDPR, which needs to be recognised by EU countries in national law. [20]
An essential point of the GDPR is informed consent, which must always be obtained before any study-specific procedure is performed. There are several possibilities for consent, shown in table I [21].

TABLE I: Different types of consent for future research (quoted from [21])

Type of consent	Description
No consent	The researcher does not obtain the donor's consent.
Blanket	A consent for future research is obtained without limitations.
Broad	A consent is given by the donor with specified limitations.
Checklist	The donor selects what types of future studies he will allow
Study-specific	The donor gives consent for each specific future study.

In most cases, broad consent is granted for biobanks, allowing the samples to be used flexibly without contacting the donor for each new study. The donor can exclude specific analyses or studies, such as genome-related studies. However, only a small number of donors refuse the broad consent [21][4].
Regarding the GDPR, the legality of broad consent could be debatable because recital 32 of the GDPR says that every consent must be informed. Since the upcoming research studies in biobanks are often not yet foreseeable, it is described in recital 33 that the donors must be allowed to restrict the use of the samples in these cases. It is also declared that the participant can withdraw the consent at any time without any reason and negative consequences for him. [4]
Pseudonymisation is also a subject in the GDPR and is important for biobanking. 'Pseudonymisation' means, according to Art. 4 GDPR, that personal data is processed without being linked to an individual unless extra information is available to link it [4]. Every personal data in a biobank needs to be pseudonymised. This means that, for example, name, birth date, and patient identifier (ID) need to be replaced by a pseudonym. [22]
For the shipment of biological samples, it is necessary that the shipment complies with the International Air Transport Association (IATA) - dangerous goods regulatory (DGR) and that the packaging and shipping are carried out by trained personnel [23].
The transfer of sensitive data needs to be done encrypted and only according to the transfer agreement and with the consent of the participant. What sensitive data is, is described in Art. 9 of the GDPR and needs to be treated with special care. If a personal data breach is recognised, the responsible person needs to inform the supervisory authority and the concerned participants in accordance with Art. 33 and 34 of GDPR. [4]
When it comes to the question of ownership, there is room for discussion. An argument against the possession of samples is that the samples are part of a human and can not belong to another person, as this violates Art. 4 of the Universal Declaration of Human Rights, Prohibition of slavery and forced labour [24]. This is why many biobanks have agreed to be custodians and not owners of the samples [25]. A different opinion is that as long as the data are pseudonymised, the samples are no longer connected to the donors and belong to the biobank [26][27].
In order to reduce the heterogeneity of biobanks, the ISO has compiled guidelines for biobanks of all types and created the ISO 20387 [1]. The standard structure begins with the scope and normative references and continues with terms and definitions. In chapters four to eight, the requirements for biobanking are written down. The content of the annexe is filled with documentation requirements, implementation guidance and quality management system options. The standard covers general, structural, process and quality management system requirements [5].

E. VASCage GmbH

VASCage GmbH was funded in 2019 and emerged from the Competence Centre For Excellent Technologies (COMET) K-Project VASCage Tyrol was started in 2014 by the Medical University Innsbruck (MUI) with the aim to improve vascular health and manage vascular disease in the elderly [28]. The project was successfully completed, and therefore, a follow-up application was submitted under the COMET programme for funding for a COMET centre focusing on stroke and vascular ageing [2]. VASCage GmbH formulates there mission as follows:

> Our mission is to conduct top quality clinical trials and life science research to translate scientific findings into new products, processes and services. (VASCage company folder p.2 [29])

Until now, VASCage GmbH already collected samples and stored them in -80 °C freezers. For the next years, VASCage wants to include more samples. The biosamples are blood, plasma, urine, stool, tissue samples, thrombi or residual tissue from vessel surgeries, all stored in freezers at -80 °C.
The mission of VASCage GmbH's biobank is to advance research in the field of vascular diseases and strokes. Thereby, VASCage GmbH is collecting samples from different cohorts, sex, age, and ethnic groups, which makes the sample storage more valuable for the broad scope and adds significance to the biobank's research potential. The biobank will help save resources as researchers can use stored samples instead of collecting new ones.
For now, VASCage GmbH has only a sample storage where every clinical study is storing their samples individually. The samples that have been stored need to be transferred to the biobank to ensure that all samples and associated data from

various studies are stored in a centralised, organised and quality-controlled manner with an ISO certification.

III. Methods

A. Literature review

At the beginning of the Semester, a literature search was performed using Google Scholar and Pubmed, and a Citavi 6 library was created for all the resources that were found. First, the focus was to get an overview of the topic and to find out what the thesis could include. Second, the focus was on regulations that might be applicable to VASCage's biobank and the ISO 20387 standard. Third, literature research on the implementation of biobanks was performed.

B. Risk assessment

A risk assessment was created and improved together with the medical supervisor from VASCage GmbH (hereinafter referred to as "VASCage") Ass. Prof. Priv. Doz. Dr. Michael Knoflach and Verena Rinnofner, the project leader of the biobank project. The risk assessment is useful for providing an overview of VASCage's challenges while building the biobank and visualising their risk priority. A top-down approach was taken for the risk assessment evaluations, where hazards and risks were identified, and causes and actions were searched for. Actions for reducing the risk were discussed, and an evaluation of the risk severity, occurrence and detection was made. Primary Risk Number (PRN) is the product of risk severity and occurrence, and together with the risk detection, the Risk Priority Number (RPN) is calculated. The risk level will be Low if the RPN is less than 9. If it is between 9 and 33, the level is Medium, and if the value is higher than 33, the level will be High.
A Description of the risk level can be found in table III. The risk rating key for evaluating severity, occurrence and detection can be seen in table II. The key for risk occurrence and detection matches with the template specification of VASCage. The rating key for severity did not fit so well for the biobank application. The conditions for a high severity were lowered so that the highest severity had to be indicated, even if the participant was affected in some way.

TABLE II: Risk rating key [30]

Risk Severity	Description
1	The hazard would not lead to severe quality impact.
2	The hazard affects the quality of the sample, data or research outcome.
3	The hazard could destroy the sample.
4	The hazard also affects the participant/donor.
Risk Occurrence	
1	Unlikely, thought possible.
2	Could occur occasionally.
3	Not surprised, will occur in a given time.
4	Likely to occur, to be expected.
Risk Detection	
1	Very likely to be detected.
2	Likely to be detected.
3	Uncertain to be detected.
4	Not likely to be detected.

TABLE III: Risk level description [30]

Risk Level	Description
Low	Acceptable; OK to proceed.
Medium	as low as reasonably practicable (ALARP); Take mitigation efforts .
High	Generally unacceptable; seek support.

IV. Results

During the risk evaluation meetings, 22 potential risks were identified, listed in table IV.

RiskID	Risk
R001	Flooding
R002	Fire
R003	Pandemic
R004	Data leaks, accidental
R005	Samples get switched
R006	Too high Temperature during internal transport
R007	Too high Temperature during external transport
R008	Violation of data integrity, accidental
R009	Samples loss during shipping
R010	Sample loss in other research facilities
R011	Sample contamination
R012	Hazard in outsourced processes.
R013	Unauthorised physical access to samples
R014	Financial issues
R015	Changing personnel
R016	Lack of qualified personnel.
R017	No clear responsibilities.
R018	Freezer Failure
R019	Data loss/IT failure
R020	Unauthorised access to Database, data leakage
R021	Power loss
R022	Software bug

TABLE IV: List of risks

R001 describes the risk that flooding occurs, which could destroy the freezers or lead to a power outage. The samples could get destroyed, or the quality could drop. A high position of the facility, a disaster management plan and a second power source could be measures to reduce this risk.
R002 is the risk of a fire, which could also lead to the destruction or quality drop of the samples. In this case, a fire alarm and an extinguishing system should be in place.
The worst-case scenario for a pandemic would be that no one is allowed to access the storage facility, and no new samples can be stored there. The measure depends highly on the pandemic and needs to be set individually.
R004 is the risk that either participant data or research results will be published accidentally. To reduce this risk, the data needs to be stored anonymously or pseudonymised and encrypted, The staff needs to get the required training, and the database needs to be access restricted and managed by an adequate sample management system.
A risk with far-reaching consequences is "R005 Samples get switched". Not only the research outcome could be influenced, but the wrong treatment for the participant could also be initiated if the analysis of the switched sample gives a clinically relevant result. Therefore, it is important that the biobank has a suitable labelling and tracking system for the samples. it must be possible to identify and track each sample at any time.
Risks R006 and R007 concern the risk of too high temperature

during the temperature. For internal transport, the risk could be reduced by short ways, quick transport and isolation during the transport. for long-distance transportation, the samples need to be cooled with dry ice, packed and transported by trained personnel, and the temperature needs to be logged during the transport. If some adversaries are detected, the biobank needs to be contacted, and corrective and protective actions need to be performed.

The data integrity could be compromised by accident. Therefore, backups, documentation training for staff and a data history need to be in place.

the risks of losing samples during shipment or in other research facilities can be reduced by only working with certified partners and making contracts with them. The sample's condition and number of samples need to be documented before and after the shipment.

The risk of "R011 sample contamination" is difficult to detect, but the occurrence can be reduced by only working with trusted study sites and laboratories with trained staff and keeping the tubes closed until usage.

Risk R012 deals with any hazards in outsourced processes. This risk can be lowered by clearly defined contracts and audits to control the processes.

Physical access to the samples needs to be restricted by using electronic locks with an access log to detect unauthorised access.

R017 is the risk that the biobank will experience economic issues and have to discontinue its business. Therefore, it makes sense for the biobank to have a financial plan and become financially independent. A disaster plan that regulates what happens with the stored samples after the close of business should ensure that the samples can still be used.

To address changing and lack of qualified personnel, it might be helpful to provide benefits and attractive work conditions for the employees. The risk that no clear responsibilities could lead to misunderstandings and overlooked tasks can be overcome by having an organisational chart with clear job descriptions and responsibilities.

In case of a freezer failure, described in R018, the storage facility needs to provide a 24/7 alarm system, and the freezer needs to read the temperature. An emergency system could also be installed, where the samples get cooled by liquid nitrogen after freezer failure.

The risk reduction of R019 has the same measures as R008. The risk of unauthorised access to the databank, which could lead to stolen data, can be reduced by access restrictions to the database, anti-virus software, pseudonymization and a biobank-specific sample management system.

The risk of power loss can be minimised by having a second power source and an emergency cooling system with liquid nitrogen.

The occurrence of a software bug can be lowered by using well-tested sample management software, and to reduce the severity, the software needs good support.

When all actions for risk reduction are implemented, a risk assessment can be made, shown in table V. Four identified risks have the highest severity evaluation because those risks affect the donor in some way. However, since the risk occurrence is low and these risks are easily detectable, the risk level is low. Two risks are identified with a not-surprising occurrence in a given time. But here, too, the resulting risk levels are low because of low severity and good detectability. Only risk "R011 Sample contamination" has a medium risk level. Considering the PRN, the risk of R011 is low. The risk level is medium because it is difficult to detect. The worst-case scenario would be that the quality of the sample gets worse. To reach this scenario, it would be necessary that the contamination is occurring and has an influence on the outcome of the result. The occurrence is low because the laboratory is working according to standards, and the tubes remain closed until usage. The impact of contamination on research results can be disregarded if it only affects individual samples and the study population is large.

TABLE V: Risk assessment

RiskID	Risk Severity	Risk Occurrence	Risk Detection	PRN	RPN	Risk Level
R001	3	1	1	3	3	LOW
R002	3	2	1	6	6	LOW
R003	3	2	1	6	6	LOW
R004	4	1	1	4	4	LOW
R005	4	1	2	4	8	LOW
R006	2	1	2	2	4	LOW
R007	2	1	1	2	2	LOW
R008	2	1	1	2	2	LOW
R009	3	1	1	3	3	LOW
R010	3	2	1	6	6	LOW
R011	2	2	3	4	12	MEDIUM
R012	2	2	2	4	8	LOW
R013	3	2	1	6	6	LOW
R014	3	2	1	6	6	LOW
R015	2	3	1	6	6	LOW
R016	2	3	1	6	6	LOW
R017	2	1	2	2	4	LOW
R018	2	2	1	4	4	LOW
R019	4	1	1	4	4	LOW
R020	4	1	2	4	8	LOW
R021	3	1	1	3	3	LOW
R022	2	1	2	2	4	LOW

V. Conclusion

This paper provides information about the history of biobanking. Starting with the sample collection of the Framingham Heart Study in 1948 and the first use of the word "biobanking" in a publication in 1996 by Loft and Poulsen. The paper continues with the guidelines and standards that have been developed over time and aim to achieve uniform biobanking. It is shown that biobanks can deviate in terms of founder, research purpose, stored sample types and storing conditions. The requirement part of this paper summarizes important regulations biobanks need to recognize and gives an introduction to ISO 20387. This includes consent, data protection and sample handling.

The results of the risk assessment reveal 22 potential risks with measures to reduce the risk level. Effective measures for

several risks are to use a biobank-specific sample management software with a good traceability system and qualified staff. One Risk was found, which could not be lowered further than to a medium risk level because of the difficult detectability of contaminated samples.

The risk assessment is applied to VASCage's sample storage, and a gap analysis to identify the measures VASCage has to take to be compliant with ISO 20387 was made in the parallel written master thesis. In the future, VASCage should update the risk assessment regularly to identify and react to changing or new risks. Also, other analyses can be performed, like a SWOT analysis, to identify strengths, weaknesses, opportunities and threats. This might help to analyse the internal and external factors to make informed decisions about their business strategies.

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