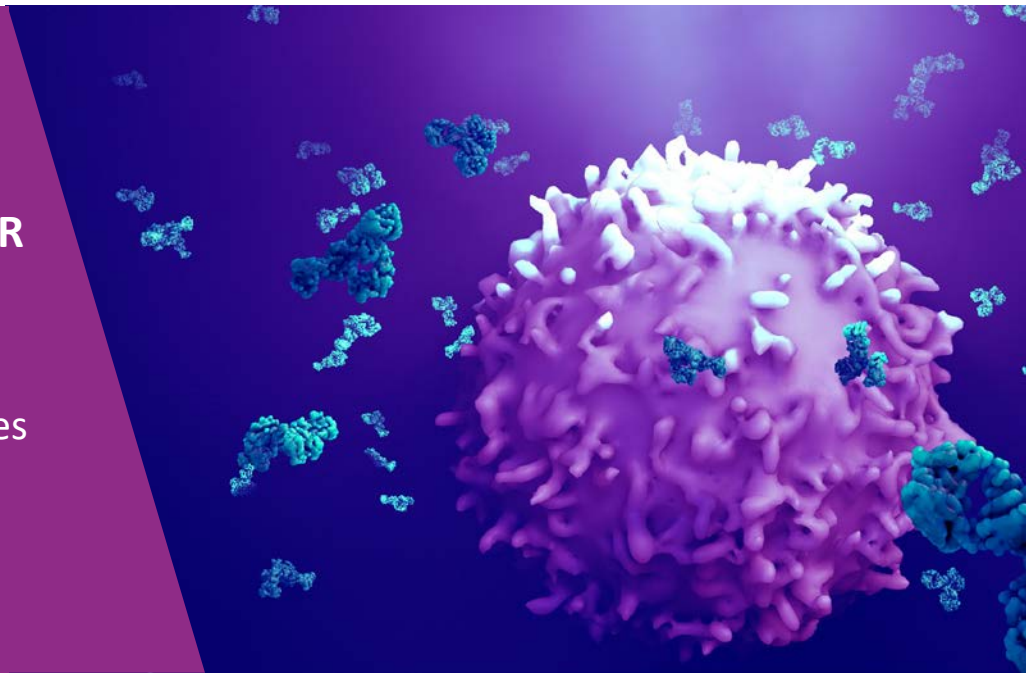
imSAVAR

IMMUNE SAFETY AVATAR

Nonclinical mimicking of the immune system effects of immunomodulatory therapies



Deliverable 5.4
Distributed network biobanking system

DELIVERABLE REPORT

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 853988.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and JDRF INTERNATIONAL.

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Abstract

The goal of this deliverable was to establish a distributed biobank system for a) sample management of samples from different donors / patients that will be used for experiments in WP 2-4 and b) sample management of samples generated in WP 2-4 experiments that will be used for further subsequent analyses. Our distributed biobank system comprises:

1) A harmonised ID system (imSAVAR ID System)
2) Definition of harmonised basic datasets linked to patient derived samples
3) Provision of an IT system for sample management (Biobank Information Management System, BIMS)
4) Standardised, quality controlled and (bio-) save sample storage
5) Best practice pre-analytical procedures / workflows for sample collection, processing and shipment
6) Implementation of data transfer from BIMS to the imSAVAR data platform

Document Information

Deliverable Report	**D5.4: Distributed network biobanking system**
Date	**30.11.2020**
Report prepared by	**Medizinische Hochschule Hannover** UNIVERSITE DU LUXEMBOURG, F. HOFFMANN-LA ROCHE AG
Project	**imSAVAR - Immune Safety Avatar: nonclinical mimicking of the immune system effects of immunomodulatory therapies** Grant Agreement No.: 853988 (IMI2-2018-15-04)
Project Coordinator	**Fraunhofer-Gesellschaft zur Foerderung der angewandten Forschung e.V.** Prof. Dr. Dr. Ulrike Köhl **Novartis Pharma AG** Dr. Jonathan Moggs
Type	**Deliverable Report | Public**

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Table of Contents

1. Results

1.1 imSAVAR ID System

imSAVAR ID is a unique identifier that is assigned to subjects, samples, and experiments derived from the collected samples for the project. It is linked to information of the subjects, biomaterials, and experiments performed on those samples. The objective of imSAVAR ID is to ensure that the relationship between subjects, samples, and experiments remain in place during the whole process. This ID system will help imSAVAR partners in generating consortium wide unique identifier for their subjects, samples, and experiments. imSAVAR partners can use the imSAVAR ID to directly connect different entities instead of making complex relationships using metadata.

Proposed ID System:

The imSAVAR ID is created by composing information about subjects, samples, and experiments in a systematic way. The imSAVAR IDs have been proposed at three levels (1) Subject (Subject ID), (2) Samples collected from subjects (Subject ID) and (3) Experiments performed on these samples (Experiment ID). Table 1 contains information about the required fields to create these IDs. Figure 1 illustrates the unambiguous link between the three levels of the ID system.

Table 1: Information needed to generate the imSAVAR ID

	Variable	Required M(Mandatory) O(Optional)	Value (e.g.)	Variable description
SUBJECTS	PROJECT	M	IMSAVAR	
	SUBJECT_SITE	M		
	SUBJECT_SEQUENCE	M	100	Internal subject sequence
SAMPLES	SAMPLE_TYPE	M	TCELL	controlled vocabulary
	SAMPLE_SITE	O		
	SAMPLE_NO	M	100	Internal unique sample Number
	SAMPLE_VISIT	M	1	1 default
EXPERIMENTS	EXPERIMENT_TYPE	M	RNA_SEQ	controlled vocabulary
	EXPERIMENT_RUN	M	2	numeric value

Implementation details:

WP5 is currently working on the implementation of a REDCap based solution for register metadata and generate imSAVAR IDs. This tool will enable partners to directly create imSAVAR IDs and link the associated information.

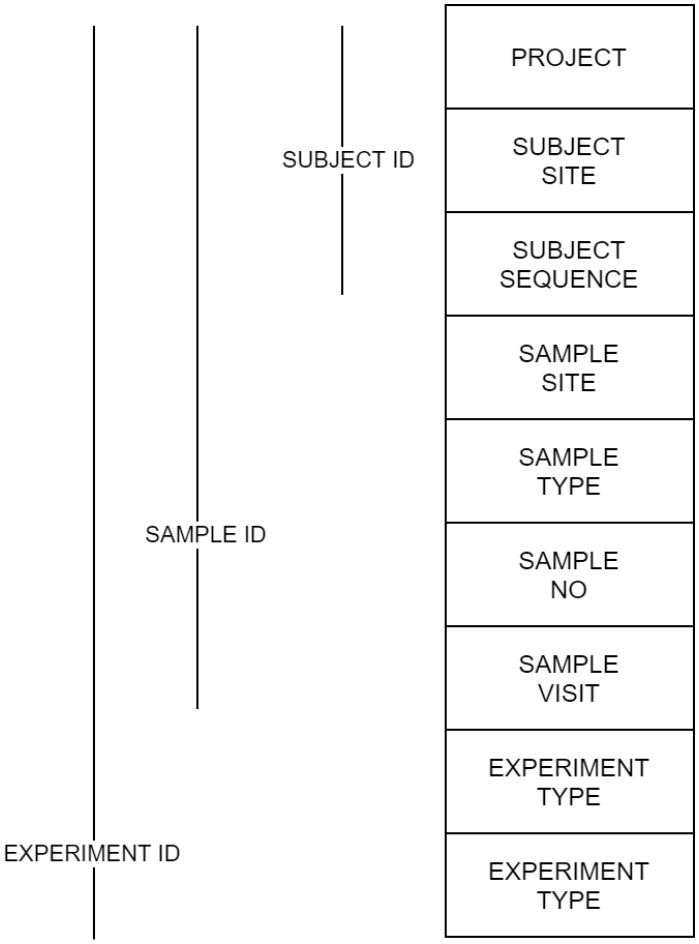

Figure 1: Three levels of the imSAVAR ID system

1.2 1.2 Definition of harmonised basic dataset for patient derived samples

To ensure uniform high sample and data quality, a harmonised basic data set will be collected for all patient derived samples (Table 2). The basic data set includes sample related data (e.g. quality data) as well as patient related data necessary as minimum specifications for patient derived samples. The requirements for sample related data depend strongly on individual sample usage and can differ from case to case. Depending on the individual requirements of the imSAVAR partners, additional parameters defining the sample quality or additional clinical data may be necessary and will be collected.

Table 2: Harmonized basic dataset for patient derived samples

Type of data	Entity	Example
Project partner-ID	Sample	MHH
Date of consent	Sample	20.10.2020
Sample-ID	Sample	4578920
Primary container	Sample	K3E EDTA
Sample type	Sample	Plasma, FFPE tissue
Organ	Sample	Liver
Collection date / time	Sample	20.10.2020

Receive date / time	Sample	20.10.2020
Freeze date / time	Sample	20.10.2020
Location of sample	Sample	Freezer 3
Storage tempratture	Sample	-80°C
Freeze / thaw cycle	Sample	2
Patient-ID	Patient	123456
Gender	Patient	male
Diagnosis (ICD-10)	Patient	C44
Year of birth	Patient	1978
Visit	Patient	3

1.3 Provision of an IT system for sample management (Biobank Information Management System, BIMS)

The Hannover Unified Biobank (HUB) is the central Biobank of the Hannover Medical School (MHH) and thus responsible for the collection, management, quality control, and quality ensurance of all MHH samples. For the registration and management of samples and documentation of sample and patient associated data the HUB uses the Biobank Information Management System (BIMS) CentraXX (KAIROS; Bochum, Germany) (https://www.kairos.de/produkte/centraxx/). The BIMS stores and manages sample IDs, quality parameters, and processing data. Additionally, it separately manages basic clinical data under strict compliance with the principles of data security and data protection developed by TMF (Technology, Methods, and Infrastructure for Networked Medical Research) and the European data protection regulation [1]. Thereby continuous sample tracking of preparation steps, retention times, and sample allocation is ensured.

Custom tracking solution for sample tracking could be attached to CentraXX by using the standard REST-API. The System even is in capable of handling any number of additional sample or data set IDs and discloses or pseudonymise selectable IDs to specified target groups. At the MHH CentraXX is running on premise and there is an agreement to ensure access and service/system continuity even after bankruptcy of the vendor/supporter. Several import/export interfaces are in place to ensure full data access in the future. Theses interfaces use futureproof technologies like FHIR, XML & CDISC.

HUB can provide access to CentraXX for imSAVAR partners for the management of imSAVAR samples. The required workflows in CentraXX are already established and user specific adaption according to individual requirements of all workflows for each imSAVAR partner can be readily carried out by the HUB IT team. The registration of samples and documentation of sample associated data includes the following work steps in CentraXX:

A) Login to CentraXX

Each employee receives a personal login including a unique user ID. This enables a clear assignment and traceability of all activities in CentraXX to one specific user.

B) Patient admission

In the first step the donor / patient can be registered in CentraXX (Figure 2). During patient admission, all relevant patient data (patient ID, diagnosis (ICD10), gender, year of birth and type / date of consent) can be entered.

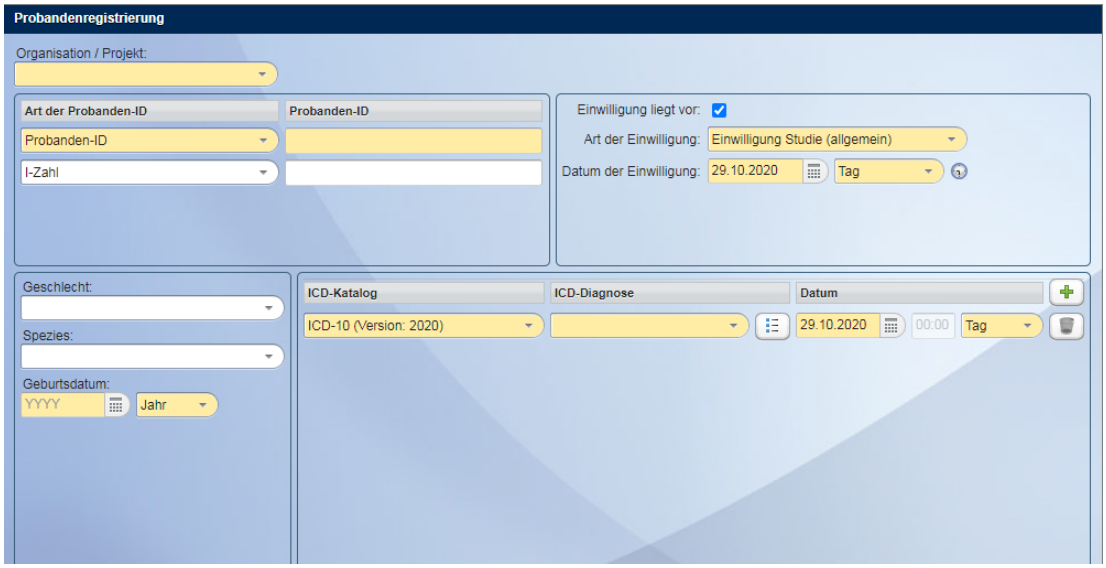

Figure 2: Patient admission in CentraXX: (Organisation = Project, Probanden ID = patient ID, Einwilligung= Consent, Geschlecht= gender, Geburtsdatum= year of birth, Datum = date)

C) Registration of primary samples in CentraXX

After collection of relevant patient data, all primary samples (e.g. blood, tissue) from one donor / patient will be registered in CentraXX (Figure 3). In this step the primary samples are connected to the respective donor and the respective imSAVAR subproject / partner via the beforementioned imSAVAR ID. In addition, the collection date and time is documented as well as the visit number/day. Input fields for all samples compiling a sample kit (all primary samples which are collected from one donor /patient per visit) will be configured by the HUB IT team according to the requirements of the imSAVAR partner. To avoid incorrect entries of the donor / patient ID (input field “Probanden ID”) and the IDs of the primary samples (input field “Proben ID”) the IDs must be automatically assessed by barcode scanning. The necessary barcode labels are available for on-site printing or can be provided as ready-to-use labels by the HUB.

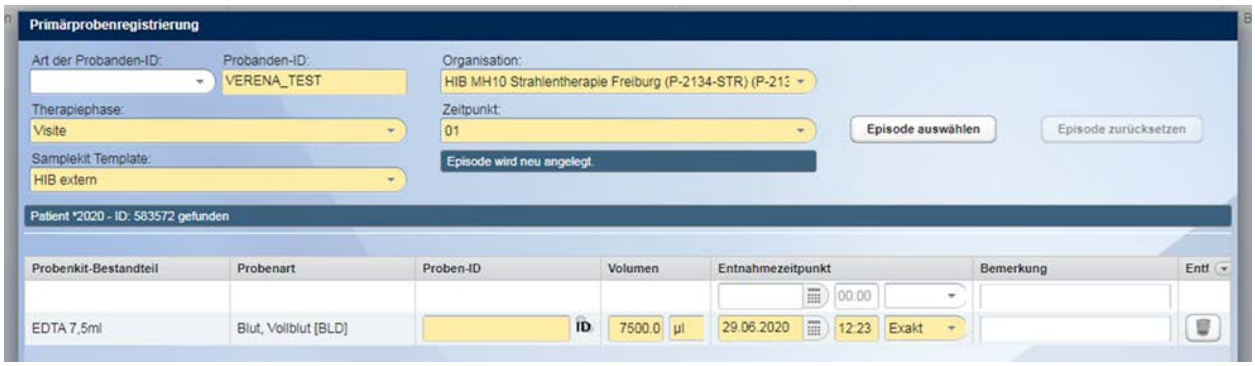

Figure 3: Example for registration of primary samples in CentraXX (registration of one EDTA blood tube 7,5ml) (Organisation = Projekt, Probanden ID = patient ID, Visite = visit, Zeitpunkt= visit number, Probenkit Bestandteil = primary sample, Probenart = sample type, Proben ID = sample ID, Volumen = sample volume, Entnahmezeitpunkt = collection date / time)

D) Registration of sample aliquots in CentraXX

Directly after collection of primary samples, the biosamples are processed (e.g. extraction of plasma, isolation of cells) and the resulting specimen are aliquoted before freezing. In this step the processed aliquots from each registered primary sample are registered in CentraXX and connected to the respective primary sample and donor / patient (Figure 4). Further, the aliquotation date / time and freezing date and

time is documented as an automatic timestamp. The templates for each single aliquote (input field "Aliquot-Vorlage) can be configured by the HUB IT team according to the requirements of the imSAVAR partner. The ID of every aliquot can be scanned into the respective input field. For unambigous identification of the aliquots, the HUB can provide tubes with a 2D barcode (Matrix™ ScrewTop V-Bottom Tubes with data matrix 2D code at the bottom [ThermoFischer Scientific, Waltham, Massachusetts]) or cryo stable barcode lables. Again, automated scanning of barcodes prevents ID misasignments.

Figure 4: Example for registration of aliquots in CentraXX (registration of plasma and buffy coat aliquots derived from one EDTA blood tube) (Auswahl zu aliquotierende Primärprobe = primary sample to be aliquoted, Auswahl Aliquot-Vorlage = selection aliquot template, Auswahl Lagerort = selection storage location, Einzelscan Aliquote = single scan aliquot ID)

E) Documentation of data

All sample data from the basic dataset are implicitly documented during the process described in A-D. For the documentation of additional data, the HUB IT team can provide customised data entry forms and workflows in CentraXX according to the requirements of each imSAVAR partner. Workflows for sample registration / data collection, sample rearrangements, and sample retrieval will be documented in CentraXX as well.

1.4 Sample storage

The imSAVAR Biobank system is a distributed network biobanking system. Therefore short- to mid-term storage of samples is generally taken over by the respective partners on site. However, the following storage conditions must be ensured: (i) Samples have to be stored at -80°C or at -190°C for viable cells, respectively. (ii) The freezer must be equipped with a temperature sensor / alarm system to avoid sample loss due to equipment failure.

For long-term storage of samples, or if partners do not meet the aforementioned requirements, samples can be transferred to the HUB, where samples are stored in the safe gas phase of liquid nitrogen tanks (–190°C). For mid-term storage at the HUB, samples are stored in an automated -80°C repository (BiOS, Hamilton, Franklin Massachusetts) (except for viable cells) with a -80°C cooled picking station for quality assured and temperature controlled preparation of requested and issued samples. All our freezing units are equipped with temperature loggers and are connected to a 24/7 alarm system and a back-up energy supply.

1.5 Best practice pre-analytical procedures workflows for sample collection, processing, and shipment

The infrastructure of the HUB as well as the biobank processes are adapted to the national and international biobank standards and guidelines of the OECD and ISBER [2, 3] and are certified in accordance to DIN EN ISO 9001 in November 2015 by TÜV North. The ISO certified processes of HUB include sample transport, preparation, and storage as well as associated data management. The HUB is a

founding member of the German Biobank Alliance (GBA). The biobanks of the GBA develop uniform quality standards and create legal and ethical guidelines for biobanking that are already applied in the imSAVAR project. GBA provides guidelines for the preanalytical handling of samples (sample collection, processing, storage and shipment of samples; QM Manual, released 11.2018) [4] which adhere to the recently published ISO standard for biobanking (ISO 20387:2018 Biotechnology Biobanking, General requirements for biobanking). All HUB processes comply with the quality standard of the GBA guidelines [4]. The HUB SOPs and the GBA QM manual will be used in imSAVAR as quality standards and as basis for the development of customised SOPs for this project where it is necessary.

1.6 Implementation of data transfer from BIMS to the imSAVAR data platform

The HUB uses CentraXX as central biobank information system. CentraXX has a comprehensive application programming interface (API) and multiple data interfaces to connect incoming and outgoing data streams (e.g. connectivity to SAP based systems). The interfaces are based on state-of-art technologies e.g. HL7, FIHR, XML, REST, JSON, CSV. Using the CentraXX reporting and data capabilities, several study projects and systems have already been successfully connected to the HUB biosample data pool in the past. Implemented tasks range from weekly status reports by eMail over complete customised CSV-exports to triggered data push via FHIR interface. A data importing pipeline (via CentraXX API or csv export) will be developed as a collaboration of MHH and UNILU to import sample metadata and other relevant information to the imSAVAR data platform."

2. Discussion

We have successfully established the basic infrastructure required for a distributed network biobanking system which is available for all imSAVAR project partners and can be quickly adapted to the needs of individual imSAVAR subproject. Currently, all partners from WP2 – 4 are in the establishment phase of their models. Furthermore, in a survey we were already able to identify 5 future biobanking use cases which will start implementation after the establishment phase (probable start 2021) (Table 3). As the "network of disease domain providers" for providing samples (D5.3), the distributed network biobanking system will continue to develop during the whole project along with the achievements in WP2 – 4 which are not yet fully foreseeable and will reach their maximum in the last year of the project. However, with our highly standardised, individually adaptable, and scalable approach, we will be able to attend all needs regarding sample and data management possibly arising throughout the imSAVAR project.

Table 3: Survey conducted to identify biobanking use cases

Participant ID participant_id	**Survey Identifier** redcap_survey_identifier	**Survey Timestamp** sample_survey_2_timestamp	**Partner** partner	**Model** model	**Sample types** sample_types	**Estimated volume of sample (per experiment)** est_volume	**Estimated number of samples / year** n_samples_year	**Complete?** sample_survey_2_complete
1		20-02-2020 07:55	JUH	Organ-on-chip	embedded tissues (IF stained), lysates, supernatant	200 µl	250	Complete (2)
2		19-03-2020 11:22	UKW	Cell Culture	Supernatant	180 µl (normally done in triplicates)	20	Complete (2)
3		14-04-2020 09:11	Fraunhofer IGB	Organ on a chip	Supernantants, Fixed tissues (chips), lysates for gene expression analysis	500 µL daily; experiment duration can be between 24h and 2 weeks, the sample size will never be more than 1 mL/daily and 14 mL per experiment	1000	Complete (2)
4		26-04-2020 06:51	IME TMP	cell co-culture T-cells/hepatocytes	supernatant, cells	200 µl, 100.000 cells	40	Complete (2)
5		26-04-2020 06:55	IME TMP	cell culture (T cell types)	supernatant, cells	200 µl, 100.000 cells	50	Complete (2)

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Acknowledgement

The authors would like to express their gratitude to the Innovative Medicines Initiative 2 Joint Undertaking (JU) for the financial support of this research under grant agreement No 853988. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and JDRF INTERNATIONAL.