ADOPT BBMRI-ERIC
gateway for health

ADOPT BBMRI-ERIC
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DELIVERABLE REPORT

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IT-TOOL FOR MONITORING COMPLIANCE OF BIOBANKS WITH CEN/TS FOR MOLECULAR DIAGNOSTICS EXAMINATIONS

Executive Summary

In 2015 and 2016, the European Committee for Standardization (CEN) published a series of CEN/TC Technical Specifications for "Molecular in vitro diagnostic examinations - Specifications for pre-examination processes". These specifications define the complete pre-analytical workflow of biological samples from collecting the sample from the patient to sample transport, processing, storage (biobanking) and isolation of an analyte (such as DNA, RNA or protein). They are relevant for biobanks, pathologists and diagnostic laboratories. In ADOPT BBMRI-ERIC we developed together with BBMRI-ERIC an online Self-Assessment-Tool that allows users to evaluate whether their own pre-analytical processes in the laboratory conform to these CEN/TS. This type of self-assessment is an important first step towards implementing these sample quality standards and thus improving the quality of biological samples.

This project has received funding from the *European Union's Horizon 2020 research and innovation programme* under grant agreement No 676550.

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Document log

Issue	Date (yyyy-mm-dd)	Comment	Author/partner
D6.3_Rev1	2017-09-01	Inclusion of discussion & next steps	Christoph Schreiner
D6.3_Rev1	2017-10-05	Revised for EU recognition to comply with GA art 29.4	Outi Törnwall

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1. Background

The CEN/TC Technical Specifications for "Molecular in vitro diagnostic examinations - Specifications for pre-examination processes" have been generated because the pre-analytical phase is a major source of errors. Pre-analytical errors are responsible for up to 70 % of all problems in laboratory diagnostics, cause enormous costs in hospitals and are responsible for non-reproducible results in research.

The following nine CEN/TS have been published:

- CEN/TS 16826-1, Snap frozen tissue – Part 1: Isolated RNA
- CEN/TS 16826-2, Snap frozen tissue – Part 2: Isolated proteins
- CEN/TS 16827-1, FFPE tissue – Part 1: Isolated RNA
- CEN/TS 16827-2, FFPE tissue – Part 2: Isolated proteins
- CEN/TS 16827-3, FFPE tissue – Part 3: Isolated DNA
- CEN/TS 16835-1, Venous whole blood – Part 1: Isolated cellular RNA
- CEN/TS 16835-2, Venous whole blood – Part 2: Isolated genomic DNA
- CEN/TS 16835-3, Venous whole blood – Part 3: Isol. circ. cell-free DNA from plasma
- CEN/TS 16945 Metabolomics in urine, serum and plasma

Currently, the CEN/TS are being transferred to ISO standards and will then be internationally valid.

Although the primary focus of the CEN/TS for molecular in vitro diagnostic examinations – specifications for the pre-examination processes is molecular diagnostics, immediate relevance is also given for biobanks since

i) the reliability of biological samples for molecular analyses is not only an issue for diagnostics but also for research, and

ii) biobanks not meeting the requirements needed by industry and medicine would exclude key users and funding sources. The CEN/TS will also gain relevance in the context of the upcoming European regulatory framework for in vitro diagnostics (EU IVD Regulation), which requests validation of several key pre-analytical parameters in the development of molecular diagnostics

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2. Approaches (Methods) & Results

2.1 Step 1 - MS Excel-based Self-Assessment-Tool Prototype

In a first step BBMRI.at developed an MS Excel-based Self-Assessment-Tool (Fig 1) for evaluating the compliance with the CEN/TS (snap frozen tissue – RNA, FFPE tissue – RNA, whole blood - RNA). It is based on the requirements and recommendations as stated in the corresponding CEN/TS.

2.2 Step 2 – REDCap-based Online Self-Assessment-Tool Prototype

The MS Excel Self-Assessment-Tool served as the basis and the requirement specification for a **prototype of an online Self-Assessment-Tool** (Fig. 2a, 2b), which BBMRI.at developed in a second step. Several different IT-tools were analyzed with respect to their suitability as a technical framework. The technical framework chosen for the online Self-Assessment Tool is Research Electronic Data Capture (REDCap), an internationally well-established, mature and secure web application for building and managing online surveys and databases developed by the Vanderbilt University. It is easy to implement, allows an individual design of the data collection instrument, and facilitates data exports, reports and basic statistics and logging.

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	Based on: FFPE-RNA (ONR CEN/TS 16827-1_2015-11-01)		BASIC y/p/n
			y = yes, p = partially, n = no
	Outside the laboratory		**y/p/n**
	Collection of tissue		y/p/n
	Information about sample donor		
should	**Donor/Patient ID** documented	*e.g. code*	y/p/n
should	**Health status of donor/patient** documented	*e.g. healthy, disease type, concomitant disease*	y/p/n
should	**Medical treatment** documented	*e.g. anaesthetics, medications, surgical or diagnostic procedures (e.g. biopsy device used for the collection);*	y/p/n
should	**Start of warm ischemia** documented	Surgery: Date of vessel ligation/arterial clamping time	y/p/n
		Surgery: Time of vessel ligation/arterial clamping time	y/p/n
	Information on the primary tissue sample		
shall	**Cold ischemia (start)** documented	Date of tissue removal from body	y/p/n
		Time of tissue removal from body	y/p/n
shall	**Tissue type and condition** documented	General tissue type and condition	y/p/n
		Organ of origin + location within	y/p/n
shall	**Start of fixation (if started outside the biobank)** documented	Date of start	y/p/n
		Time of start	y/p/n
		Fixative type	y/p/n
		Fixation condition	y/p/n
	Information on the primary tissue sample processing:		
shall	**Modifications after removal from body** documented	*e.g. labelling for specimen orientation such as ink-marking, stitches, incisions*	y/p/n
shall	**Selection/use of transport containers** performed	*e.g., cooling box, vacuum packaging, ..*	y/p/n
shall	**Selection/use of stabilisation procedures for transport of unfixed primary tissue** performed	*e.g., cooling methods, fixation*	y/p/n
shall	**Labelling of the transport container** performed	*e.g., registration-no., barcode (1D or 2D), primary sample type, quantity, and organ tissue of origin);*	y/p/n
shall		*e.g. documented when several aliquots of a single sample with different features are in one container*	y/p/n
	Transport requirements		y/p/n
	Inside the laboratory		**y/p/n**
	Primary tissue sample receipt		y/p/n
	Fixation of the specimen		y/p/n
	Evaluation of the pathology of the specimen and selection of the sample		y/p/n

Fig.1: MS Excel-based prototype of a Self-Assessment-Tool for Conformity with CEN/TS

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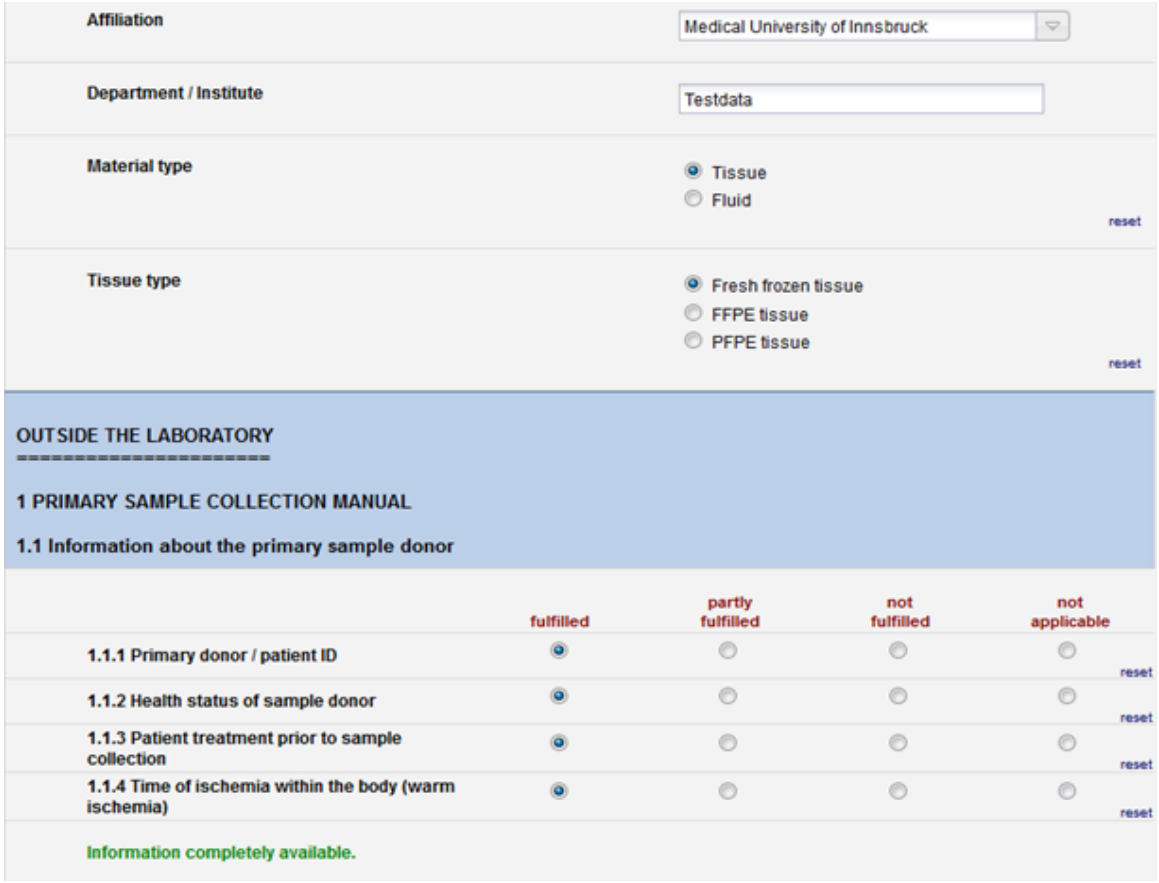

Fig. 2a: BBMRI.at prototype of an Online Self-Assessment-Tool for Conformity with CEN/TS (screenshot 1)

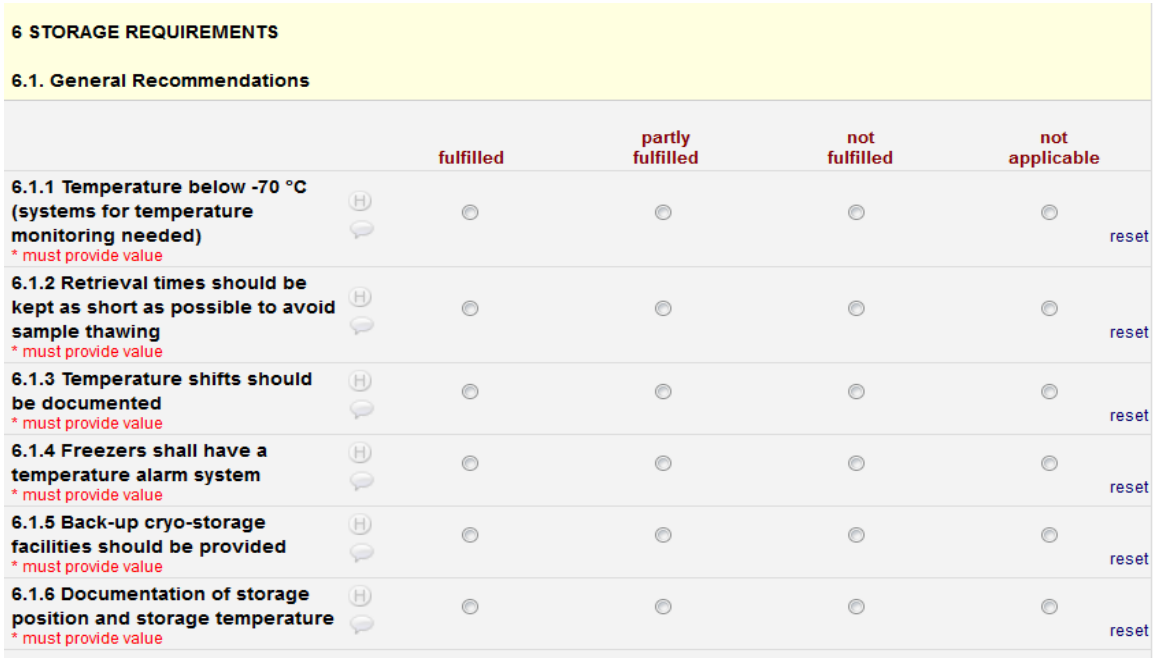

Fig. 2b: BBMRI.at Prototype of an Online Self-Assessment-Tool for Conformity with CEN/TS (screenshot 2)

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2.3 Step 3 – REDCap-based Online Self-Assessment-Tool for BBMRI-ERIC-wide use

Both the MS Excel-based (Fig. 1) and the REDCap-based online Self-Assessment-Tool prototypes (Fig. 2a,b) have been introduced to the BBMRI-ERIC community and have been optimized and extended by BBMRI-ERIC Quality Manager Andrea Wutte and the BBMRI-ERIC Quality Management Expert Group, with our support, to include all nine CEN/TS for molecular in vitro diagnostics examinations.

Fig. 3 and 4 show screenshots of the current Self-Assessment-Tool.

In the current Self-Assessment Tool biobank users are asked to fill-in main contact data, the biobank type, and the ICD-10 of the sample collection to be evaluated (Fig.3).

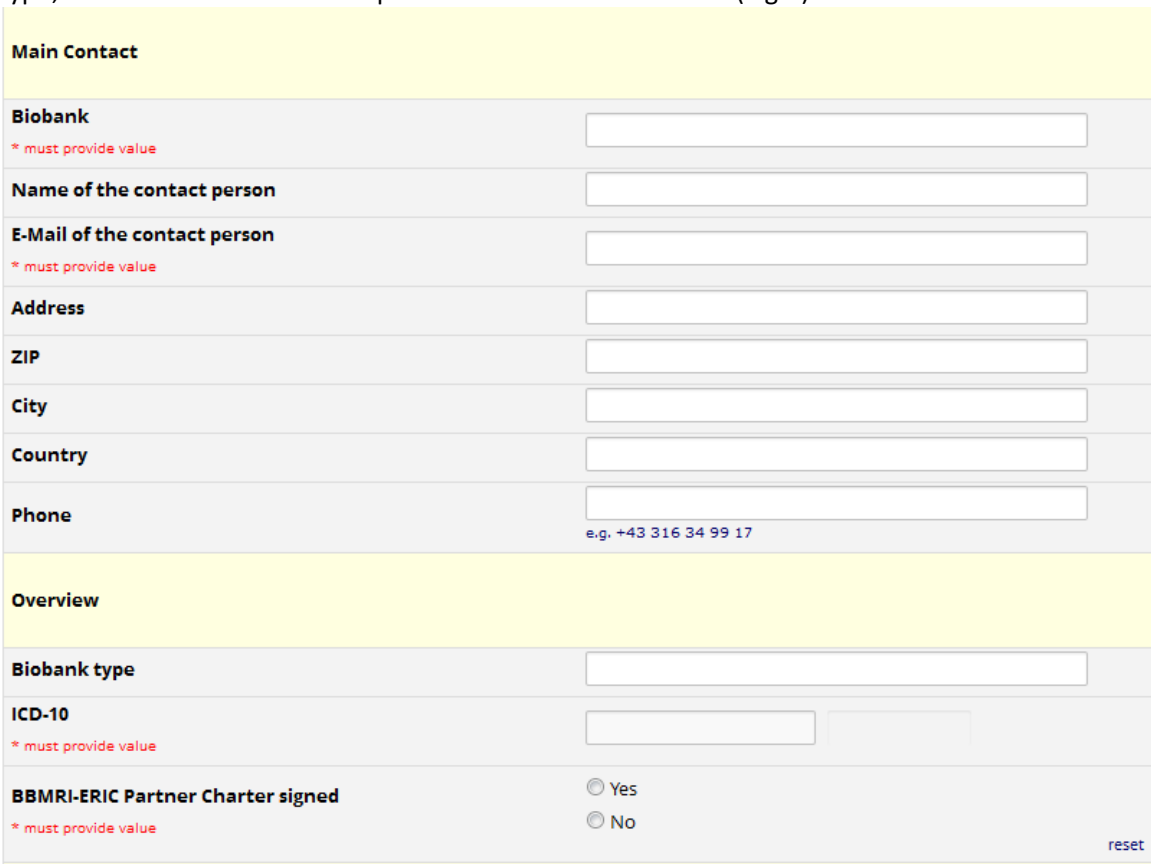

Fig. 3: Current Online Self-Assessment-Tool for Conformity with CEN/TS (screenshot of survey head)

In each of the nine Self-Assessment-Tools the users are asked point by point whether they fulfil the CEN/TS “shall”-requirements and “should”-recommendations (yes/no). Fig. 4 gives an impression of some of the questions in the Self-Assessment-Tool for Venous Whole Blood – ccfDNA.

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EDTA tubes used? **should** * must provide value	○ Yes ○ No e.g. EDTA used instead of container with ccfDNA stabiliser	reset
The use of serum tubes avoided? **should** * must provide value	○ Yes ○ No	reset
Primary venous whole blood collection and stabilization		
Identity of person collecting the blood is documented? **shall** * must provide value	○ Yes ○ No	reset
Date of blood collection documented? **shall** * must provide value	○ Yes ○ No	reset
Time of blood collection documented? **shall** * must provide value	○ Yes ○ No	reset
Appropriate labelling of the blood collection tube used? **shall** * must provide value	○ Yes ○ No e.g. routine procedure or procedure with additional information (e.g. 2D-barcode)	reset
Manufacturer's instructions of the blood collection tube or set followed? **shall**	○ Yes ○ No	reset
Manufacturer's instructions for filling the tube followed? **shall** * must provide value	○ Yes ○ No	reset
Manufacturer's instructions for mixing or inverting the tube followed? **shall** * must provide value	○ Yes ○ No	reset

Fig.4: Screenshot of the pre-examination processes of venous whole blood – part3

3. Conclusions & Discussion

With the help of ADOPT BBMRI-ERIC which was funded under the umbrella of the European Union and the research and innovation program Horizon 2020 it was possible to generate and implement this Self-Assessment-Tool.

The Self-Assessment-Surveys can serve several purposes:

- Self-assessment by the biobanks of its pre-analytical processes to check whether they conform to the CEN/TS. This shall help the biobanks to identify gaps between the current process and the target status and initiate a process of improvement by adapting its pre-analytical processes and corresponding SOPs.

- Information for BBMRI-ERIC that a certain sample collection of the biobanks fulfils the requirements of the CEN/TS and application for an appropriate labelling of the "CEN/TS

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Conformity" of that collection in the BBMRI-ERIC Directory. To achieve this, users have to complete the survey and submit it to BBMRI-ERIC. With the label/sign "CEN/TS conform" the biobanks will receive more attention from their customers regarding their quality defined samples and related data.

No other network or research infrastructure provides such a service to its members. With the help of this Self-Assessment-Survey a harmonization and thus the comparability of the data and samples is striven for. In order for researchers from academia and industry to see which biobanks in Europe provide CEN/TS compliant samples. With regard to the research of new biomarkers and personalized medicine, comparable samples and data are provided.

4. Next Steps

The Self-Assessment-Tool is currently in a correction loop. Before the launch of the tool several questions have to be clarified and defined within BBMRI-ERIC, e.g. the question of access to the tool, hosting of the tool, which person in BBMRI-ERIC receives and has access to the submitted evaluations, etc. Furthermore, a way to highlight (label/sign) CEN/TS conform sample collections in the BBMRI-ERIC Directory to make the high quality of samples in BBMRI-ERIC biobanks visible for researchers from industry and academia is being worked on. It is planned to launch the Self-Assessment-Tool in 2017.

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