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An IT-Supported Evaluation Tool for Biobanks Based on International Guidelines to Improve the Biosample Quality

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Abstract. Background: The quality of samples stored within a biobank relies on the specimen collection, the transportation, the pre-analytical processing and the long-term storage. Standard Operating Procedures (SOPs) are essential tools to guarantee the quality of samples. Objectives: The aim of this paper is to present an IT-supported tool (Pre-An Evaluation Tool) that allows assessing the compliance of current pre-analytical procedures (defined in SOPs) of a biobank with international guidelines. The Pre-An Evaluation Tool was implemented based on CEN technical specifications for pre-analytical procedures using REDCap. Results: The data collection instrument of the Pre-An Evaluation tool consists of more than 250 items related to the CEN technical specifications. In order to create a dynamic questionnaire, items following a branching logic were implemented. Conclusion: The Pre-An Evaluation tool is a user-friendly tool that facilitates the assessment of the coverage of the CEN technical specifications by specific SOPs. This tool can help to identify gaps within SOPs and therefore contribute to the overall quality of biological samples stored within a biobank.

Keywords. Biobank, sample handling, evaluation

1. Introduction

Biobanks store biological samples together with related clinical data, informed consent declarations and information regarding the pre-analytical processes and storage conditions. Biological samples are used for research purposes that aim to integrate biological findings, genomic data, molecular technologies and phenotype data in order to improve the knowledge of human diseases and to develop new diagnostic and therapeutic approaches [1]. High quality samples are an essential quality indicator for (bio-) medical research outcomes [2]. The quality of samples relies on the specimen collection, the pre-analytical processing as well as the long-term storage. Bad sample quality can result in inaccurate data and, as a consequence, in compromised research outcomes [3]. For instance, transport delays or deviations can lead to low quality DNA or RNA and therefore to low quality data. Also, degradation of enzymes and nucleic acids might be influenced by the duration of tissue fixation [4]. Standard Operating Procedures (SOPs) that provide a strong standardization of sample handling help to

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assure quality in a laboratory environment. However, SOPs are not only defined to describe sample handling procedures but also the conception of experiments and analysis [5]. Depending on the size, the background and the certification of a laboratory, SOPs are often documented at different levels of detail. The implementation of harmonized standard operating procedures for biobanking is a key objective of the Austrian national node (BBMRI.at) of the pan-European Biobanking and BioMolecular Resource Research Infrastructure (BBMRI) [6]. In order to trigger such a harmonization process, the current state had to be assessed. Therefore, it was necessary to evaluate the compliance of the current pre-analytical procedures in Austrian biobanks with internationals standards and guidelines, such as the WHO/IARC, OECD, or the CEN guidelines.

The aim of this paper is to present an IT-supported tool (Pre-An Evaluation Tool) that allows assessing the compliance of current pre-analytical procedures of a biobank with international guidelines. This tool should enable to gather information about to which extent the currently installed SOPs cover the requirements defined within international guidelines in a quick and useful manner using a questionnaire. The tool should provide a framework to assess information at different levels of granularity in order to subsequently identify commonalities and differences between SOPs and to put a step towards harmonization and standardization of SOPs.

The remainder of this paper is organized as follows: Section 2 includes a description of the material and methods involved in the IT tool development. In Section 3, the results are described in detail. Section 4 discusses the obtained results and provides an outlook and a conclusion.

2. Material and Methods

This section describes the material and methods used to implement the proposed Pre-An Evaluation Tool.

2.1. International Standards and Guidelines

Currently, several different international standards and guidelines exist that provide recommendations regarding the collection, reception, processing, storage and retrieval of high-quality samples in biobanks. Examples for such standards and guidelines are the WHO/IARC guidelines, the OECD guidelines or the CEN technical specifications. After having analyzed all of these standards, it was decided to use the CEN technical specifications as the basis for the implementation of our Pre-An Evaluation Tool. These provide concrete guidelines for handling, documenting and processing samples of high quality for the following sample types: (1) venous whole blood, (2) serum, (3) plasma, (4) urine, (5) snap-frozen tissue, (6) formalin-fixed and paraffin-embedded (FFPE) tissue, and (7) PAXgene-fixed and paraffin-embedded tissue. Specifically, the following guidelines listed in Table 1 were used to assess the compliance of current pre-analytics based on important recommendations to enhance the quality of fluid and tissue samples.

The guidelines were analyzed in detail in order to identify a common structure that could be used for comparison with the current pre-analytical procedures established within a biobank and the implementation of the Pre-An Evaluation Tool.

Table 1. List of the CEN Technical Specifications used for the implementation of the Pre-An Evaluation Tool

CEN Technical Specifications
CEN/TC 140 Molecular in-vitro diagnostic examinations - Specifications for pre-examination process for blood - genomic DNA (Version 2013/10)
CEN/TS 16835-1 Molecular in-vitro diagnostic examinations - Specifications for pre-examination process for venous whole blood – Part 1: Isolated cellular RNA (Version 2015/07)
CEN/TC 140 Molecular in-vitro diagnostic examinations - Specifications for pre-examination process for metabolomics in urine, venous blood serum and plasma (Version 2015/01)
CEN/TC 140 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Isolated genomic DNA (Version 2014/12)
CEN/TC 140 Molecular in-vitro diagnostic examinations - Specifications for pre-examination process for metabolomics in urine, venous blood serum and plasma (Version 2015/01)
CEN/TC 140 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for venous whole blood - Isolated circulating cell free DNA (Version 2014/12)
NVN-CEN/TS 16826-1 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for snap frozen tissue – Part 1: Isolated RNA (Version 2015/09)
CEN/TS 16827-3 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for FFPE tissue – Part 2: Isolated DNA (Version 2015/08)
NVN-CEN/TS 16826-2 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for snap frozen tissue – Part 2: Isolated proteins (Version 2015/09)
CEN/TS 16827-1 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for FFPE tissue – Part 1: Isolated RNA (Version 2015/08)
NVN-CEN/TS 16827-2 Molecular in-vitro diagnostic examinations - Specifications for pre-examination processes for FFPE tissue – Part 2: Isolated proteins (Version 2015/09)

2.2. Research Electronic Data Capture (REDCap)

The basic structure of the Pre-An Evaluation tool was developed by extracting the most important steps and requirements for pre-analytical processes in biobanking from the CEN technical specifications (e.g. documentation of information about the sample donor ID, documentation of protocol deviations). These requirements were first listed in a Microsoft Excel matrix in order to identify a common structure for the several different material sub-types from the various CEN technical specifications. In a workshop, this matrix was discussed by stakeholders from different disciplines (e.g. quality managers, computer scientists, medical experts). The stakeholders approved of the matrix. Thereafter a suitable framework for the implementation needed to be identified. Such a framework had to fulfill the following requirements, which were pre-defined by the work-package leader and his team and committed by the management committee of the project (consisting of different stakeholders such as medical experts, computer scientists, quality managers):

- web-based
- secure
- dynamic/dependent fields
- easy to implement
- user-friendly
- scalable
- flexible

In order to facilitate the evaluation and the quick analysis of the results avoiding media disruption, the evaluation tool needed to be IT-based. As we wanted to use a tool that needs to be installed and implemented in one place while granting access for all national partners of the BBMRI.at project, we decided to use a web-based tool. Whenever a web-based tool is selected, a strong focus has to be put on security aspects. To develop and implement a user-friendly evaluation tool, which is an import prerequisite for IT-based tools, the usage of dependent fields (fields that depend on the input given by another (previous) field) was strongly recommended. The evaluation tool should also be flexible and scalable in order to allow and motivate re-usage by non-IT specialists for similar purposes.

The Research Electronic Data Capture (REDCap) framework was used for the implementation of our "Pre-An Evaluation Tool". REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [7]. REDCap was developed by Paul Harris and his colleagues at the Vanderbilt University [7]. Today the REDCap consortium consists of more than 1,500 active institutional partners in more than 90 countries. The Department of Medical Statistics, Informatics and Health Economics of the Medical University of Innsbruck is one of the members of this REDCap consortium and runs this system in order to facilitate several different studies, where data is collected and managed (e.g. using electronic case report forms). REDCap is a PHP-based framework using a MySQL database. It offers basic functionalities that are important for the Pre-An Evaluation Tool in order to assess the compliance of current pre-analytical procedures with international guidelines. It is easy to implement and allows an individual design of data collection instruments by a point-and-click approach. Apart from common option for data collection fields, such as text boxes, drop-down fields, radio buttons, sliders, it also offers calculated fields and facilitated a so-called branching logic, which enables the implementation of dependent fields and therefore supports the dynamic compilation of the final questionnaire. For example, if a participant is male (sex), there is no need to answer questions concerning the participant's pregnancy. These questions are not displayed when using a branching logic that activates a field (e.g. concerning pregnancy) only if the variable sex is female ([sex]=female).

3. Results

The Pre-An Evaluation tool based on the aforementioned CEN technical specifications was implemented using REDCap and consisted of one data collection instrument. The Pre-An Evaluation Tool was logically subdivided into three parts: (1) affiliation and material type information, (2) steps performed outside the laboratory (e.g. documentation of information about the sample donor, transport requirements), and (3) steps performed inside the laboratory (e.g. storage requirements, selection of storage containers). The first part collects basic information about the partner completing the questionnaire in order to facilitate a proper data analysis for each partner. Additionally, the partners have to select the specific material types and sub-types for which the questionnaire was completed (see Fig. 1). The second and third part of the Pre-An Evaluation tool contained information according to the CEN technical which also offer a subdivision according to processes

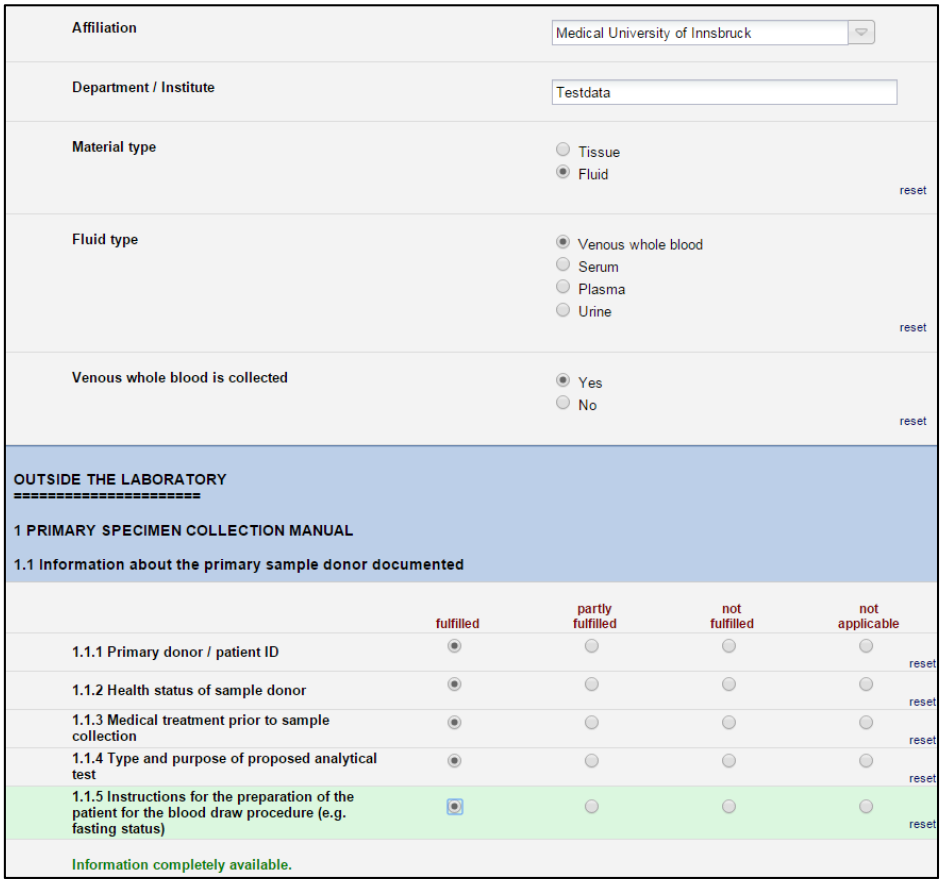

Figure 1 Excerpt from the implemented Pre-An Evaluation Tool using REDCap

outside and inside the laboratory. All material types (tissue, fluid) and sub-types covered by the CEN technical specifications (see 2.1) were taken into account for the Pre-An Evaluation tool. This selection of the type and the material sub-type influenced the content of the subsequent question items as the tool provides flexible content depending on the material sub-types selected. This allowed us to bring only such questions into the focus that are relevant for the specific material sub-type. We implemented the data collection instrument of the Pre-An Evaluation Tool by providing four pre-formulated answers (single choice): (1) fulfilled, (2) partly fulfilled, (3) not fulfilled, and (4) not applicable. These answers described the extent to which a specific recommendation of the CEN technical specification is fulfilled by a biobank (see Fig. 1).

For example, the “Testdata” Department of the Medical University of Innsbruck completed the questionnaire stating that the Primary donor / patient ID of a specimen is documented. As all required information regarding the “Information about the primary sample donor” is documented, we wanted to provide the user, who is completing the questionnaire, with immediate feedback to which extent the requirement of the CEN guidelines are covered by his/her SOPs. Therefore, we implemented a mechanism for several batteries of questions that provides such feedback based on their input (fulfilled,

Information completely available.
([q1] <> "") and ([q2] <> "") and ([q3] <> "") and ([q4] <> "") and ([q1] = 1) and ([q2] = 1) and ([q3] = 1) and ([q4] = 1)

Information partly available.
([q1] <> "") and ([q2] <> "") and ([q3] <> "") and ([q4] <> "") and !((([q1] = 1) and ([q2] = 1) and ([q3] = 1) and ([q4] = 1)) or (([q1] = 3) and ([q2] = 3) and ([q3] = 3) and ([q4] = 3)) or (([q1] = 4) and ([q2] = 4) and ([q3] = 4) and ([q4] = 4)))

Information not available.
([q1] <> "") and ([q2] <> "") and ([q3] <> "") and ([q4] <> "") and ([q1] = 3) and ([q2] = 3) and ([q3] = 3) and ([q4] = 3)

Information not applicable.
([q1] <> "") and ([q2] <> "") and ([q3] <> "") and ([q4] <> "") and (([q1] = 4) and ([q2] = 4) and ([q3] = 4) and ([q4] = 4))

Figure 2 Branching logic for a battery of four questions (1…fulfilled, 2…partly fulfilled, 3…not fulfilled, 4…not applicable)

partly fulfilled, not fulfilled or not applicable). We used separate fields that indicate, whether the information is (1) completely available, (2) partly available, (3) not available or (4) not applicable. For the implementation of this mechanism, the branching logic was used. An example for the branching logic related to the information summary for an array of four questions is given in Fig. 2.

Altogether the questionnaire of the Pre-An Evaluation Tool consisted of more than 300 items. The number of items for each material sub-types related to part 2 and part 3 of the questionnaire (outside and inside the laboratory) are listed in Table 2. Within this table, the items related to the affiliation and the material types as well as the special items for the immediate user feedback (information completely available/partly available/not available/not applicable) were not displayed.

Validation of the Pre-An Evaluation Tool: In order to guarantee the validity, usefulness and good usability of the Pre-An Evaluation Tool, it was iteratively tested and improved. First, it was tested by the implementers. Then, a pilot version was sent to the major BBMRI.at partners (Medical University of Innsbruck, Medical University of

Table 2. Number of items of the Pre-An Evaluation Tool for each material sub-type

Material sub-type	Number of items	
	Part 2: Outside the laboratory	Part 3: Inside the laboratory
Venous whole blood	18	8
Serum	17	15
Plasma	20	18
Urine	15	13
Snap-frozen tissue	14	27
FFPE tissue	15	33
PFPE tissue	15	30

Vienna, Biobank Graz, University of Veterinary Medicine Vienna, Paracelsus Medical University). They were asked to provide feedback on the content as well as on the usability of the tool. No training or expertise is required to use the tool. The users were provided with short instructions on the tool and were able to use it without any problems. The pilot version of the Pre-An Evaluation Tool was thereafter revised according to feedback of the participants. The reported issues (e.g. splitting singe question items into two items) lead to minor revisions of the tool. Then, a second pilot evaluation round was triggered including the same partners which lead again to a revision of the tool (mainly typo fixing). Finally, the approved version of the Pre-An Evaluation Tool was provided and will be used for future evaluation. The tool also offers a reporting mechanism, which facilitates the export of the data collection to various different statistical packages (e.g. SPSS, STATA, R, SAS). This allows performing an assessment and comparison of the different participating institutions after finalizing the evaluation phase.

4. Discussion

This paper describes the implementation of the Pre-An Evaluation Tool that facilitates the assessment of the compliance of current pre-analytical procedures within a biobank with international guidelines in biobanking. The basic structure of the Pre-An Evaluation Tool is pre-defined by the CEN technical specifications. We decided to use the (upcoming) CEN guidelines as they are concrete guidelines for handling, documenting and processing samples, and since they are going to become international ISO standards within the next few years. They provide important recommendations to ensure high quality for biological samples which is a major prerequisite for high-quality research outcomes.

The Pre-An Evaluation Tool itself was implemented using REDCap. We decided to use this framework as it fulfills all of our pre-defined requirements. It is an internationally used framework for capturing and managing data. REDCap allowed us to implement the Pre-An Evaluation Tool in a highly dynamic and customized manner, which offers the future survey participants maximum comfort, when completing the survey.

A major point of discussion was not related to the implementation of the Pre-An Evaluation Tool itself, as it is flexible and can be adjusted and adapted easily but to the pre-defined answers of the questionnaire. One could state that - according to a specific SOP - for example the sample donor's name is either documented (fulfilled), not documented (not fulfilled) or, for certain reasons, not applicable (e.g. for animal biobanks) but it certainly cannot be partly fulfilled. Even though we were aware of this point, we decided to provide such an answer option for the following reason: Within the BBMRI.at project, there exist several different types of biobanks. There are several centralized biobanks having a common quality management system and SOPs, but there are also many decentralized sample collections established for specific research study purposes, which don't have shared SOPs or quality management systems. Therefore, it is not always possible to answer "yes" or "no" for a partner, sometimes it is "partly fulfilled" (some collections' SOPs provide the required information, others don't).

Altogether we conclude that the Pre-An Evaluation tool is a user-friendly tool that facilitates the assessment of the coverage of the CEN technical specifications by specific SOPs. This tool can help to identify gaps within SOPs and therefore contribute to the overall quality of biological samples stored within a biobank.

Currently, we are conducting an assessment of the compliance of current pre-analytical processes with international guidelines for Austrian biobanks participating in the BBMRI.at project using the proposed Pre-An Evaluation Tool. The presented tool is highly flexible and can be adapted in order to meet other requirements related to the quality assurance of pre-analytical procedures in biobanking.

The usage of the presented Pre-An Evaluation Tool as a basis for a self-assessment tool for quality management in biobanking is discussed on an international level within the BBMRI-ERIC[2] infrastructure.

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