Letter to the Editor

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Quality management at the national biobanking level – establishing a culture of mutual trust and support: the BBMRI.at example

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To the Editor,

In biomedical research, irreproducible results are increasingly recognized as a major threat for scientists and the public and causing significant losses of private and public investments in research. Recent investigations have revealed that unreliable results are to a large extent caused by poor biological reagents and reference materials [1]. The low quality of those materials often results from improper or unstandardized pre-analytical procedures [2]. Therefore, an increasing number of professional biobanks evolve with the primary aim of providing high-quality biomaterials which are processed, stored and delivered under reasonable, standardized conditions. On a European level, these biobanks are supported by BBMRI-ERIC (Biobanks and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium [http://www.bbmri.eu]), as well as by its national nodes. In Austria, BBMRI.at was established in 2013 and involves the Medical Universities of Graz, Innsbruck and Vienna, the Veterinary University of Vienna, the Paracelsus Medical Private University Salzburg, the Alpen-Adria Universität Klagenfurt and the University of Vienna (http://www.bbmri.at).

We hereby outline the Austrian endeavors toward a harmonized quality management with reciprocal quality audits as an efficient means to harmonize quality management and as a sign of mutual trust and support within the national node BBMRI.at. The positive experience of the Austrian academic biobanks regarding their joint adoption of internationally valid standards might encourage other Biobank consortia to follow the example of BBMRI.at.

The primary objectives of BBMRI.at's work package on quality management (WP-QM) were (a) to facilitate the establishment/improvement of ISO 9001-based quality management systems (QMS), (b) to harmonize operations on the basis of international benchmarks and (c) to lay the foundation for intra-consortial cross-audits providing both subject-specific consulting for the auditee

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and insight into established structures for auditors delegated by biobanks with less developed QMS. The governance structures of BBMRI.at/WP-QM and the interface to BBMRI-ERIC are depicted in Figure 1.

In the absence of a biobank-specific QMS standard when the project was started, the BBMRI.at consortium agreed on local adherence to ISO 9001:2008 (later: 2015) as a basis for their individual QMS. This decision was based on the pragmatic fact that major players within the consortium were at this time already certified according to this standard, which meant cumulative experience and less overall expenditure. On the other hand, ISO 9001 is a generic quality management standard that is easily adaptable for various purposes, and therefore widely used by the biobanking community [3].

Subsequently, pre-analytical processes ("realization processes") were harmonized to facilitate the processing of biomaterial according to common protocols within different partner biobanks, e.g. in the framework of multi-centric studies, and to improve cross-biobank comparability, in case researchers need to use samples from different partner biobanks for answering one specific research question. A series of technical specifications (TS) on pre-analytical sample processing by the European Committee for Standardization (CEN) Technical Committee CEN/TC 140 "in-vitro diagnostics" under the main title "In-Vitro Diagnostic Examinations – Specifications for Pre-examination Processes" (CEN/TS) [4] was taken as a common basis. These CEN/TS available for different sample types (e.g. tissue, blood or other body fluids) and analytes (e.g. DNA, RNA or protein) contain provisions in the form of requirements and recommendations for pre-analytical procedures carried out inside and outside the laboratory, as a considerable portion of errors occurs before the sample reaches the laboratory [5]. The CEN/TS are being or some have already been developed further into ISO standards [6]. In the framework of WP-QM, the available CEN/TS were operationalized, and harmonized process flows were constructed and integrated into the local QMS (Figure 2A). By this, it was possible (i) to check if all CEN/TS requirements/recommendations were addressed in the QM realization processes as concrete steps/stages and covered by a respective document (e.g. standard operating procedure, SOP), (ii) to assign quality indicators to the distinct process stages in a targeted manner (Figure 2B) and (iii) to consider appropriate procedures for process stages not covered by the CEN/TS (e.g. sample access). The implementation of the CEN/TS into routine operations was facilitated by BBMRI.at work package 1 "Sample management", which provided IT-based self-evaluation tools assessing the compliance with the requirements of the different CEN/TS [7, 8].

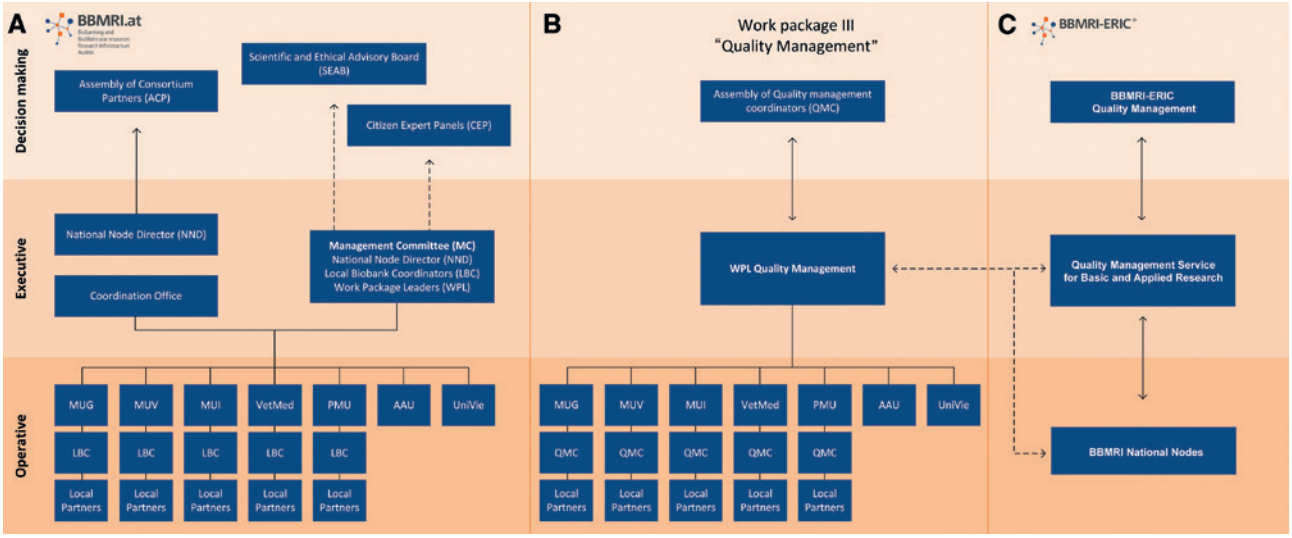

Figure 1: Governance structure of BBMRI.at (A), structural organization of work package quality management (B), and interface to BBMRI-ERIC (C).

(A) Governance structure of BBMRI.at. Strategies are mapped out by the Assembly of Consortium Partners (ACP), consisting of the cooperating universities' rectorate representatives, and then implemented by the Local Biobank Coordinators (LPC) and the Work Package Leaders (WPL), which form together the Management Committee (MC) under the guidance of the National Node Director (NND) and with the valuable input of a Scientific and Ethical Advisory Board (SEAB). Biobanking itself is realized locally at each consortium partners' site. (B) Structural organization of work package 3 "quality management". The work package is realized by locally nominated quality management coordinators (QMC), with the work package leading team (WPL) defining strategies and playing a facilitating role. Moreover, the WPL manages the interface to non-medical partner institutes and maintains contacts with (C) the BBMRI-ERIC QM service and QM representatives of other BBMRI national nodes.

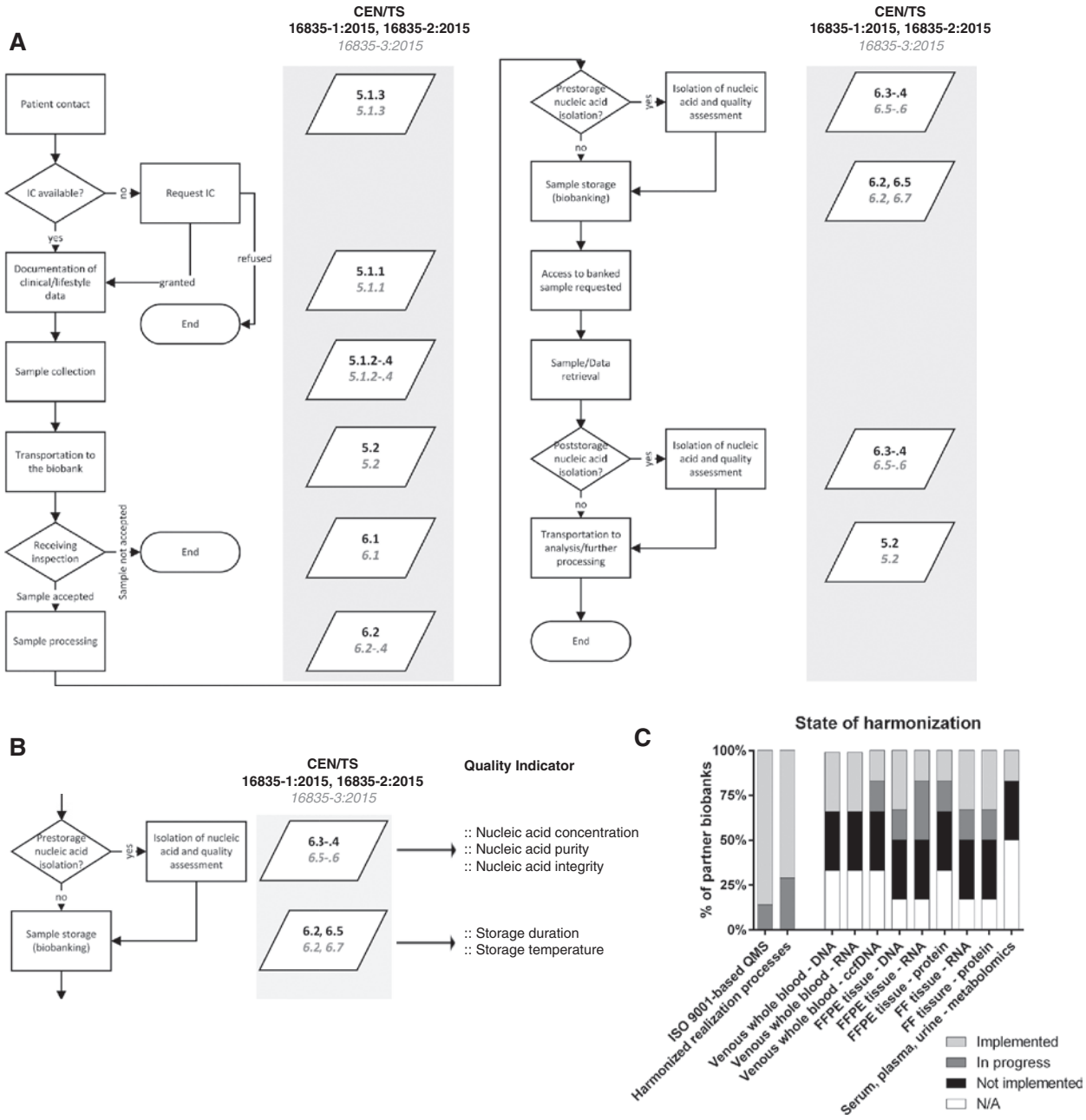

Figure 2: Harmonized operations on the basis of CEN/TS (A) facilitate the identification of appropriate quality indicators (B). Status of BBMRI.at work package QM (C).
(A) Operationalization of CEN/TS 16835-1 "Molecular in vitro diagnostic examinations – specifications for pre-examination processes for venous whole blood – Part 1: Isolated cellular RNA" (bold), CEN/TS 16835-2 "– Part 2: Isolated genomic DNA" (bold), and CEN/TS 16835-3 "– Part 3: Isolated circulating cell free DNA from plasma" (gray italics). CEN/TS chapters (given in white parallelograms within the gray fields) were translated into process stages. In a second step, additional process steps, indispensable for biobanking, but not covered by the CEN/TS (missing parallelograms in gray fields) were included. These flow charts serve as tools for basic evaluations of realization processes (e.g. is every process stage covered by a specification document?) and help to find appropriate quality indicators. (B) Example of deducing quality indicators from the steps of the process flow chart. (C) Percentage of BBMRI.at-associated biobanks/biobank sections with ISO 9001-based QMS and harmonized realization processes on the basis of CEN/TS for pre-examination processes. N/A, not applicable (biobank does not collect the respective material); FF, fresh frozen; FFPE, formalin fixed paraffin embedded; ccfDNA, circulating cell-free DNA; QMS, quality management system.

This approach was further evolved by BBMRI-ERIC and is now – as BBMRI-ERIC Self-Assessment Surveys – available for other biobanks to evaluate their biobank collections. If collections are processed according to CEN/TS requirements, they are highlighted in the BBMRI-ERIC sample directory [9].

Of the seven participating biobanks/biobank sections, six (86%) were at the end of 2018 included into a certified QMS according to ISO 9001, whereas only one biobank reported that implementation of an ISO 9001-based QMS is still underway. Moreover, five biobanks (71%) reported having their main realization processes in compliance with harmonized process flow charts (see Figure 2C). Notably, no biobank/biobank section reported having not made any progress regarding the harmonization of QMS and/or realization processes. Due to the very recent introduction of the first CEN/TS and their far-reaching requirements, their implementation is still in progress. However, approximately half of the biobank sections have started implementing the applicable CEN/TS or are already operating according to the specifications (see Figure 2C). Hence, the Austrian Biobank Catalog (http://catalog.bbmri.at/) currently includes nine collections comprising ~250.000 samples (as per 05/2019), where the material was processed in a way that meets the requirements of the relevant CEN/TS (http://catalog.bbmri.at/search.html?_cachebust=2.6.2&mode=list). These collections are also listed in the directory of BBMRI-ERIC (https://directory.bbmri-eric.eu/).

The establishment of intra-consortial cross-audits based on ISO 9001:2008 required a high degree of mutual trust as the biobanks agreed to provide in-depth insight into internal processes to other biobanks that may have to compete for funding sources. An audit program for the first audit round (2017/2018) was compiled, which covered all chapters of ISO 9001:2008 (later: 2015) and included all cooperating biobanks. For this, checklists based on ISO 9001:2008 were compiled by translating the requirements of the standards into corresponding questions, which could be answered with “fulfilled”, “partly fulfilled” or “not fulfilled”. Each audit was preceded by an audit plan that was timely delivered to the auditees and resulted in a written audit report, which was disclosed to all BBMRI.at biobanks. Moreover, aggregated results of the audit program were disseminated to the biobanking community via BBMRI.at and BBMRI-ERIC newsletters and on the corresponding websites.

In conclusion, establishing a QMS means that individually conducted processes have to be harmonized with generally accepted provisions. Cross-audits of biobanks revealed to be an efficient means for capacity building in quality management and harmonization at national and perhaps also international levels. Although a certain level of trust is a prerequisite for biobanks to participate in a cross-auditing program, the trust-building effect was seen as a major additional outcome.

Under this aspect, it is advisable to face quality-related challenges together and to avoid simultaneous re-inventions of the wheel. The Austrian biobank consortium BBMRI.at followed this mission and established not only harmonized QMS and realization processes based on internationally valid standards, but also mutual trust that allowed performing consortium-wide cross-audit based on an audit program developed by BBMRI.at. During the next 5-year period of BBMRI.at, Austrian biobanks will pursue the implementation of CEN/TS (or corresponding ISO documents) and consider the implementation of the newly established biobank standard ISO 20387:2018 [10], which includes biobank-specific aspects that were not fully covered by ISO 9001 or CEN/TS.

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