ADOPT BBMRI-ERIC

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DELIVERABLE REPORT

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Executive Summary

In this handbook, produced jointly with the BBMRI-ERIC National Nodes in the context of the ADOPT BBMRI-ERIC Project, we list the current best practice documents, regulations and standards that are important for sample quality. Additionally, we provide information on the BBMRI-ERIC services regarding auditing and evaluation of biobanks, information on conformity testing and a comprehensive package of additional guidelines and information collected previously in several EU-projects, consortia and networks. All above-mentioned information has now been compiled within one handbook to be utilized as a guidance document for biobanks to optimally meet users' need in biomarker research, development and validation.

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1. Background

The health care industry spends annually billions of dollars on biomarker research for precision medicine and there is a growing need to speed up the time-frame from discovery to product. New, more comprehensive analysis technologies are envisioned to help the discovery process and importance of collaboration between academic and industrial partners has become evident. While biobanks are envisaged to play a substantial role in biomarker discovery, development and validation, the utilization of biobank samples and data for product development is setting new requirements for biobank design. Modern biomarkers comprise a broad spectrum of analytes and analytical technologies (e.g., in situ techniques on tissues, such as immunohistochemistry or in situ hybridizations; and analyses of isolated biomolecules, such as genomic DNA, free circulating DNA, RNA, proteins or metabolites by various omics technologies). In order to ensure reliability of analytical data generated by the various techniques, the biological samples have to meet specific quality criteria and standardization of biobank processes is required to achieve reliable results. Furthermore, to meet the needs of biomarker development in precision medicine, the biological samples should represent the whole biological spectrum of diseases. Therefore, access to several biobanks in different countries complying with common quality standards, as established by BBMRI-ERIC and its National Nodes, is a key requirement for biomarker research and development. In this handbook, produced jointly with the BBMRI-ERIC National Nodes during the ADOPT BBMRI-ERIC Project, we provide a comprehensive package of standards, guidelines, and information that have been collected in several EU-projects, consortia and networks. This information is compiled within one handbook to be utilized as guidance for biobanks to optimally meet users' need in biomarker research, development and validation.

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2. Best practice reference documents, regulations and standards

- Organization for Economic Co-operation and Development (OECD): ***Best Practice Guidelines for Biological Resource Centers***

- World Health Organization International Agency for Research on Cancer (IARC): ***Common Minimum Standards and Protocols for Biological Resource Centers Dedicated to Cancer Research***

- National Institutes of Health / International Society of Biological and Environmental Repositories (ISBER): ***Best Practices for Repositories: Collection, Retrieval, and Distribution of Biological Materials for Research***

- National Institutes of Health/National Cancer Institute's Biorepositories and Biospecimen Research Branch (BBRB*):* ***Best Practices for Bio-specimen Resources***

- ***EU In vitro diagnostic regulation (IVDR)***: The implications of the new IVDR to biobanks were investigated in the ADOPT BBMRI-ERIC Deliverable 6.1.

- European Committee for Standardisation (CEN) developed ***Technical specifications (CEN/TS) for molecular in vitro diagnostic examinations***. Nine CEN/TS have been published. The development of CEN/TS into international standards within the International Standardisation Organisation (ISO) is ongoing:

Technical specification	International standard (ISO)
CEN/TS 16826-1:2015, Snap frozen tissue – Part 1: Isolated RNA	=> **ISO 20184-1:2018**, Snap frozen tissue – Part 1: Isolated RNA
CEN/TS 16826-2:2015, Snap frozen tissue – Part 2: Isolated proteins	=> **ISO 20184-2:2018**, Snap frozen tissue – Part 2: Isolated proteins
CEN/TS 16827-1:2015, FFPE tissue – Part 1: Isolated RNA	=> **ISO 20166-1:2018**, FFPE tissue – Part 1: Isolated RNA
CEN/TS 16827-2:2015, FFPE tissue – Part 2: Isolated proteins	=> **ISO 20166-2:2018**, FFPE tissue – Part 2: Isolated proteins
CEN/TS 16827-3:2015, FFPE tissue – Part 3: Isolated DNA	=> **ISO 20166-3:2018**, FFPE tissue – Part 3: Isolated DNA
CEN/TS 16835-1:2015, Venous whole blood – Part 1: Isolated cellular RNA	=> ISO pending 2019

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CEN/TS 16835-2:2015, Venous whole blood – Part 2: Isolated genomic DNA	=> ISO pending 2019
CEN/TS 16835-3:2015, Venous whole blood – Part 3: Isol. circ. cell-free DNA from plasma	=> ISO pending 2019
CEN/TS 16945:2016, Metabolomics in urine, serum and plasma	=> ISO pending 2019

- ***ISO Standard for biobanking:***

  In 2018, the International Standard Organisation (ISO) published an international standard for biobanking: ***ISO 20387:2018 Biotechnology — Biobanking — General requirements for biobanking***. BBMRI-ERIC contributed to the development as Liaison to ISO.

  The ISO standard for biobanking defines the general requirements for the competence, impartiality and consistent operation of biobanks, including quality control requirements to ensure appropriate quality of biological material and data collections. The biobanking standard is applicable to all organizations performing biobanking, including biobanking of biological material for research and development from multicellular organisms (e.g. human, animal, fungus and plant) and microorganisms. Biobank users, regulatory authorities, organizations and schemes using peer-assessment, accreditation bodies, and other relevant operators can also use this document for confirming or recognizing the competence of various biobanks. The biobanking standard does not apply to biological material intended for food/feed production, laboratories undertaking analysis for food/feed production, and/or therapeutic use (www.iso.org).

  The Quality Management (QM) service of BBMRI-ERIC offers biobankers a ***Self-Assessment Survey*** to monitor their compliance with the general requirements for biobanking.

  The following international standards may be relevant to biobanks offering special services to customers (users):

International standard (ISO)
ISO 9001:2015 Quality management systems – Requirements
ISO 15189:2012 Medical laboratories – Requirements for quality and competence
ISO 17025:2005 General requirements for the competence of testing and calibration laboratories

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ISO Guide 34:2009 General requirements for the competence of reference material producers
ISO 17043:2010 Conformity assessment – General requirements for proficiency testing
ISO 19011:2011 Guidelines for auditing management systems

3. Auditing and evaluation of biobanks by BBMRI-ERIC

BBMRI-ERIC has established a QM Service for basic and applied research in the area of biobanking. Relevant standards and guidelines applicable to biobanking are **ISO 20387:2018**, **ISO 9001:2015**, ***OECD Best Practices*** and ***IARC Guidelines***.

Different types of audits applicable to biobanks include:

- 1st party audit: internal audit
- 2nd party audit: external provider audit; other external interested party audit
- 3rd party audit: certification and/or accreditation audit; statutory, regulatory and similar audits

BBMRI-ERIC can conduct 1st and 2nd party audits with the aim to support biobanks heading for 3rd party audits.

ISO 20387:2018 is published to demonstrate competence and impartiality in biobanking. Most likely this standard will be subject to the 3rd party accreditation rather than certification audits.

BBMRI-ERIC is well-positioned to conduct audit programs. It operates as an experienced biobank network partner and supports biobanks and scientific partners in implementing and improving quality and management systems. In contrast to accredited national **C**onformity **A**ssessment **B**odies (CABs or NABs), BBMRI-ERIC experts (Auditors and Technical Experts, Scientist and Peers) can be deployed as exercise partners to have a pre-evaluation of their own biobank management processes in terms of conformity to ISO20387. The BBMRI-ERIC audit program is based on the principles of **ISO19011: 2018** and audits are conducted according to these criteria. To comply with the principles of Fitness for Purpose, BBMRI-ERIC audit objectives are tailored to biobanks based on relevant standards and guidelines. The BBMRI-ERIC auditors and experts are assigned in accordance with their experience and competence. Those biobanks reviewed by BBMRI-ERIC receive a BBMRI-ERIC quality mark. This quality mark does not correspond to accreditation by a CAB, but can certainly be seen as a first step towards a 3rd party accreditation.

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4. Conformity assessment

CASCO is the ISO committee that works on issues relating to conformity assessment and contributed to the biobanking standard development process. CASCO develops policy and publishes standards related to conformity assessment. It does not perform conformity assessment activities itself.

Conformity assessments activities are performed by accredited Conformity Assessment Bodies (CABs or NAB), and regulated by **Regulation (EC) no 765/2008 of the European Parliament and of the Council.**

European co-operation for Accreditation (EA) is a not-for-profit association, registered in the Netherlands. It is formally appointed by the European Commission in Regulation (EC) No 765/2008 to develop and maintain a multilateral agreement of mutual recognition, the EA MLA, based on a harmonized accreditation infrastructure. The EA MLA exists to facilitate fair trade, ensure product and service quality and reduce technical barriers to trade. EA currently has 50 Members. The EA Members are National Accreditation Bodies (NAB or CAB) that are officially recognized by their national governments to assess and verify – against international standards – organizations that carry out conformity assessment activities such as certification, verification, inspection, testing and calibration. BBMRI-ERIC is currently building up co-operation with EA.

A list of the accredited European CABs is available. In the case of mutual recognition, the CAB bodies that are members of ILAC (see below) may carry out accreditation assessments.

ILAC is an **international organisation for accreditation** bodies operating in accordance with ISO/IEC 17011 and involved in the accreditation of CABs including calibration laboratories (using ISO/IEC 17025), testing laboratories (using ISO/IEC 17025), medical testing laboratories (using ISO 15189) and inspection bodies (using ISO/IEC 17020). Accreditation is the independent evaluation of CABs against recognised standards to carry out specific activities to ensure their impartiality and competence. Implementation of national and international standards enables government, procurers and consumers to trust the provided calibration and test results, inspection reports and certifications.

ILAC dealt with ISO 20387: 2018 and has made the following decision available in Resolutions of the 22nd ILAC Assembly, Singapore 31 October 2018:

- General Assembly resolves that the standard applicable to biobanks **for the purposes of accreditation** will be ISO 20387 Biobanking – General requirements for biobanking, to be used as a standalone standard.

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5. Guidance documents to biobanks

- **Establishment of a biobank:**
  - The BBMRI-LPC project (FP7) produced a ***Handbook for Practical Biobanking*** providing information about the different types of biobanks (clinical and population-based), the establishment of a biobank, the legal and ethical landscape, the types of information and samples to be collected (incl. SOP and ISO based QC for management, handling and storage). It also provides data about several biobanks in Europe with emphasis on the Eastern Europe as a less covered area. Important aspect was IT and bioinformatics solutions as well as possibilities to link biobanks with the national health and disease registries. Last but not least, access to the biobank data and samples, and education and training have been covered. All this basic information is supported with relevant scientific literature and review articles. The BBMRI-LPC Handbook for Practical Biobanking provides a quick primer to an emerging biobank and a roadmap for an existing biobank. Keeping in mind the advent of the personalized medicine and personal prevention, it is topical for each country to start a biobank and the current handbook serves this purpose very well.

  - IARC (International Agency for Research on Cancer) has published an online platform entitled ***Biobank learning*** for the dissemination of learning and training material for biobank-based research professionals. It includes resources developed in the framework of the B3Africa project and the BCNet initiative as well as other relevant projects and initiatives. It also provides links to resources developed by other organizations. The material included provides information about sample and data collection and management, quality as well as ethical and legal issues.

- **Sample collection, processing, automation:**

  - The BBMRI-LPC project (FP7) investigated sample management and analysis. Approximately 20 large-scale biobanking facilities participated in a network activity to provide an evidence base for continued integration and improvement of biobanking facilities and procedures. Services provided at the collaborating centers have been described and discussed in terms of processes, instrumentation and QC measures. ***An external quality assurance scheme; workshop and report*** and ***Common catalogue of biobanking services. Workshop***

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and report have been published as a BBMRI-LPC WP9 deliverable reports D9.3 and D9.5, respectively.

- **Quality management and certification:**
  - **The Quality Management (QM) service of the BBMRI-ERIC** offers biobankers self-assessment surveys to monitor compliance with relevant standard requirements.
  - ***Procedure and checklist for on-site visit evaluation*** has been published as an ADOPT WP2 deliverable report D2.1.
  - ***IT tool for monitoring compliance of biobanks with CEN TS molecular diagnostic examination*** has been published as an ADOPT BBMRI-ERIC deliverable report D6.3.
  - BRISQ - Biospecimen reporting for improved study quality guidelines represent a resource tool aiming to strengthen communication and publications around biospecimen-related research More information available in an article by Moore HM *et al* (2011) entitled ***Biospecimen reporting for improved study quality (BRISQ)***
  - The impact of pre-analytical factors on biomarker assay performance is especially relevant in the context of companion diagnostics. Examples of FDA-listed companion diagnostics devices and their biomarker features have been previously described in a chapter of the ***Handbook of Biomarkers & Personalized Medicine*** (Stumptner C, Sargsyan K, Kungl P, Zatloukal K. Crucial role of high quality biosamples in biomarker development. in Handbook of Biomarkers & Personalized Medicine, edited by Claudio Carini, Mark D Fidock, Alain van Gool, Taylor & Francis, p. 128-34, in press)
- **Data linked to samples:**
  - ADOPT BBMRI-ERIC Project has collected a Colon Cancer Cohort dataset from BBMRI-ERIC member biobanks as a use case for piloting access to European biobanks. In this context, clinical data attributes for Colon Cancer were defined (***Manuscript in preparation***)
  - ***MIABIS 2.0*** standard represents the minimum information required to describe biobanks and sample collections at aggregate level. The MIABIS standard aims to facilitate the reuse of bio-resources and associated data by harmonising biobanking and biomedical research (Merino-Martinez et al., 2016)

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- **Analysis of samples:**
    - Requirements for biochemical analyses: Biobank samples are recommended to be analysed by ISO certified laboratories.
        - **ISO 9001:2015** Quality management systems – Requirements
        - **ISO 15189:2012** Medical laboratories – Requirements for quality and competence
        - **ISO 17025:2005** General requirements for the competence of testing and calibration laboratories
        - **ISO Guide 34:2009** General requirements for the competence of reference material producers
        - **ISO 17043:2010** Conformity assessment – General requirements for proficiency testing
        - **ISO 19011:2011** Guidelines for auditing management systems

    - Requirements for omics analyses have been investigated by ADOPT BBMRI-ERIC and have been published as a WP6 deliverable report D6.4 ***Best practice document for optimal usage of omics technologies for biomarkers***

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6. Additional information and useful links

Biobank Catalogues

BBMRI-ERIC Directory https://directory.bbmri-eric.eu
BBMRI-LPC www.bbmri-lpc-biobanks.eu/cataloque.html
EuroBioBank www.eurobiobank.org/sample-catalogue

Biobank Networks and Societies
BBMRI-ERIC www.bbmri-eric.eu
ESBB www.esbb.org
ISBER www.isber.org
BBRB www.biospecimens.cancer.gov/default.asp
P3G www.P3G.org

7. References

Moore HM et al. Biospecimen reporting for improved study quality (BRISQ). J Proteome Res. 2011 Aug 5;10(8):3429-38. doi: 10.1021/pr200021n. Epub 2011 Jun 21.

Merino-Martinez, R, Norlin, L., van Enckevort, D., Anton G, Schuffenhauer, S., Silander, K., Mook, L., Holub, P., Bild, R., Swertz, M., and Litton, J.E. Toward Global Biobank Integration by Implementation of the Minimum Information About Biobank Data Sharing (MIABIS 2.0 Core). Biopreserv. Biobanking 14:4, 298-306, 2016

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