



MAKING NEW TREATMENTS POSSIBLE

GOOD STANDARDISATION PRACTICE IN BIOMEDICAL RESEARCH

ANDREA WUTTE

AW, September 24, 2019

CliniMARK summer-school, Spetses 23-27 September 2019

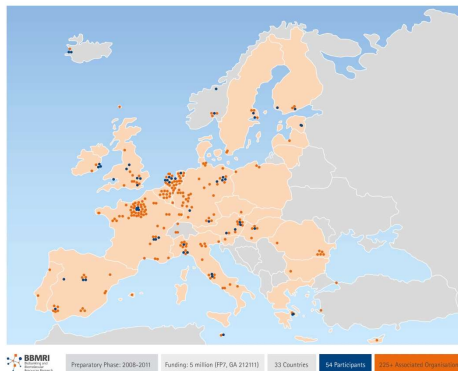
1

BBMRI-ERIC HISTORY OF ORIGIN

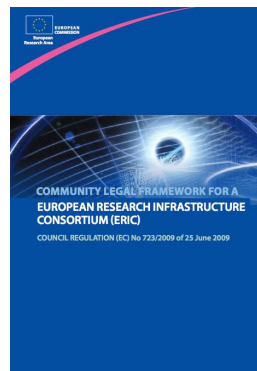
1st ESFRI Roadmap 2006



The Preparatory Phase, Application 2008 - 2013

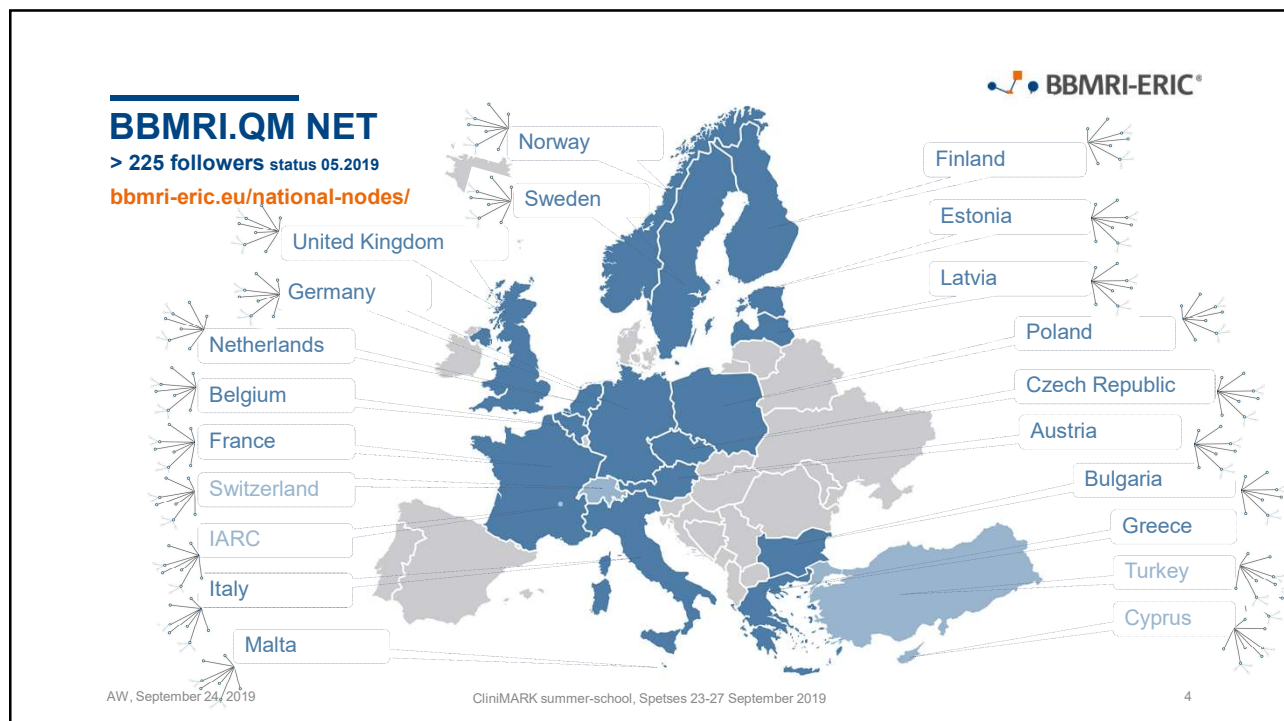
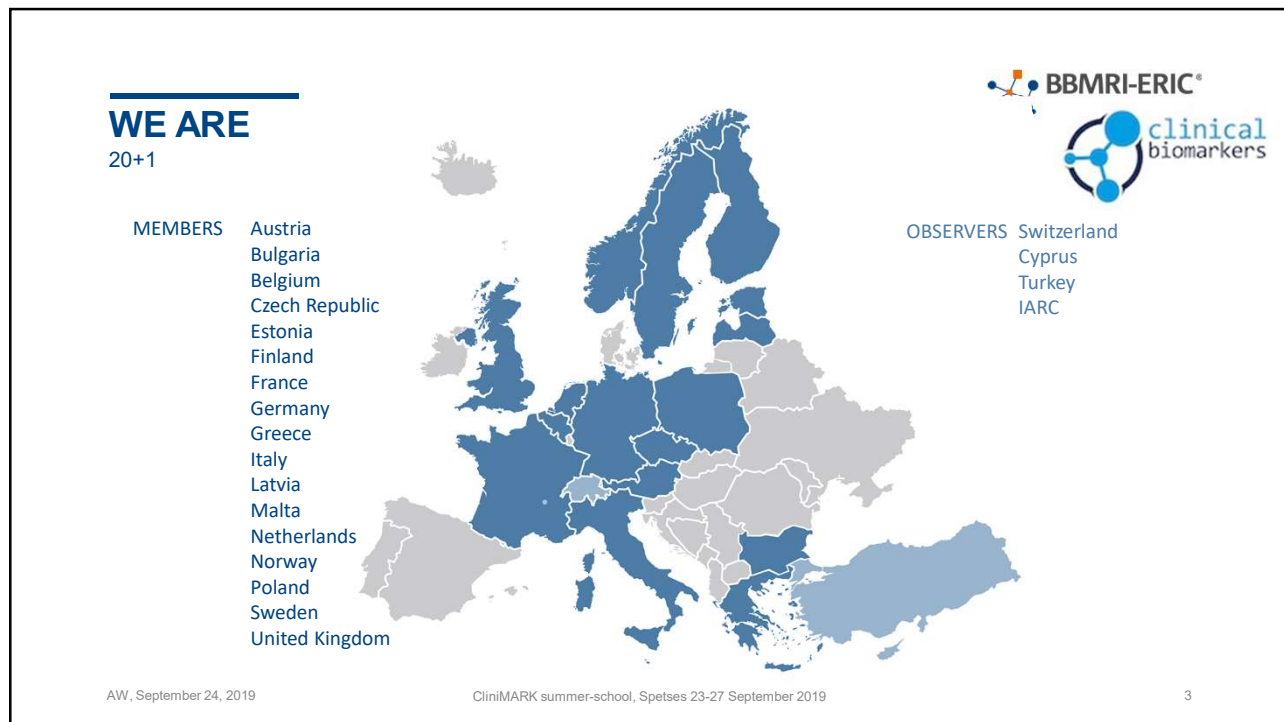


BBMRI-ERIC Status December 2013



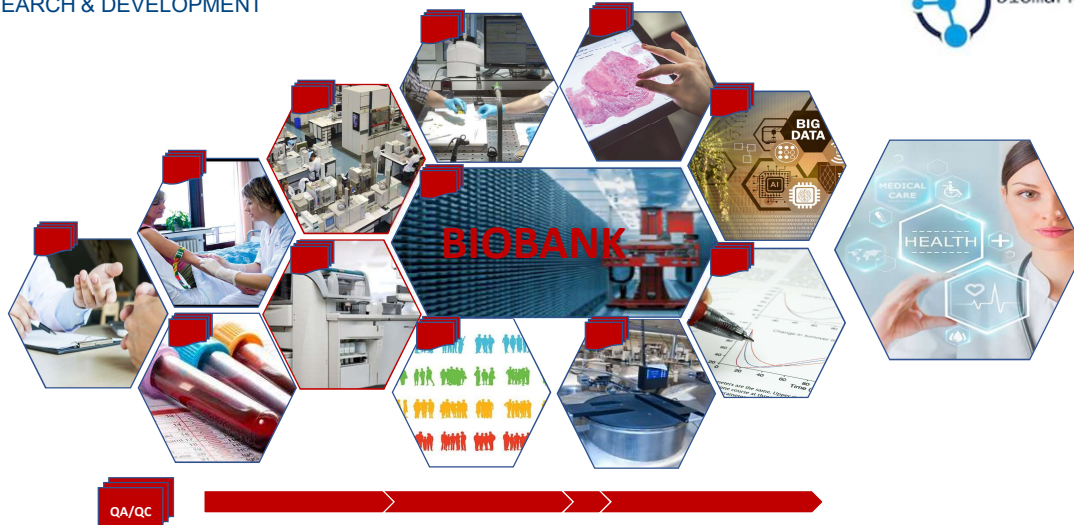
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WORKFLOW IN PERSONALIZED MEDICINE

RESEARCH & DEVELOPMENT



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QUALITY

MANAGEMENT SERVICE

"If we want researchers to be able to produce reliable findings, we need to make sure that they have access to samples and data of appropriate defined quality."

As a European research infrastructure, our ultimate goal is to make samples comparable across different countries and different biobanking systems"



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LIAISON TO ISO TECHNICAL COMMITTEES

ISO A GLOBAL NETWORK OF NATIONAL STANDARDS BODIES (160 MEMBERS)



ISO/TC 276

“Biotechnology”

ISO 20387:2018 (E)

Biobanking -- General requirements for biobanking

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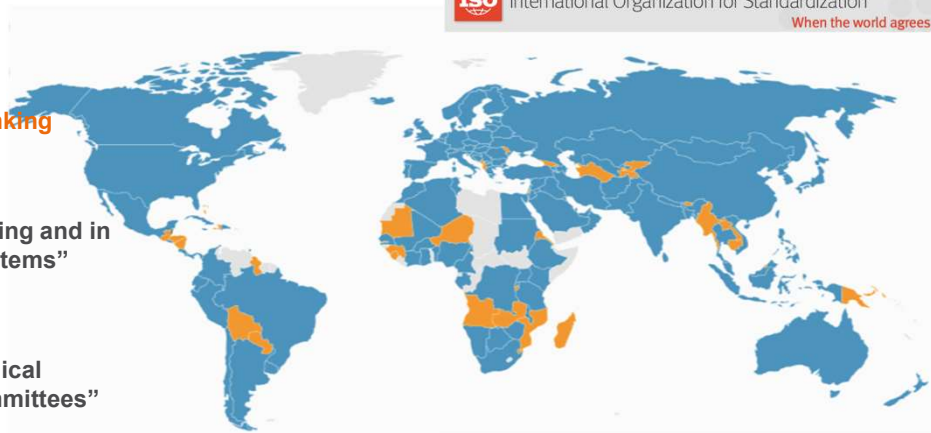
ISO/TC 212

“Clinical laboratory testing and in vitro diagnostic test systems”

--

CEN/TC 140

“In vitro diagnostic medical devices - European committees”



International Organization for Standardization

When the world agrees









Reference: www.iso.org

Member bodies Correspondent members Subscriber members

STANDARDS FOR BIOMEDICAL RESEARCH

EXAMPLES



-  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 17020:2012 Conformity assessment – Requirements for the operation of various types of bodies performing inspections
-  ISO 20387:2018 Biobanking – Requirements for biobanking
-  ISO/TS 20658:2017 Medical laboratories — Requirements for collection, transport, receipt, and handling of samples
-  ISO 19011:2011 Guidelines for auditing management systems
-  And others... depending on your needs* Examples follow. [search iso.org](http://www.iso.org).

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INTEGRATED MANAGEMENT

SYSTEMS (IMS)

ISO 9001:2015
QUALITY MANAGEMENT
SYSTEMS -
REQUIREMENTS

CEN/TS – ISO
PRE-EXAMINATION
SAMPLE HANDLING

ISO 20387:2018
GENERAL
REQUIREMENTS FOR
BIOBANKING

IMS
COMBINES MULTIPLE
MANAGEMENT SYSTEM
STANDARDS

ISO 15189:2015
MEDICAL
LABORATORIES
REQUIREMENTS FOR
QUALITY AND
COMPETENCE

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ISO 20387:2018

TABLE OF CONTENT

- 1 Scope
- 2 Normative references
- 3 Terms and definitions
- 4 General requirements
- 5 Structural requirements
- 6 Resource requirements
- 7 Process requirements
- 8 Quality management system requirements
- Annex A (normative) Documentation requirements
- Annex B (informative) Implementation guidance for Annex A
- Annex C (informative) Quality management system options
- Bibliography

WEB-CONFERENCE SERIES 2019

23 units / April-Dec

<http://www.bbMRI-eric.eu/services/bbmri.qm-webcon-series>

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Biotechnology — Biobanking —
General requirements for biobanking
*Biotechnologie — Biobanking — Allgemeine Anforderungen an
-biobanking-*

ISO
Reference number
ISO 20387:2018(E)
© ISO 2018

Reference: www.iso.org

ISO 20387:2018

TABLE OF CONTENT



7 Process requirements

7.1 General

7.2 Collection of biological material and associated data

7.2.1 Documented information requirements

7.2.2 Pre-acquisition information

7.2.3 Collection procedure CEN/TS – ISO standards for pre-examination processes

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Reference: www.iso.org 

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PRE-ANALYTICAL ERRORS



“Pre-analytical errors still account for nearly 60% - 70% of all problems occurring in laboratory diagnostics, most of them attributable to mishandling procedures during collection, handling, preparing or storing the specimens”.

Lippi G. et al. Pre-analytical quality improvement: from dream to reality. Clin Chem Lab Med. 2011 Jul; 49(7):1113-26.



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SPECIMEN PROCESSING

CEN/TS – INTERNATIONAL STANDARD (ISO)



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: Isolated circ. cell-free DNA from plasma

CEN/TS 16945 **metabolomics in urine, serum and plasma**



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ISO 20184-1 **frozen tissue** – Part 1: Isolated RNA
ISO 20184-2 **frozen tissue** – Part 2: Isolated proteins

ISO 20166-1, **FFPE tissue** – Part 1: Isolated RNA
ISO 20166-2, **FFPE tissue** – Part 2: Isolated proteins
ISO 20166-3, **FFPE tissue** – Part 3: Isolated DNA

ISO 20186-1, **venous whole blood** – Part 1: Isolated cellular RNA
ISO 20186-2, **venous whole blood** – Part 2: Isolated genomic DNA
ISO 20186-3, **venous whole blood** – Part 3: Isolated circ. cell-free DNA from plasma

Pending 2019

ISO/TS 20658:2017, **Medical laboratories — Requirements for collection, transport, receipt, and handling of samples**

Reference cen.eu / iso.org



SCOPE OF THE STANDARD

...gives recommendations/guideline for the handling, documentation storage and processing of **xxx** specimens intended for **xxx** analysis during the pre-analytical phase before a molecular assay is performed.

...applicable to molecular in vitro diagnostic examinations, laboratory developed tests performed by medical laboratories and molecular pathology labs, laboratory customers, developers and manufacturers of in vitro diagnostics, institutions and commercial organizations performing **biomedical research, biobanks, and regulatory authorities**)“

Reference cen.eu/iso.org

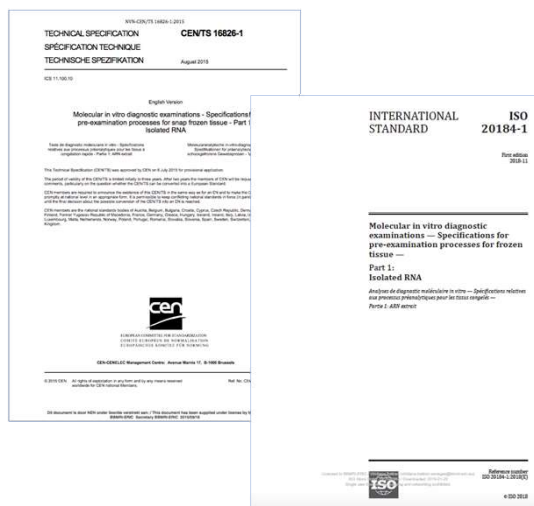


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GENERAL CONTENTS OF THE STANDARD



- Scope, Normative reference, Terms and definitions
- Outside the laboratory
 - *Primary specimen collection manual, sample donor, sample processing, transport,*
- Inside the laboratory
 - *Sample reception, fixation, evaluation of the pathology, post fixation, processing of embedding, aliquoting, storage, isolation processes (RNA, DNA, Proteins..), using commercial kits, laboratories' own protocols, Quantity and quality assessment, storage of isolated RNA, DNA, ccfdNA, Proteins..*
- *Quality control of RNA, DNA, Proteins..., impact of preanalytical workflow steps on specimen quality, time dependencies of analyte integrity*

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THE STANDARD REQUIREMENTS EXAMPLES



Information about the specimen donor / patient	Y	N	NA
Donor/patient ID was documented shall	x	x	e.g. in form of a code
Health status of donor/patient was documented should	x	x	e.g. healthy, disease type, concomitant disease, demographics (e.g. age, gender)
Routine medical treatment prior to tissue collection was documented should	x	x	e.g. anaesthetics, medications, surgical or diagnostic procedures
Appropriate consent from donor/patient was documented should	x	x	

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THE STANDARD REQUIREMENTS

EXAMPLES



Information about the specimen	Y	N	NA
Start of ischemia within the body (warm ischemia) - ischemia-relevant vessel ligation/clamping time point (usually arterial clamping time) - was documented shall	x	x	not needed where small tissue biopsy resection for freezing is performed
Time, date and method of removal were documented shall	x	x	e.g. core-needle biopsy, resection, biopsy device used for the collection
Tissue type, origin and condition were documented shall	x	x	e.g. diseased, unaffected by the disease; including references to any marking made by surgeon, radiologist or pathologist
ID of person collecting the specimen was documented should	x	x	

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THE STANDARD REQUIREMENTS

EXAMPLES



Specimen processing				
Tissue that need to be frozen for diagnostic purposes can originate from a large tissue specimen or can be a small tissue specimen like biopsies e.g. taken by endoscopy or taken from patients during a surgical procedure where fast frozen section diagnosis is required.				
Post-mortem tissues can be frozen for diagnostic purposes. However, preservation of protein is dependent on the time interval between death and autopsy and the temperature of storage of the body after death.				
Modifications or additions after removal from the body were performed and documented shall	x	x	x	e.g. labelling for the orientation of the specimen (ink-marking, stitches, incisions,...)
If pathology diagnosis is required: sampling was performed by or under guidance of medically qualified pathologist shall	x	x	x	e.g. board certified pathologist (see 6.2)
If pathology diagnosis is not required: evaluation, selection and documentation was performed by other qualified persons	x	x	x	
Direct freezing was performed in order to prevent the influence of cold ischemia should	x	x		
Specimen or sample was frozen outside the laboratory (e.g. in the operating theatre): 6.2 was performed without delay	x	x	x	
Specimen or sample was frozen inside the laboratory: fresh tissue transport was performed without delay shall (5.2)	x	x	x	

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THE STANDARD REQUIRMENTS

EXAMPLES



Isolation of total protein				
Histopathologic characterization was performed and documented? shall	x	x		e.g. on hematoxylin/eosin (H&E sections; documentation by internationally defined histopathological classification: e.g. WHO/IARC Classification of Tumours
If molecular diagnosis was to be done, fraction of target cell was evaluated prior to protein isolation shall	x	x	x	
Quantity of target cells was sufficient to perform examination shall	x	x		
When the specimen or sample is not used for diagnosis, e.g. for research, a similar approach is recommended.				
Was any unintended thawing of the tissue observed and was this documented shall	x	x	x	
Specimen or sample thoroughly minced or cut into small pieces in it's frozen state and thoroughly dispersed with lysis puffer containing inhibiting substances shall	x	x		e.g. major impact on the stabilisation of the protein integrity and yield
Homogenization of frozen specimen or sample in lysis buffer was processed immediately shall	x	x		
If the processed specimen or sample contains freezing medium, was this documented? shall	x	x		
All tools, used to manipulate the frozen sample, were clean shall	x	x		

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THE STANDARD REQUIRMENTS

EXAMPLES



Isolation of total protein				
...	Y	N	NA	
Before use, all tools were cooled to at least -20°C (in order to minimize contamination with protease, kinase or phosphatases) should	x	x		
Histotechnologists were wearing gloves shall	x	x		
After the cutting of each frozen tissue specimen/sample, microtome was cleaned shall	x	x		
If there is a doubt in correct identification of specimen or sample, an identification verification test was performed shall	x	x	x	
The isolation of protein is a key step in the diagnostic workflow, which shall be especially focused on during the validation of the entire workflow.				

...TO BE CONTINUED IN THE CONTEXT OF THE STANDARD...

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NEW CEN/TS AND ISO STANDARDS

IN THE PIPELINE UNTIL 2020



- 4 CEN/TS for **venous whole blood circulating Tumor and Organ Cells** (DNA, RNA, Proteins, staining procedures)
- 1 CEN/TS for **Venous Whole Blood Exosomes** / cell-free circulating RNA
- 1 CEN/TS for **Saliva** (DNA)
- 1 CEN/TS for **Frozen Tissues** (DNA)
- 1 CEN/TS for **Urine and other body fluids** (cell-free DNA)
- 3 CEN/TS for **Fine Needle Aspirates** (RNA, DNA, Proteins)
- 1 CEN/TS for **Saliva and Stool Microbiomes** (DNA)
- 1 CEN/TS for **FFPE Tissues** (in-situ staining procedures)

H2020 Project SPIDIA4P, GA No. 733112



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METHOD VALIDATION

PREVIEW – DRAFT INTERNATIONAL STANDARD (DIS-STAGE)



Biotechnology — Biobanking — General requirements for the validation and verification of processing methods for biological material in biobanks

ISO 97889

DRAFT INTERNATIONAL STANDARD
ISO/DIS 21899

ISO/TC 276 Secretariat: DIN
Voting begins on: 2019-03-07 Voting terminates on: 2019-05-30

THIS DOCUMENT IS A DRAFT CIRCULATED FOR COMMENT AND APPROVAL. IT IS SUBJECT TO CHANGE WITHOUT NOTICE. IT MAY BE SUBJECT TO A DRAFT INTERNATIONAL STANDARD. PLEASE BE AWARE.

IN ADDITION TO THEIR EVALUATION, AS THIS DOCUMENT IS A DRAFT, COMMENTS SHOULD BE SUBMITTED TO THE SECRETARIAT. COMMENTS MAY BE SUBMITTED TO THE SECRETARIAT BY THE DATE OF THE DRAFT CIRCULATION. COMMENTS SHOULD BE SUBMITTED TO THE SECRETARIAT BY THE DATE OF THE DRAFT CIRCULATION. COMMENTS SHOULD BE SUBMITTED TO THE SECRETARIAT BY THE DATE OF THE DRAFT CIRCULATION.

This document is circulated as received from the committee secretariat.



Reference number
ISO/DIS 21899:2019(E)

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Septe



BBMRI-ERIC SELF-ASSESSMENT SURVEYS

BBMRI-ERIC[®]
clinical biomarkers

TECHNICAL SPECIFICATION CEN/TS 16626-1
SPECIFICATION TECHNIQUE
TECHNISCHE SPEZIFIKATION August 2019

English Version
Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for snap frozen tissue – Part 1: Isolated RNA

INTERNATIONAL STANDARD ISO 20184-1
First edition 2018-11
Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for frozen tissue – Part 1: Isolated RNA

IT-based SAS RedCap[®]

Self Assessment
Molecular in vitro diagnostic examinations – Specifications for pre-examination processes for snap frozen tissue – Part 1: Isolated RNA

The integrity of molecular data depends on the quality of sample collection, transport, storage and processing. These activities are critical to the success of the study and the quality of the data generated. The purpose of this survey is to assess the quality of the pre-examination processes for snap frozen tissue and to identify areas for improvement.

The survey consists of two parts: a self-assessment questionnaire and a peer-review questionnaire. The self-assessment questionnaire is designed to collect information on the pre-examination processes for snap frozen tissue and to identify areas for improvement. The peer-review questionnaire is designed to collect information on the pre-examination processes for snap frozen tissue and to identify areas for improvement.

Main Contact

1) Name of contact person
2) Name of contact person
3) E-mail of contact person
4) Address
5) ZIP
6) City
7) Country
8) Phone

Overview

9) Study type
10) Study ID

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BBMRI-ERIC SELF-ASSESSMENT SURVEYS

ACCESS BBMRI-ERIC WEBSITE



Self-Assessment Survey

Please fill in your contact information:

*Name

*E-mail address

*Affiliation

*Address/Country

www.bbMRI-eric.eu/services/self-assessment-survey/

Access conditions on request



Please provide us with some information by answering the following questions:

* Is your organisation located in a BBMRI-ERIC Member/Observer State? See <http://www.bbMRI-eric.eu/national-nodes/>

☐ Yes ☐ No

* Are you in contact with the coordinating office from the National Node in your country? See <http://www.bbMRI-eric.eu/national-nodes/>

☐ Yes ☐ No

* Have you purchased the required CEN Technical Specifications as a basis for your sample handling procedure? See <http://www.bbMRI-eric.eu/services/standardisation/>

☐ Yes ☐ No

* Please select the required BBMRI-ERIC Self-Assessment Surveys from the list below:

☐ Specifications for Pre-examination processes for snap frozen tissue - Part 1: Isolated RNA; CEN/TS 16826-1:2015

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QUALITY MARK IN THE DIRECTORY



Self Assessment

Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for snap frozen tissue - Part 1: Isolated RNA

The integrity of molecular in vitro diagnostic primary samples collected, transport, storage and processing from the patient to the laboratory is essential for the reliability of the results of the analysis.

The pre-examination processes for the laboratory (LIS) performed technical specifications to determine information relevant to the analysis.

BBMRI-ERIC Clinical Biomarkers in vitro diagnostic examinations - Non-clinical for pre-examination processes for snap frozen tissue - Part 1: Isolated RNA

This self-assessment survey will help you to create and optimize your sample processing.

The self-assessment survey is designed to be a self-assessment tool for your laboratory. It is not a certification process. It is a self-assessment tool for your laboratory. It is not a certification process. It is a self-assessment tool for your laboratory.

Report Contact

E1: Institution

E2: Name of contact person

E3: E-mail of contact person

E4: Address

E5: ZIP

E6: City

E7: Country

E8: Phone

E9: Fax

Comments

E10: Institution from

E11: BBMRI-ERIC



Fluids Collection 3 - Health aging study - Plasma and Serum	Population-based	Serum, Plasma	CEN/TS 16945:2016	726
Fluids Collection 4 - Health aging study - Urine	Population-based	Urine	CEN/TS 16945:2016	88
Fluids Collection 5 - EPATH study - Urine, Plasma, and Serum	Disease specific, Population-based	Plasma, Serum, Urine	CEN/TS 16945:2016	8584
Fluids Collection 6 - BioPersMed Cohort - Urine, Plasma, and Serum	Disease specific, Population-based	Plasma, Serum, Urine	CEN/TS 16945:2016	178475

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BBMRI-ERIC QUALITY MANAGEMENT SERVICES

FOR BASIC AND APPLIED RESEARCH

Principles of auditing

Managing the audit

Performing an audit

Competence and evaluation of
BBMRI auditors

SERVICE 2019



Concept paper

BBMRI-ERIC AUDIT PROGRAMME



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AUDITING



BBMRI-ERIC QUALITY MANAGEMENT SERVICES

FOR BASIC AND APPLIED RESEARCH



KNOWLEDGE HUB

- International standards (ISO 9001, ISO 20387, ISO 15189, CEN Technical Specifications, etc.)
- Quality management in EU funded projects
- Quality management in national and international research projects
- ❖ Webinars, counseling



TRAINING & SUPPORT

- International biobanking standards
- General quality management systems
- Integrated management systems
- Interface management systems
- ❖ Online training (Members)
- ❖ Inhouse training, Workshops
- ❖ Summerschools, Master courses



AUDITING

- BBMRI-ERIC Self-Assessment Survey for biobanks / researchers
- BBMRI-ERIC Audit

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CONTACT

<http://www.bbmri-eric.eu/services/quality-management/>
 Andrea Wutte – andrea.wutte@bbmri-eric.eu



KNOWLEDGE HUB



TRAINING & SUPPORT



AUDITING

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Co-funded within SPIDIA4P, a project that has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733112.

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BBMRI-ERIC HEADQUARTERS

TEAM, SERVING ALL 20+1 MEMBERS / OBSERVERS

THANK YOU !

NATIONAL NODES & CONTACT FOR LOCAL BIOBANKS

