

COMMON MINIMUM TECHNICAL STANDARDS AND PROTOCOLS FOR BIOBANKS DEDICATED TO CANCER RESEARCH

MAIMUNA MENDY, ELODIE CABOUX, RITA T. LAWLOR,
JESSICA WRIGHT, AND CHRISTOPHER P. WILD

IARC TECHNICAL
PUBLICATION NO. 44

COMMON MINIMUM TECHNICAL STANDARDS AND PROTOCOLS FOR BIOBANKS DEDICATED TO CANCER RESEARCH

MAIMUNA MENDY, ELODIE CABOUX, RITA T. LAWLOR,
JESSICA WRIGHT, AND CHRISTOPHER P. WILD

IARC TECHNICAL
PUBLICATION NO. 44

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, 69372 Lyon Cedex 08, France

©International Agency for Research on Cancer, 2017

Distributed by
WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland
(tel: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int).

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The authors alone are responsible for the views expressed in this publication.

The International Agency for Research on Cancer welcomes requests for permission to reproduce or translate its publications, in part or in full. Requests for permission to reproduce or translate IARC publications – whether for sale or for non-commercial distribution – should be addressed to the IARC Communications Group, at: publications@iarc.fr.

Cover image: Paraffin-embedded tissues processed and stored within the context of various IARC research projects (Credit: R. Dray/IARC).

This book is also available in electronic format from
<http://publications.iarc.fr>.

IARC Library Cataloguing in Publication Data

Common minimum technical standards and protocols for biobanks dedicated to cancer research / Maimuna Mendy, Elodie Caboux, Rita T. Lawlor... [et al.]

(IARC Technical Publications; 44)

1. Biological Specimen Banks – Standards 2. Biological Specimen Banks – Organization & Administration
3. Biological Specimen Banks – Methods 4. Neoplasms
I. Mendy, M. II. Title III. Series

ISBN 978-92-832-2463-1
ISSN 1012-7348

(NLM Classification: W1)

Table of contents

Contributors	iv
Acknowledgements	v
Foreword	vi
Preamble	vii
Abbreviations	ix
Section 1	1
Glossary and definitions	
Section 2	5
Role of biobanks in cancer research	
Section 3	11
Recommendations for biobanks	
Section 4	55
Selected protocols	
References	63
Annex 1	69
IARC policy on access to human biological materials	
Annex 2	75
Guidelines for informed consent	
Annex 3	80
Template consent form for biobanking	
Annex 4	91
Template Material/Data Transfer Agreement (MTA/DTA)	
Annex 5	97
Biobank, collection, study, and sample minimum data set and associated standards	
Disclosures of interests	101

Contributors

Authors

Dr Maimuna Mendy

Head, Laboratory Services and Biobank Group
International Agency for Research on Cancer (IARC)
Lyon, France

Dr Elodie Caboux

Laboratory Services and Biobank Group
International Agency for Research on Cancer (IARC)
Lyon, France

Dr Rita T. Lawlor

ARC-NET Centre for Applied Research on Cancer
University of Verona
Verona, Italy

Dr Jessica Wright

Study Manager, Sheffield Clinical Trials Research Unit
The University of Sheffield
Sheffield, United Kingdom

Dr Christopher P. Wild

Director, International Agency for Research on Cancer (IARC)
Lyon, France

Reviewers

The authors are grateful to the following expert colleagues who contributed comments, advice, corrections, and protocols in the preparation of this book.

Dr Joakim Dillner

Karolinska Institutet
Stockholm, Sweden

Ms Marianne Henderson

Senior Advisor for Division Resources, Office of the Director, Division of Cancer Epidemiology and Genetics
Senior Advisor on Biobanking, Center for Global Health, National Cancer Institute, National Institutes of Health, Division of Health and Human Services
Rockville, MD, USA

Dr Jan-Eric Litton

Director General, Biobanking and BioMolecular resources Research Infrastructure—European Research Infrastructure Consortium (BBMRI-ERIC)
Graz, Austria

Dr Manuel Morente

Biobank Scientific Director, Spanish National Cancer Research Centre (CNIO)
Coordinator, Spanish National Biobank Network
Past-President, European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB)
Madrid, Spain

Dr Sabina Rinaldi

Biomarkers Group, Section of Nutrition and Metabolism
International Agency for Research on Cancer (IARC)
Lyon, France

Dr Ghislaine Scélo

Genetic Epidemiology Group, Section of Genetics
International Agency for Research on Cancer (IARC)
Lyon, France

Ms Anne-Marie Tassé

Executive Director, Public Population Project in Genomics and Society (P3G)
Montreal, Canada

Dr Jim Vaught

President, International Society for Biological and Environmental Repositories (ISBER)
Editor in Chief, *Biopreservation and Biobanking*
Senior Research Fellow, International Prevention Research Institute, Lyon, France

Dr Kurt Zatloukal

Deputy Head, Institute of Pathology
Medical University of Graz
Graz, Austria

Mr Ma'n H. Zawati

Executive Director, Centre of Genomics and Policy
McGill University
Montreal, Canada

Production Team

Karen Müller

English Editor

Sylvia Lesage

Publishing Assistant

Acknowledgements

We would like to acknowledge the authors of *Common Minimum Technical Standards and Protocols for Biological Resource Centres Dedicated to Cancer Research* (published by IARC in 2007): an IARC Secretariat composed of Dr Elodie Caboux, Dr Amelie Plymoth, and Dr Pierre Hainaut, joined by the Working Group participants.

The authors would like to thank Ms Sally Moldan, for her excellent contribution towards the compilation of this book, and the members and partners of the Low- and Middle-Income Countries (LMICs) Biobank and Cohort Building Network (BCNet), for sharing their real-life experiences working in resource-constrained settings.

Foreword

Biological specimens collected, processed, and stored under optimal conditions increasingly provide a necessary foundation for cancer research. Information obtained from such samples opens opportunities to learn more about the causes, prevention, and treatment of the disease. International comparisons made possible by the study of sample collections from different parts of the world are also invaluable in the pursuit of the evidence base for cancer control.

However, the above-mentioned opportunities are accompanied by many challenges and potential pitfalls. At times, pragmatic decisions have to be made in response to the constraints faced when conducting clinical or population-based studies. These constraints may be technical, may relate to infrastructure or finance, or may be ethical, legal, or social in nature. Being unaware of these types of risk to successful biobanking can place important scientific advances in jeopardy.

In this context, it is a great pleasure to introduce this publication

from the International Agency for Research on Cancer (IARC). The purpose of the text is to provide clear and practical advice on the common practices needed to create and maintain biobanks, recognizing that the circumstances faced by the curators of biobanks vary across the world. The international cooperation that went into formulating these Common Minimal Technical Standards provides confidence that the content is realistic, while at the same time maintaining the minimal standards needed in order for the biospecimens to be valid and to yield the reliable research data being sought. In providing this Foreword, I would like to place on record my thanks to all authors and reviewers who have contributed to this final product, as well as to all the contributors to *Common Minimum Technical Standards and Protocols for Biological Resource Centres Dedicated to Cancer Research*, known as the “Green Book”, published by IARC in 2007.

In publishing this book, my hope is for a balanced focus, not only on

what goes into a biobank but also on what comes out. There is a risk that biobanks remain untouched or underexploited, a deposit that is rarely put to work for the common good. While this book aims to ensure that what goes into a biobank is of high quality and well managed, it has as its ultimate objective to drive the use of those same biospecimens in research. This will involve the analysis of biospecimens, but to maximize the benefits it will also require linkage to other well-documented epidemiological and clinical data sets. In this period of spiralling numbers of cancer cases and costs of cancer care, the failure to use stored samples to answer critical research questions is indefensible.

In conclusion, I trust that readers will find this publication to be a support to successful biobanking and will find herein one important foundation for cancer research in the 21st century.

Dr Christopher P. Wild
Director, International Agency
for Research on Cancer

Preamble

The International Agency for Research on Cancer (IARC) published *Common Minimum Technical Standards and Protocols for Biological Resources Centres Dedicated to Cancer Research*, known as the “Green Book”, in 2007. The recommendations and protocols in that publication were largely based on guidelines, procedures, and documentation on biorepositories developed by several working groups, institutions, regulatory bodies, and organizations, including the World Health Organization.

However, biobanking has developed at a rapid pace over the years, driven mainly by the push for personalized medicine, the need for high-quality biological resources and associated data for scientific research, and technological advancement of analytical platforms for molecular and genetic research. These developments have enabled the collection and analysis of large numbers of biospecimens in combination with epidemiological and clinical data collected across populations and involving multiple biobanks.

In response to these developmental changes and to promote collaborative projects, a wide range of biobanking stakeholders are establishing approaches and mechanisms for the harmonization of resources, including data. These stakeholders include international organizations, societies, and institutions, such as the United States National Cancer Institute (NCI), the International Society for Biological and Environmental Repositories (ISBER), the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB), and the Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium (BBMRI-ERIC). Their activities include the improvement of biobanking protocols and standards to provide high-quality samples and to adequately address ethical, legal, and social issues (ELSI).

This IARC Technical Publication includes guidelines and recommendations for biobanks not only in high-income countries but also in low- and middle-income countries

(LMICs). The recommendations are based on validated and/or evidence-based guidelines, taking into account the current knowledge of biobanking practices and standards resulting from projects such as Standardisation and Improvement of Generic Pre-analytical Tools and Procedures for In Vitro Diagnostics (SPIDIA), BBMRI–Large Prospective Cohorts (BBMRI–LPC), and the International Genomics Consortium (IGC), as well as the European Committee for Standardization (CEN) Technical Specifications for molecular in vitro diagnostic examinations and International Organization for Standardization (ISO) norm 15189 (ISO, 2012). ISO 15189 is currently under revision (<https://www.iso.org/obp/ui/#iso:std:iso:15189:ed-3:v2:en>), and the working groups of the Technical Committee of ISO 276 (http://www.iso.org/iso/home/standards_development/list_of_iso_technical_committees/iso_technical_committee.htm?commid=4514241) are dealing with biobanking quality issues, including terminology, bioresearch, bioprocessing, pre-analytical methods, isolation of

analytes, and data processing and integration.

This book also includes sections on sample sharing, ELSI, and harmonization guidelines important to support collaborative research efforts that make use of biological materials. In particular, the section on open access deals with the principles of sharing and provides recommendations for biobanks in relation to sample and data sharing, which is key to establishing research collaboration. The section on governance provides guidelines on governance structures for biobanks for transparent and ef-

fective running of the facilities. Templates for informed consent and Material and Data Transfer Agreements are available in the Annexes section.

This new book also benefits from the experience and knowledge gained by IARC from coordinating the LMICs Biobank and Cohort Building Network (BCNet) and managing an international biobank, which contains diverse collections of specimens and data drawn from studies across the world, including the European Prospective Investigation into Cancer and Nutrition (EPIC) collection.

The guidelines and recommendations are applicable to biobanks operating in different geographical locations, and although the book's focus is on biobanks dedicated to cancer research, the principles and guidelines outlined here are also applicable to non-cancer biobanks.

Table 1 presents a list of the main sources of information used to develop the recommendations presented in this book. Whenever appropriate, the book indicates references and links to more extensive documentation and protocols.

Table 1. Guidelines, procedures, and documentation on biobanks

Title	Authors/origin
Tissue banking for biomedical research	National Cancer Centre Singapore
Biorepository protocols	Australasian Biospecimen Network (ABN)/Australia
Standardizing tissue collection and quality control procedures for a European virtual frozen tissue bank network	European Human Frozen Tumour Tissue Bank (TuBaFrost)
Human tissue and biological samples for use in research: operational and ethical guidelines	Medical Research Council (MRC)/United Kingdom
2012 Best practices for repositories: collection, storage, retrieval, and distribution of biological materials for research	International Society for Biological and Environmental Repositories (ISBER)/International
NCI best practices for biospecimen resources	National Cancer Institute (NCI)/USA
Guidance on regulations for the transport of infectious substances	World Health Organization (WHO)/International
United Nations recommendations on the transport of dangerous goods, model regulations, 19th revised edition	United Nations Economic Commission for Europe (UNECE)/International
Recommendation Rec(2006)4 of the Committee of Ministers to Member States on research on biological materials of human origin	Council of Europe Committee of Ministers
Collection, transport, preparation, and storage of specimens for molecular methods: approved guideline	Clinical and Laboratory Standards Institute (CLSI)/USA
The Human Proteome Organization	Human Proteome Organization (HUPO)
Case studies of existing human tissue repositories: "best practices" for a biospecimen resource for the genomic and proteomic era	RAND Corporation/USA
Biological resource centres: underpinning the future of life sciences and biotechnology	Organisation for Economic Co-operation and Development (OECD)/International
OECD best practice guidelines for biological resource centres	Organisation for Economic Co-operation and Development (OECD)/International
Standard operating procedure for the collection of fresh frozen tissue samples	European Organisation for Research and Treatment of Cancer (EORTC)

Abbreviations

ACD	acid citrate dextrose
BBMRI-ERIC	Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium
BBMRI-LPC	BBMRI–Large Prospective Cohorts
BCNet	LMICs Biobank and Cohort Building Network
BRIF	Bioresource Research Impact Factor
BRISQ	Biospecimen Reporting for Improved Study Quality
CEN	European Committee for Standardization
CO ₂	carbon dioxide
CSF	cerebrospinal fluid
DBS	dried blood spot
DEPC	diethylpyrocarbonate
DIN	DNA integrity number
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DR	disaster recovery
dsDNA	double-stranded DNA
DTA	Data Transfer Agreement
EDTA	ethylenediaminetetraacetic acid
ELSI	ethical, legal, and social issues
EPIC	European Prospective Investigation into Cancer and Nutrition
ESBB	European, Middle Eastern and African Society for Biopreservation and Biobanking
EU	European Union
FBS	fetal bovine serum
FFPE	formalin-fixed, paraffin-embedded
GA4GH	Global Alliance for Genomics and Health
gDNA	genomic DNA
HBV	hepatitis B virus
HIV	human immunodeficiency virus
IARC	International Agency for Research on Cancer
IATA	International Air Transport Association
ICAO	International Civil Aviation Organization

ISBER	International Society for Biological and Environmental Repositories
ISO	International Organization for Standardization
IT	information technology
LIMS	laboratory information management system
LMICs	low- and middle-income countries
LN ₂	liquid nitrogen
MIABIS	Minimum Information about Biobank Data Sharing
miRNA	microRNA
MTA	Material Transfer Agreement
NCI	United States National Cancer Institute
NIH	United States National Institutes of Health
OCT	optimal cutting temperature
OECD	Organisation for Economic Co-operation and Development
P3G	Public Population Project in Genomics and Society
PCR	polymerase chain reaction
QA	quality assurance
QC	quality control
QMS	quality management system
qPCR	quantitative PCR
R&D	research and development
RIN	RNA integrity number
RNA	ribonucleic acid
rRNA	ribosomal RNA
RT-PCR	reverse transcription PCR
SOPs	standard operating procedures
SPREC	Sample PREanalytical Code
ssDNA	single-stranded DNA
TNM	tumour–node–metastasis
TuBaFrost	European Human Frozen Tumour Tissue Bank
UNECE	United Nations Economic Commission for Europe
UV	ultraviolet
WHO	World Health Organization

Glossary and definitions

Unless otherwise defined in another context in this book, important terms are defined below.

Some of the definitions are according to the 2012 International Society for Biological and Environmental Repositories (ISBER) guidelines (ISBER, 2012).

It should be noted that the International Organization for Standardization (ISO) standards that are currently under development and will be released within 2 years (ISO/TC 276 Biotechnology) will include a section on biobanking definitions.

Adverse event

Any event that caused harm or had the potential to cause harm to any biobank personnel or visitors, including but not limited to breach of security of the premises and its contents, or harm to biospecimens or data integrity or linkage.

Aliquot

Aliquoting is a process in which a specimen is divided into separate parts, which are typically stored as individual samples. The term “aliquot” may also be used as a noun to denote a single sample. It is advisable to store aliquots in separate containers, to minimize loss due to unexpected equipment failure.

Analyte

A substance or chemical constituent that is determined in an analytical procedure.

Annotation

Additional information associated with a particular point in a document or other piece of information.

Anomaly

An unexpected event occurring within the quality management system,

usually detected by staff of the area in which the event occurred, which may result in non-compliance with the quality management system or with the requirements of the user.

Anonymization

The process in which identifying information or details are removed from the data collected with a sample, so that the sample donor remains anonymous.

Associated data

The clinical, pathological, and epidemiological information related to patients who provided a sample. The information relates to characteristics of the sample, the study participant, and biological experiments that can be used to generate knowledge.

Autopsy

The postmortem examination of

organs and tissues of a body, to determine cause of death or pathological conditions.

Biobank

Infrastructure for the collection, archiving, and storage of biospecimens and their associated data, and the procedures and related services connected to the biospecimens and associated data. The services include informing individuals who are approached to participate in a study, obtaining their consent, collecting and processing specimens for secure long-term storage, accessing and retrieving specimens appropriate for analysis, processing for preparation of biomaterials (e.g. DNA, RNA, proteins), quality control, and packaging and shipping of specimens. Many types of biobank are relevant to cancer research. They include, among others, tumour and tissue biobanks for specimens and data obtained in the course of normal clinical procedures; specialized collections of specimens and data developed in the context of clinical trials, mechanistic studies, or diagnostic or prognostic studies; and collections of specimens and data developed in epidemiological studies and biomarker studies. Biobank samples include tissues, blood, cell lines, DNA, and proteins derived from individuals with a history of hereditary or familial cancer. Biobanks are also known as biorepositories.

Biobanking

The process of storing material or specimens and associated data for future use.

Biohazard

An organism, or a substance derived from an organism, that poses a threat to (primarily) human health. This can include medical waste and samples of a microorganism, virus, or toxin (from a biological source)

that can affect human health. It can also include substances harmful to animals.

Biological resource

A collection of biological specimens and associated data that are acquired for a defined purpose. The custodian of the collection is responsible for the management of the biological resource. Biological resources may be stored in a biobank or laboratory and in databases, depending on the number of samples, the volume of information, and the governance structure of the biobank.

Biological safety hood

A cabinet designed to provide a microbe-free work environment, which enables work on samples in an isolated area.

Biorepository

See “Biobank”.

Coding

Substituting a code for personally identifying information in such a way that linkage is only possible through a key.

Cold chain

A temperature-controlled supply chain.

Cold ischaemia

The condition of a tissue sample after its removal from the body until its stabilization or fixation.

Collection

The practice or technique of collecting a specimen, or a specific sample or group of samples, that has been isolated for future research purposes.

Consignee

Any individual, agency, institution, or organization that receives specimens and assumes responsibility for storing, dispensing, and tracking the disposition of specimens.

Container

An enclosure for one or more units of a specimen or specimens.

Controlled areas

Restricted work areas of low microbial and particulate content in which non-sterile materials are prepared.

Custodian

The person responsible for the management of a biological resource. The custodian works with other key stakeholders in the management of the resource, including the tracking of all relevant documentation for the resource, and is responsible for ensuring that policies on access to the resource are in place and are implemented according to appropriate guidelines.

Database

A structured collection of records or data that is stored in a computer system so that a computer program or a person using a query language can consult it to answer queries.

Dehydration

The removal of water from a tissue.

De-identification

A process that ensures that a person's identity cannot be connected with information or samples donated by them.

Desiccant

A desiccant is a hygroscopic substance that induces or sustains a state of dryness (desiccation) in its vicinity. Commonly encountered pre-packaged desiccants are solids that absorb water.

Deviation

An intentional or unintentional event that departs from a set procedure or normal practice.

Dewar

A specialized container that holds

liquefied gases. A dewar may also be referred to as a dewar flask or dewar vessel, or a liquid nitrogen tank.

Distribution

A process that includes receipt of a request for specimens, selection of appropriate specimens, and final inspection, in conjunction with subsequent shipment and delivery of specimens to another biobank, specimen collection centre, or laboratory.

Donor

A person who donates or gives an organ, blood, or blood products to another person.

Dry ice

Solid-phase carbon dioxide (CO₂). CO₂ solidifies at -78.5 °C.

End user

A health-care practitioner, scientist, or laboratory staff member who performs an appropriate procedure, test, or archival function.

Error

A deviation from a standard operating procedure (SOP) during specimen retrieval, processing, testing, quarantining, labelling, storage, or distribution that might adversely affect the specimen.

Ethical, legal, and social issues (ELSI)

The ethical, legal, and social issues associated with the development and operation of a biobank.

Identifier

Information (e.g. name, social security number, medical record number, or pathology accession number) that would enable the identification of the subject. For some specimens, this information might include the taxon name and the collection number.

Incident

Any unplanned occurrence that deviates from standard operating procedures (SOPs) or applicable government laws and regulations during specimen retrieval, processing, labelling, storage, or distribution that may affect subsequent use of those specimens.

Individual

The person who is the subject of protected health information.

Informed consent

A decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence, inducement, or intimidation.

Institution

The body responsible for specimen collection and archiving that commits itself to the development, management, and long-term maintenance of a biobank. Although the organizational nature of such institutions may vary widely, they are primarily clinical cancer centres, academic medical centres, research institutes closely associated with clinical centres, or central organizations dedicated to the management of biobanks.

Institutional review board (IRB)

See “Research ethics committee (REC)”.

Label

Any written, printed, or graphic material on or affixed to a specimen container or package.

Liquid nitrogen (LN₂)

Coolant used to cool and store samples. Nitrogen becomes liquid

at -196 °C. Samples stored in the vapour phase of liquid nitrogen are -190 °C and warmer, depending on the distance from the liquid phase.

Liquid nitrogen tank

See “Dewar”.

Lyophilized

Dehydrated for storage by conversion of the water content of a frozen specimen to a gaseous state under vacuum. Also called “freeze-dried”.

Material Transfer Agreement (MTA)/ Data Transfer Agreement (DTA)

An agreement or contract that governs the transfer of research materials and/or data between two organizations, when the recipient intends to use them for research purposes. It defines the rights and obligations of the provider and the recipient with respect to the use of the materials and/or data.

Monitoring system

A system that monitors the temperature and environmental conditions, including alarms, in conjunction with remote access, security features, and electronic data storage.

Participant

A person who takes part in a trial. Participants must usually meet certain eligibility criteria.

Patient

A person who receives medical attention, care, or treatment.

Pre-analytical data

Factors that may have an impact on the integrity of the sample during the collection, processing, and storage processes. These data include information on the treatment of the sample, including the conditions and the duration of the treatment.

Preservation

The use of chemical agents, alterations

in environmental conditions, or other means during processing and storage to prevent or retard biological or physical deterioration of a specimen.

Procedure

A series of steps that, when followed in order, are designed to result in a specific outcome.

Processing

Any procedure used after specimen collection but before distribution, including preparation, testing, and releasing the specimen to inventory and labelling.

Pseudo-anonymization

The process whereby identifiable personal information is anonymized, but in such a way that the personal identifiers are replaced by one pseudonym, which can be linked across multiple data records without revealing the identity of the person.

Quality

Conformance of a specimen or process with pre-established specifications or standards.

Quality assurance (QA)

An integrated system of management activities involving planning, implementation, documentation, assessment, and improvement to ensure that a process or item is of the type and quality needed for the project.

Quality control (QC)

The system of technical activities that measures the attributes and performances of a process or item against defined standards, to verify that the stated requirements are fully met.

Quality management system (QMS)

The organizational structure, procedures, processes, and resources needed to implement quality management.

Re-identification

A reversible process that allows data from which identifiers have been removed, and replaced by a code, to be re-identified and linked to a specific individual by, for example, using the code or linking different data sets.

Removal

See "Retrieval".

Repository

An entity that receives, stores, processes, and/or disseminates specimens, as needed. This term encompasses the physical location as well as the full range of activities associated with its operation. A repository may also be referred to as a biorepository or a biobank.

Research ethics committee (REC)

A board, committee, or other group formally designated by an institution to review the ethical, legal, social, scientific, and financial implications of biomedical research involving humans as subjects, to approve the initiation of the research, and to conduct periodic reviews of such research. In some countries, this body is known as an institutional review board (IRB) or a research ethics board (REB).

Retrieval

The removal, acquisition, recovery, harvesting, or collection of specimens.

Safety

Processes, procedures, and technologies to ensure freedom from danger or harm.

Sample

A single unit containing material derived from one specimen.

Shipping manifest

A written description of the contents of a shipped package.

Snap-freezing

The process by which the temperature of samples is lowered very rapidly to below -70 °C using dry ice or liquid nitrogen.

Specimen

A specific tissue sample, blood sample, and so on taken from a single subject or donor at a specific time.

Standard operating procedures (SOPs)

A set of detailed written instructions to achieve uniformity of the performance of a specific function.

Storage

Maintenance of specimens under specified conditions for future use.

Subject

A living or deceased individual who is the source of the specimen in accordance with established medical criteria, procedures, and privacy regulations. In some countries, the term "Donor" or "Individual" may be used in the same context as "Subject", especially in the context of human specimens.

Traceability

The ability to locate a specimen during any step of its donation, collection, processing, testing, storage, and disposition.

Warm ischaemia

The condition in which the tissue is deprived of its normal blood supply, containing oxygen and nutrients, while the tissue is at body temperature.

Role of biobanks in cancer research

The role of biobanks in biological research in general and their impact on medical, societal, and economic issues have been discussed in two reports from the Organisation for Economic Co-operation and Development (OECD) (OECD, 2007, 2009). The OECD publications address the importance, justification, and sustainability of developing biobanks for research. In 2014, the Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium (BBMRI-ERIC), an umbrella organization for biobanking in Europe, was established to provide a focal point for biobanking activities in Europe and to provide fair access to quality-controlled human biological samples and associated data for cross-biobanking research (van Ommen et al., 2015; Mayrhofer et al., 2016).

2.1 Importance of biobanks

2.1.1 Biobanks are critical for cancer research

Human biological specimens have been used for many decades for translational purposes in cancer research, to investigate disease pathogenesis, to test scientific hypotheses, and to assess biomarkers identified in experimental studies. The advent of new technologies opens unprecedented opportunities to assess the status of the human genome and its expression, the complex networks of interactions between biomolecules, and the functional and clinical consequences of their alteration (NCI, 2016).

Therefore, studies on human specimens are also becoming critical for the process of discovering new

mechanisms involved in causing cancer or in determining its progression, resistance or response to treatment, and clinical outcome (Riegman et al., 2006a).

Biobanks are the foundation of three rapidly expanding domains of biomedical science:

- molecular and genetic epidemiology (aimed at assessing the genetic and environmental basis of cancer causation in the general population as well as in families);
- molecular pathology (aimed at developing molecular-based classification and diagnostic procedures for cancers); and
- pharmacogenomics/pharmacoproteomics (aimed at understanding the correlation between an individual patient's genotype or phenotype and response to drug treatment).

2.1.2 Biobanks are important for developing personalized medicine and/or precision medicine

With conventional diagnostic methods, risk factors of importance, as well as the opportunity to prevent diseases that may emerge later, are often overlooked when the focus is on the symptoms manifested. Collecting and analysing biological specimens is a necessary procedure for pathology-based diagnosis and to enable patients to benefit from the applications of molecular and genetic cancer research.

Personalized medicine and precision medicine are transforming diagnosis in medicine and are leading towards patient-centred and multifaceted diagnostics (Hall et al., 2011).

Personalized medicine is an emerging practice of medicine that uses an individual's genetic and environmental profile to guide decisions made about the prevention, diagnosis, and treatment of disease. This concept has been refined and its scope expanded to include the approaches, decisions, and practices in medical facilities, resulting in the new term "precision medicine".

Precision medicine is defined by the United States National Institutes of Health (NIH) as "an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle" (Precision Medicine Initiative Working Group, 2015). In precision medicine, genomic and epigenomic analyses with associated data can be used to define individual patterns of disease and susceptibility. Performing molecular-based assessments may become a systematic requirement at different stages of patient follow-up, potentially leading to bet-

ter individual prevention, diagnosis, prognosis, treatment, and monitoring.

2.1.3 Biobanks have an impact on biotechnological and medical innovation

In the continuum from laboratory discovery to medical application, biobanks play a key role in life science research and development (R&D). Progress in medicine depends on innovation, development, and the translation of laboratory findings into clinical practice. Access to human biological specimens and associated data is often a prerequisite for such R&D advances.

Therefore, the development of high-quality biobanks with innovative research platforms has accelerated and facilitated this translational process. This is due mainly to technological advances and reductions in the cost of information technology (IT), used for data storage and for the assembly, evaluation, and analysis of large numbers of samples, as well as increases in analytic capabilities and the drastically reduced costs of DNA sequencing, with results available within a shorter time frame. Similar advances in mass spectrometry have drastically lowered the cost and expanded the ability to characterize proteins and the metabolites present in biological samples.

2.1.4 Importance of networking and exchanges between biobanks

Cancer is a burden faced by people across the globe. Occurrence and mortality rates vary in different parts of the world. In addition, studies of many rare forms of cancer are limited by the difficulty of recruiting a sufficient number of cases within any single collection centre, or even within one country.

Networking, or harmonizing, of biobanks can encourage the col-

lection of higher-quality samples and data, enable larger research projects to take place, and reduce duplication of effort (Yuille et al., 2008; Harris et al., 2012). For cancer biobanks, networking can enable the study and classification of rare cancers; a cancer type is considered rare if fewer than 5 cases are diagnosed in a population of 10 000, and rare cancers make up at least 20% of new cancer cases (ESMO, 2010; van Ommen et al., 2015; Mayrhofer et al., 2016).

Networking implies a multidirectional flow of information, expertise, and biological materials between cancer centres and research institutions and requires the adoption of common technical standards for specimen collection, storage, and annotation, and for data collection and management. Biobanks have an important role in facilitating such exchanges and in providing logistics and infrastructure for multi-centre research projects involving cancer centres, academic medical centres, and diagnostic and health-care facilities. Biobank networks involved in the collection, processing, storage, and dissemination of biological specimens can range from small operations with single projects in research or university laboratories to large operations in hospital, academic, or commercial biobanks. National, regional, and international networks are also developing to provide resources from diverse populations. For example, the Low- and Middle-Income Countries (LMICs) Biobank and Cohort Building Network (BCNet), coordinated by the International Agency for Research on Cancer (IARC), has established a virtual catalogue to document the resources of its members.

The operational model and governance of networks depend on their focus and mission. One such model is the *federated* model, where the biobanks maintain their samples and

contribute to a common network project when necessary. Another model is the *project-based* model, where the biobanks collect samples for a specific project (Vaught et al., 2009).

Several factors can contribute to the success of a biobank network. They include:

- well-defined goals, effective coordination, and funding mechanisms;
- efficient communication between the relevant medical disciplines and the global scientific community;
- standard operating procedures (SOPs), compatible informatics systems, and harmonized informed consent and material transfer policies and procedures; and
- tools to enable de-identified, up-to-date follow-up and retrieval of information and clinical data on participants.

These tools are key to the success of biobank networks.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study, a population-based study that was initiated in the 1990s and coordinated by IARC, is an example of an effective networked project. The project involved partners from 10 European countries and 23 EPIC centres, and each centre collected biospecimens and data. Blood samples and associated data, including lifestyle and dietary information, were collected at baseline. Blood samples from participants in eight out of the 10 European countries are kept in the IARC central biobank. For two Scandinavian countries, blood samples are kept locally.

Although EPIC has a central biobank for the baseline samples, the tissue samples from individuals who develop cancer are kept at the centre, and this forms the EPIC federated biobank.

The EPIC study has provided opportunities for researchers to investigate lifestyle and cause of

death (Bergmann et al., 2013) as well as dietary intake in relation to mortality among people who develop different types of cancer, such as colorectal cancer (Aleksandrova et al., 2014) and prostate cancer (Rohrmann et al., 2013), and other diseases, such as ischaemic heart disease (Crowe et al., 2012).

2.1.4.1 Tools for effective networking

Several important tools have been developed in recent years for effective networking and resource sharing between biobanks. Some examples are the following (see also Section 3.8).

- The Minimum Information about Biobank Data Sharing model (MIABIS 1.0 and MIABIS 2.0). MIABIS 1.0 recommends the minimum data items and the format of the items required to enable the exchange of biological samples and data, and required to initiate collaborations between biobanks (Norlin et al., 2012). MIABIS 2.0 provides an ontology that represents the administrative entities and includes data about the biobanks where specific specimens of interest are stored; this ontology can be helpful to answer research-relevant questions, such as those about the scope and curation status of the specimens and the contact information for curators of biobanks (Brochhausen et al., 2013).
- The Sample PREanalytical Code (SPREC) (Lehmann et al., 2012) identifies and records the main pre-analytical factors that may have an impact on the quality of sampled clinical fluids and solid biospecimens and their simple derivatives during collection, processing, and storage. However, the SPREC tool may be less important with the release in 2015 of the European Committee for Standardization (CEN)

norms (CEN/TS 16826, 16827, and 16835) (CEN, 2015) and with the new ISO 276 standards, which will become available within 2 years.

- The CEN norms deal with the standardization of the entire process of sample handling, from primary sample collection to analysis. They are based on studies undertaken to determine the important influencing factors. The Technical Specifications draw on the effort to codify and standardize the different steps in the pre-analytical phase.

2.1.4.2 Visibility and standardized citation schemes

Being part of an international network and contributing to a global catalogue of available resources, with the possibility of creating population-based biobanks, provides opportunities for biobanks to benefit from the experiences and tools developed for networks. Increased participation in research will result in an increase in the visibility of biobanks and their recognition as an important part of research infrastructure. These attributes can serve to augment the confidence of researchers and donors in the institutions and countries that the established resources are managed effectively and used optimally.

Recently, a programme of guidelines for reporting bioresource use and standardized citation schemes has been established to formally recognize the efforts involved in generating, maintaining, and sharing high-quality bioresources.

Two current initiatives aim to put in place standardized procedures for formally recognizing the contributions of biobanks in research through citations in scientific publications: the Citation of BioResources in Journal Articles (CoBRA) guidelines for the reporting of bioresource use in research articles (Bravo et al., 2015) and the Bioresource Research Impact Factor (BRIF), a standardized

citation scheme. Biobanks joining the BRIF citation scheme will have increased visibility and will benefit from participation in network projects (Cambon-Thomsen et al., 2011).

The formal recognition of the role of biobanks in scientific research will encourage sharing of biological resources and will increase the visibility of biobanks both nationally and internationally.

2.2 Issues in developing biobanks and using stored specimens

Developing and using the resources in a biobank requires the active involvement of many professionals and has ethical and legal implications. Section 3.1 is dedicated to putting these ethical, legal, and social issues (ELSI) into perspective. However, it is useful to highlight some of the key documents and principles that can guide decision-making when establishing a biobank. Key documents include the following:

- the WMA Declaration of Taipei on ethical considerations regarding health databases and biobanks (WMA, 2016);
- the WMA Declaration of Helsinki, which provides the general framework in which questions relating to medical research can be addressed (WMA, 2013);
- the more specific guidance issued by the OECD: *Guidelines on Human Biobanks and Genetic Research Databases* (OECD, 2009) and *Best Practice Guidelines for Biological Resource Centres* (OECD, 2007);
- best practice principles outlined by organizations such as the United States National Cancer Institute (NCI) (NCI, 2016) and ISBER (ISBER, 2012);
- guidance from the Global Alliance for Genomics and Health (GA4GH) (GA4GH, 2016) and the Public Population Project in Genomics and Society (P3G) (P3G, 2016); and

- European Union (EU) legislation, including the General Data Protection Regulation (European Commission, 2016).

Another useful approach derives rights and responsibilities from a set of four ethical principles guiding biomedical research: respect for autonomy, non-maleficence (to do no harm), beneficence (to do good), and justice (Beauchamp and Childress, 2013). Protecting the rights of individuals arising from these principles includes the development of appropriate methods to obtain informed consent from a potential participant and the development of research protocols that are fully compatible with the principles of beneficence, non-maleficence, and justice. The institutions and investigators that develop and manage biobanks also have a responsibility to protect personal data, ensure biological and environmental safety, and make collections accessible and available for reuse for research purposes under (the consented) defined conditions. Access requests should take into account the non-renewable nature of the specimens in setting priorities for scientific use, and the distribution of specimens for research should be governed by the use of clear and documented Material Transfer Agreements (MTAs). These rights and responsibilities are further defined and addressed in the remainder of this book.

2.3 Principles for sustainable biobanks

Developing a biobank is expensive. Added to the maintenance and running costs, this can place financial strain on underresourced institutions. These constraints are a significant obstacle to developing biobanks in low- or middle-income countries and for the long-term sustainability of biobanks worldwide. Overcoming these obstacles requires a significant concerted effort of national and

international solidarity. The public sector (local and national governments and international bodies and organizations) has a responsibility to contribute to the funding of the basic infrastructure of biobanks, because of the important contribution of biobanking to research on global health and diseases. In contrast, the responsibility for the development and maintenance of sustainable and usable resources lies primarily with the institutions.

Institutions and the public sector should make provision for:

- infrastructure
- maintenance of infrastructure
- equipment
- running costs
- trained personnel
- data management systems
- quality management systems (QMSs)
- procedures to deal with ELSI.

In addition, users of the biobanking infrastructure facilities should contribute through cost reimbursement, for the financial and structural sustainability of biobanks. Thus, biobanks should establish user fees for access to human specimens, data, and services, to cover the costs of collecting, annotating, storing, retrieving, and processing the delivered biospecimens. However, human biospecimens should not under any circumstances be commercialized. Regardless of the role of industry in core funding, which is a matter of debate with serious implications, the legal responsibility and custodianship of the specimen collection and storage must remain within institutions. This is because people who agree to provide their samples donate to the institution and not to researchers or individuals, and the samples will remain in the primary institution after the research project ends or the researcher leaves the organization. To ensure continuity in the management of the samples, the institution should nominate another person who will assume primary responsibility for the samples.

In defining mechanisms for sustainability or stability, there is a need to develop safeguards for preservation of participant confidentiality and protection against improper use of human biospecimens and data. In addition, the stability of biobanks relies heavily on the value of the stored resources, in terms of their quality and scientific relevance and the use of the samples.

Financial forecasts have demonstrated that the actual costs associated with biobanking are significantly higher than recognized by researchers and funding bodies (Matharoo-Ball and Thomson, 2014). Cost recovery is essential for biobank sustainability and stability. Although each institution will have to decide on the cost-recovery model that will best serve its purposes, common elements to be considered include costs related to personnel, equipment, supplies, and service contracts.

The models should be considered in the context of relationships between the users, funding agencies, academia, and universities, and possibly also industry partners. Contingency plans in case of unexpected incidents and inadequate supporting infrastructure, such as flood or fire disasters, interruption in electricity supply, and poor Internet connectivity, should be included in any model.

2.4 General considerations for establishing a biobank

Several factors must be taken into account when setting up and running a biobank. A detailed description of these requirements is provided in the *2012 Best Practices for Repositories: Collection, Storage, Retrieval, and Distribution of Biological Materials for Research*, developed by ISBER (ISBER, 2012). Some aspects of particular importance in setting up a biobank for cancer research are highlighted here.

2.4.1 Institutional commitment

Many factors contribute to the decision to establish and run a biobank. In practice, the process often starts with the willingness of medical doctors and scientists to develop a resource useful for diagnosis, prognosis, and research purposes. However, the establishment of a biobank must not rely only on individual action but also requires a clear commitment by the host institution, which also needs to ensure that collections are developed within appropriate legal, ethical, clinical, scientific, and technical guidelines, to provide historical continuity in specimen management and record-keeping. Finally, the biobank should ensure that the stored materials can be made available for research.

The purpose of the biobank must be clearly formulated and documented. In case of loss of funding or other adverse events that may prevent the institution from maintaining its commitment, it is the responsibility of the institution to take the necessary steps, depending on the applicable legal/ethical requirements. There may be an obligation to destroy the samples or to transfer the collected specimens and data to another institution that will take over the commitment for the long-term maintenance of the resources. There may be specific obligations related to such a transfer.

2.4.2 Ethical, legal, and social issues (ELSI) and governance

ELSI considers local, national, and international cultural, legal, social, and ethical norms. For example, the EU Data Protection Directive states that under EU law, personal data can be gathered legally only under strict conditions, for a legitimate purpose (European Commission, 1995). Furthermore, people or organizations that collect and manage personal information must protect it from misuse and must respect certain rights of the

data owners, which are guaranteed by EU law.

However, there are conflicting data protection rules in different countries, which need to be observed during international exchanges. Therefore, common EU rules have been established to ensure that personal data have a high standard of protection everywhere in the EU. The EU Data Protection Directive also provides specific rules for the transfer of personal data outside the EU, to ensure the best possible protection of data when they are exported abroad.

ELSI and governance recommendations relating to governance structures, informed consent, data protection, return of results and incidental findings, and data and sample sharing are presented in Section 3.1.

An important governance issue to highlight when establishing and maintaining biobanks relates to public engagement programmes and the establishment of clear channels of communication with partners and stakeholders. Therefore, transparency in procedures and operations is critical, and clear descriptions of the roles and responsibilities of personnel should be communicated to partners and stakeholders. Given that participation is voluntary and that most biobanks operate on a non-economic basis, biobanks need public trust and support. It has become common practice for large-scale population biobanks to engage in consultation with the public and other stakeholders before the biobank is established (UK Biobank Ethics and Governance Council, 2015, 2016). Methods of communication could include, for example, consultation with community representatives, focus group meetings, workshops, interviews, public meetings, polls, and surveys. Public consultation is particularly important when ethnic or cultural minorities are approached to participate in biobank collections. Section 3.1 provides further information on transparency and

communication with key stakeholders, and Section 3.1.2.5 describes community engagement in relation to the consent process.

2.4.3 Biobank management and staffing

Biobanks should be adequately staffed, and the personnel selected for these tasks must be well qualified and have an appropriate level of specialized training. The biobank should be placed under the overall supervision of a biobank manager with sufficient training, experience, and seniority to fulfil the scope of the activities of the biobank. The manager is responsible for operations, including compliance with appropriate

regulations, and has a critical role in receiving, processing, and responding to requests for access to stored specimens. The manager can act as a technical advisor to the access committee during the review of access applications.

Running a biobank requires dedicated staff members for specimen processing and storage and for data management. The job description, tasks, and reporting system of all supervisory and technical staff members must be documented. This is of particular importance in instances where biobank staff members also perform other tasks within the institution (e.g. pathology service or service activities in molecular biology). Staff members must have

adequate educational backgrounds, experience, and training to ensure that assigned tasks are performed in accordance with the biobank's established procedures. Updated training should be conducted on a periodic basis for personnel, in accordance with applicable regulations and roles within the biobank.

Other personnel who are not necessarily staff members of biobanks but should be aware of the purpose and goals of obtaining high-quality bioresources are clinicians, researchers, technicians, nurses, surgeons, pathologists, and anaesthetists. The involvement of a pathologist in this process is crucial to ensure that patient care is not compromised (NCI, 2016).

Recommendations for biobanks

3.1 Ethical, legal, and social issues (ELSI) and governance

This section provides advice on developing an internal governance system for biobanks. It references recommendations and best practices of international organizations, including OECD (2007, 2009), ISBER (2012), GA4GH (2016), and NCI (2016), among others. However, the background of law and guidance is continually developing and should be monitored. For example, the new EU General Data Protection Regulation (European Commission, 2016) has implications for patients' rights in medical research, CEN norms, and ISO standards.

Governance, in the context of biobanks, is not one-size-fits-all. During the establishment of a biobank, governance systems should be designed to take into account the biobank's scope and the context in which it

operates (Laurie, 2011). A good internal governance system should:

- ensure that the biobank remains faithful to its purpose, encouraging trust between the various stakeholders;
- be guided by a set of overarching principles when making decisions, including being transparent, accountable, consistent, proportionate, efficient, coordinated, equitable, and fair; and
- be dynamic and able to adapt over time.

The internal governance approaches introduced in this section are based on a good governance structure or framework (Section 3.1.1) and documentation on:

- informed consent (Section 3.1.2);
- data protection, confidentiality, and privacy (Section 3.1.3);
- return of results and incidental findings (Section 3.1.4); and
- access to and sharing of samples

and data (Section 3.1.5; see also Annex 1).

Further sections consider quality (Section 3.4) and records management (Section 3.6).

Good governance includes engaging with the public during the establishment of a biobank and throughout the life-cycle of the biobank. Therefore, the approach to public engagement must be considered from the outset. In addition to engaging with participants, the biobank may need to engage with the scientific community, researchers, patient groups, and/or the wider public using a variety of methods, for example by consultation on study designs and policies, involvement on committees, or publication and outreach. Good biobank governance also includes a strong commitment to researchers, ensuring quality, efficiency, and transparency of service. Therefore, the

following recommendations should be put into practice in collaboration with project principal investigators.

3.1.1 Governance framework

A good governance framework should define the organizational structure of the biobank, for daily management and oversight of its strategic policy. This framework usually includes lists and descriptions of the biobank’s personnel, committees, and policies that are required to enable the correct functioning of the biobank. The level of policies and procedures governing the biobank should be scalable to its nature, size, and available resources. For example, smaller biobanks may have more limited policies, whereas

larger biobanks will need to develop a detailed protocol and procedures.

The policies are usually stipulated in a governance document that describes the objectives and scope of the biobank, the organizational structure, the scientific and economic strategy of the biobank (which will be articulated in an annually updated business plan), and contingency plans in the event of closure. The governance document also includes policies on data protection and privacy as well as the procedures governing specific operational activities of the biobank.

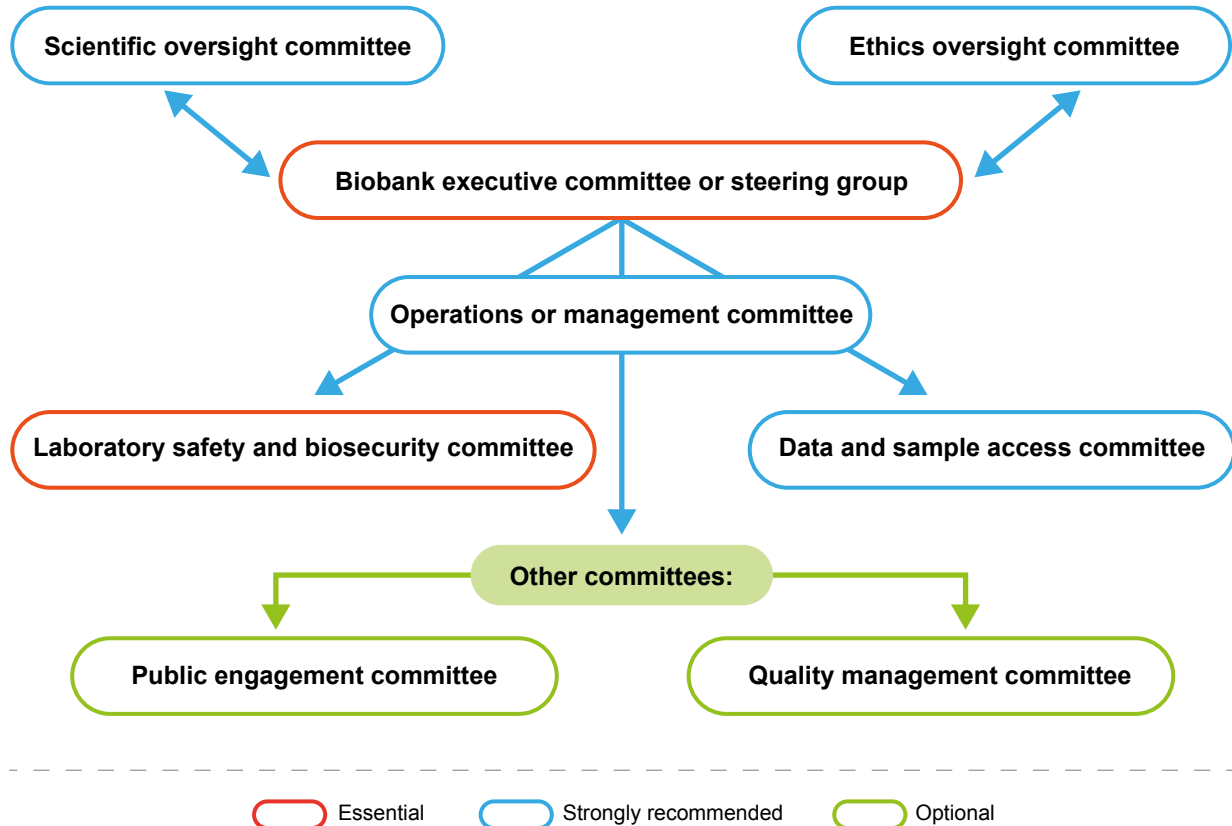
Defining the structure and mandate of committees and describing policies is an effective way to ensure adherence to proper governance. However, if there are too

many committees or policies, or if they are ill-defined, this can impede procedures and cause delays.

3.1.1.1 Governance organization

The biobank should have a structure of committees and appropriately qualified personnel in relevant roles to oversee its governance. The size, type, and number of committees and their composition will vary depending on the size and purpose of the biobank. Careful consideration should be given when participants, patient groups, or public representatives are asked to serve on biobank committees. Their roles on the committee should be clearly communicated, and training should be provided. The following types of committee may be considered (Fig. 1).

Fig. 1. Sample committee structure for internal biobank governance.



Executive committee or steering group

All biobanks should have an executive committee or steering group. The responsibilities of this committee may include overall management, defining strategic objectives, monitoring progress, revising and/or adopting policies, and developing a communications strategy. This committee may also conduct an annual review meeting to consider the QMS.

Ethics oversight (or advisory) committee

The ethics oversight committee advises the executive committee on strategy, developments, and procedures relating to ethical oversight, including legal and policy issues. The committee could include, for example, ethicists, scientific researchers, medical experts, lawyers, social scientists, and members of the public or participant organizations. In some cases, this committee may be part of a larger infrastructure, such as a local hospital ethics committee. In some countries, this committee may be a legal requirement.

Laboratory safety and biosecurity committee

All biobanks should establish, or have access to, a committee on laboratory safety, which may also consider general health, safety, and security issues.

Data and sample access committee

Biobanks should consider establishing a data and sample access committee, to oversee access requests, monitor related procedures, and ensure that participants' interests are protected and biobank protocols are followed. In some cases, this committee is external to the biobank and is composed of independent members.

Operations or management committee

The role of the operations or management committee is to support the executive committee for the strategic decisions of the biobank and to provide expertise in all aspects of biobanking operations (e.g. safety; quality and efficiency, including processing, storage, and distribution of biospecimens).

Larger biobanks may require additional committees, such as the following.

Scientific oversight (or advisory) committee

This committee would provide scientific feedback to the executive committee, advise on scientific strategy and current developments, consider the pertinence of new collections, or advise on procedures. Membership should include relevant professionals. In some biobanks, this committee could be combined with an ethics oversight committee. In some countries, this committee may be a legal requirement.

Public engagement committee

This committee could help biobank personnel and associated researchers to better understand public opinion. For some larger biobanks, advisory panels of study participants meet regularly and provide feedback on new projects and review study materials, newsletters, and questionnaires. Examples are the Avon Longitudinal Study of Parents and Children (ALSPAC) teenage advisory panel (UK Biobank Ethics and Governance Council, 2009) and the NIH Precision Medicine Initiative Cohort Program subcommittee, which has significant participant representation (Precision Medicine Initiative Working Group, 2015).

In terms of personnel, the biobank should have clear reporting lines and accountability, with documented levels of authority and responsibility associated with each role. Clear responsibilities for staff members enable the biobank management to ensure that the biobank's activities comply with ethical and legal requirements (OECD, 2009). An organizational chart and list of staff members and their responsibilities should be developed, alongside an organizational plan, which defines the organization and management of the biobank and its relationship to external parties. Roles and responsibilities should be clearly defined, to establish who has legal responsibility in relation to the biobank, who has day-to-day operational responsibility, and who is acting as the custodian of the resources.

Specific roles within the biobank will depend on the institutional context but may include the following.

- A designated director, who is responsible for implementing biobank policies. The roles and responsibilities of this person in their institution should be clearly defined.
- A biobank coordinator or manager, who reports directly to the steering group. To eliminate conflicts of interest, it is recommended that the biobank manager is not an active investigator or a biobank user. The biobank manager may also be designated the custodian of the resource, with the following responsibilities:
 - establishing procedures;
 - ensuring that ethical guidelines are adopted and respected;
 - implementing the decisions of the relevant committees in relation to the control, access, and use of the material;
 - maintaining close collaborations with principal investigators;
 - distributing information about the biobank and related research; and
 - other responsibilities, which should be defined in advance.

- A biobank quality manager, who is responsible for the QMS and for periodic review of all SOPs, and has overall responsibility for quality control (QC) and quality assurance (QA).
- A data steward, who is responsible for data protection and privacy.

3.1.1.2 Documentation: plans, policies, and procedures

Documentation requirements include plans, policies, and specific SOPs. The documents should be compatible with international standards such as the ISO standards for biobanking and the CEN norms that articulate how activities of the biobank are to be performed (see Section 3.4 for more details about ISO and CEN). Some general principles in relation to these documents should be followed:

- Documents should be developed in the context of a QMS, which includes document version control.
- Documents should be developed in the context of an up-to-date risk assessment undertaken alongside a procedure that takes into account risks to the health and safety of people.
- Documents should include a time frame for review and revision; 2 years is a recommended time frame (NCI, 2016).
- To facilitate cooperation between biobanks, documents should adhere to internationally accepted technological standards and norms, ensuring that these are clearly referenced (OECD, 2009).
- High-level policies, including data and sample access policies and terms of reference of committees, should be publicly and freely available, for example on a website.
- Biobanks should consider implementing monitoring strategies with scheduled audits to ensure that policies and procedures are followed.

- Researchers should submit reports annually and at the end of their projects, including information on publications and patent applications (OECD, 2009).
- The biobank should maintain a system for reporting adverse events, anomalies, and non-compliance with the QMS; this reporting system supports corrective and preventive actions and enables any relevant documents to be updated (CCB, 2014).

A critical document is the biobank programme document (or biobank protocol), which contains information about the scientific rationale, scope, design, and strategy for the biobank. Other biobank plans, policies, and procedures should be developed in line with this protocol. The biobank's mission should be clearly outlined in terms of its purpose, the types of research or other users supported (scope), and the types of samples and data collected. Additional considerations include which services are provided (e.g. specific research assays, storage of samples) and whether legacy samples can be incorporated into the biobank. This protocol and associated key biobank documents should be approved by a research ethics committee, and renewed approval should be required if the documents are amended (OECD, 2009).

An annually updated business and continuity plan or model is essential, especially if the biobank is planning to charge for use of the resources (Vaught et al., 2011). The business plan should include a strategy for both medium-term and long-term sustainability. A budgeting or costing exercise will assist in the development of such a plan.

All biobanks should also develop a quality management policy and a policy on access to samples and data from the biobank (see Annex 1).

Additional policies to consider include:

- a governance policy, containing information about the biobank's governance structure and the responsibilities of management (OECD, 2009);
- a retention policy, covering biospecimen availability and whether collections can be shared or destroyed;
- a policy on storage options;
- a safety policy for staff and visitors;
- a policy on transportation of material;
- a policy on disposal of material and biosafety and biosecurity;
- policies covering ethical issues, including information on the protection of the confidentiality and privacy of participants (see Section 3.1.3), informed consent, return of results and incidental findings, and so on;
- a policy on the intellectual property generated from the use of the resources and research results;
- a publication policy, governing publications arising from the use of the biobank; and
- policies on how the termination of the biobank would be handled.

Guidelines recommend that accompanying SOPs should be put in place to govern all biobank activities: recruitment; consent; staff training; biosafety; the collection, receipt, processing, and storage of samples; sample QC; laboratory QA; participant de-identification; data collection, recording, storage, and management; data protection; the monitoring, calibration, maintenance, backup, and repair of equipment; the procurement and monitoring of supplies (disposables and reagents); the distribution and tracking of samples; records and documentation; reporting of non-conformity and complaints; and disaster management.

All staff members should be trained in the procedures at the biobank, and this should be documented.

Key points: biobank governance

- Good governance involves considering structures and documentation from the outset.
- The biobank should, at a minimum, have an executive committee or steering group and have (or have access to) a laboratory safety and biosecurity committee.
- A scientific oversight committee, an ethics oversight committee, an operations or management committee, and a data and sample access committee are strongly recommended.
- Other committees are optional, depending on the size and scope of the biobank, including a public engagement committee and a quality management committee.
- In terms of personnel, it is critical that clear reporting lines and accountability exist, with documented levels of authority and responsibility associated with each role. An organizational chart should be made and communicated to all biobank staff members.
- Key biobank personnel may include a director of the biobank.
- Other personnel should include a biobank coordinator or manager, who reports directly to the steering group. A biobank quality manager and a data protection officer are also strongly recommended.
- A critical document is the biobank protocol, which includes information about the scientific rationale, scope, design, and strategy for the biobank. The protocol and associated documents should be approved by an independent research ethics committee.
- A business plan or model that considers long-term sustainability and provides a continuity plan is essential, especially if the biobank is planning to charge for use of the resources.
- All biobanks are strongly advised to develop a quality management policy and a biobank access policy, based on the model of the biobank.
- Extensive guidance is provided on other policies and SOPs that may be implemented, depending on the context of the biobank.

3.1.2 Informed consent

The approach to informed consent is a key consideration when establishing a new biobank, and a policy should be developed (see Section 3.1.1.2). Requesting appropriate informed consent has become a cornerstone for the collection of samples and data for use in research, and is supported by relevant guidance and legislation. This section presents recommendations to assist a biobank in developing a consent policy and associated documentation, and covers the following areas (see also Annex 2):

- types of consent;
- what information to provide to potential participants;
- potentially ethically or legally challenging issues;
- what to consider during the process of requesting consent;
- what to consider if the country or the

research area would benefit from community engagement in relation to the consent process;

- what to do if the potential participant does not fully understand the language of the researcher who is administering the consent;
- what to do if the potential participants do not have the legal capacity to consent for themselves;
- considerations when including samples or data from deceased participants in the biobank;
- the continuing nature of consent;
- when participants might need to be re-contacted to request new or updated consent; and
- how to approach withdrawal of consent.

3.1.2.1 Types of consent

Many biobanks use a broad consent, which allows patients or research par-

ticipants to consent to a broad range of uses of their data and samples. Although broad consent allows for a broad range of research activities, it is regarded by research ethics committees as specific enough to be considered “informed”, because guidance is provided on the nature of the future undetermined research uses (e.g. research on breast cancer and associated conditions). It is important to note that broad consent forms usually contain a series of statements specific to the biobank, and not statements related to specific research projects. Table 2 outlines the different types of consent associated with biobanks and sample collections, together with key points about each approach and notes on information to be provided to participants.

Further guidance on designing and implementing a broad informed consent is provided in Annex 2.

Table 2. Types of consent and key considerations

Type/subtype of consent	Uses	Key points	Information to be provided to participants
Consent waiver	Existing collections	An ethics committee agrees that existing samples and anonymous data can be used for research or biobanking without a new/updated consent. Consent waivers should be an exceptional measure for high-value collections. If a similar collection can be prospectively obtained, this should be done.	None
Opt out	Leftover clinical samples from treatment when expected uses are low-risk New uses of existing collections	This approach needs specific review by an ethics committee. Part of the participant's routinely taken sample and anonymous data can be used for research, unless the participant takes action to opt out. This approach should not be used for collection of additional/new samples for research projects or biobanking.	Information on the biobank should be available to the participant population, with details of how to opt out (e.g. information sheets given directly to patients, leaflets distributed with hospital appointments, and clearly visible posters).
Opt in, with subtypes			
Specific consent	Research projects involving sample collection that are complicated for the participant to understand, including clinical trials	Consent forms usually contain a series of statements specific to the project. Restricts samples and data to the specific research project described. Ethics approval is needed.	Information is provided that refers to one research project or a linked group of projects.
Specific and broad consent	Used for specific projects or activities (e.g. surgical treatment or clinical trials) involving sample collection when there is a future plan for biobanking	The consent form for a specific project or trial includes provision on the addition of participant data and samples to a biobank. The consent form for surgical treatment should include a clause on adding any remaining samples and anonymized clinical data to a biobank. May restrict use for biobank to anonymized samples and data. Ethical and scientific approval will be required for future biobanking or research with samples collected via this route. An existing biobank must have ethics approval for samples to be accepted via this route and should have standard approved wording to include on the consent forms and information sheets.	Information on the intended biobanking activity should be included in the project information sheet, plus information in other relevant sections of the information sheet, if possible. For surgical treatment, information about the biobank should be provided (see advice for "Opt out" above, including posters, etc.).
Broad consent	Used when samples are taken for the purpose of a biobank For multiple sampling events and multiple projects	This approach provides information and choice to participants about the biobank's activities. The consent forms usually contain a series of statements specific to the biobank, and not statements related to specific research projects. Ethical approval is mandatory for this approach. Ethical and scientific review is usually needed before distribution of samples and data to researchers.	Topics for a biobank information sheet are included in Annex 2.
Dynamic consent	Used when (multiple) samples are taken for the purpose of a biobank, or a research project When the scope of the biobank or project may change over time When the biobank envisages regular contact with participants	The consent process and continuing communication with the participant usually happen via an IT-based infrastructure. The platform can be used for other communications relating to the study. If the biobank enables this, the participant can opt in or out of parts of the biobank's planned research and amend this over time, and find out which projects their samples have been used in. Ethical approval is needed for this approach.	Through the use of an IT system, the participants themselves can choose how much information they wish to receive, i.e. in-depth or brief information. The information can cover both the biobank's scope and information on the governance of the biobank. More in-depth information could be provided on potential uses of the samples, to enable participants to opt in or out of certain uses.

IT, information technology.

3.1.2.2 What information to provide to potential participants

Information about the biobank and biobanking activities is usually provided to potential participants using a participant information sheet in conjunction with a consent form (in some cases, these two documents together are called the informed consent form). The information provided will vary depending on the nature of the biobank and the type of consent requested. Further details are provided in Table 2 and Annex 2.

3.1.2.3 Potentially ethically or legally challenging issues

The following potential uses of samples and data are examples of issues that may be considered ethically or legally challenging:

- transfer of samples or data across national borders; it is important to be aware of regional and national regulations, such as the EU Data Protection Directive of 1995 (Article 26) (European Commission, 1995) and the EU-U.S. Privacy Shield adopted by the EU Commission on 12 July 2016 (http://ec.europa.eu/justice/data-protection/international-transfers/eu-us-privacy-shield/index_en.htm);
- use of samples in experiments involving animals;
- creation of cell lines from the samples, including stem cell lines;
- use of samples and data by commercial researchers;
- research linked to reproduction, including use of embryos;
- return of individual research results and incidental findings (this is an important topic that warrants extensive discussion, which is beyond the scope of this document); and
- research into high-penetrance genes linked to disease.

When information sheets and consent forms are being developed, the biobank should consider whether

it may be involved in any potentially challenging uses and include information about these in the information sheet and/or the consent form as appropriate, in addition to the core elements usually included as part of a consent form. The consent form should provide the participant with a means to opt out of uses that the participant feels are ethically questionable. The consent form may also require specific opt-in provisions if they are legally required by national or regional laws; an example is transfer of data outside of Europe, according to the EU Data Protection Directive (European Commission, 1995). A means to opt out of certain uses should be provided by the biobank only if this is recordable (i.e. in a database), actionable (i.e. when distributing the samples for research), and practicable (e.g. given the number of participants or the number of samples distributed).

3.1.2.4 What to consider during the process of requesting consent

It is important to consider the following aspects during the consent process.

- Where possible, the information sheet should be distributed ahead of the meeting with the potential participant.
- The potential participant must be given adequate time to read and consider the information sheet and should be offered the option to decide and give consent at a later visit if required.
- The person administering the consent process must be convinced of the capacity of the potential participant to give consent. If they are not convinced, Section 3.1.2.6 (on participants without the legal capacity to consent) may be applicable. Alternatively, the potential participant may require assistance in reading the form.

- The person requesting consent should not coerce the potential participant in any way.
- The person requesting consent should encourage open discussion and give the potential participant the opportunity to ask questions.
- The person requesting consent should ensure that the potential participant is informed about their right to withdraw consent, about the risks and benefits of participating in the project, and about any other important issues.

3.1.2.5 What to consider if the country or the research area would benefit from community engagement in relation to the consent process

The consent process needs to be appropriate for the local cultural context, and in some cases this means that wider community engagement is appropriate (H3Africa, 2013). In cases where wider community engagement is needed, consultation on the biobank's consent processes and documents should take place with the wider community, local leaders, and professionals. The requirement for community involvement in the consent process may also be specified in local ethical or legal guidance. In some of these cases, prior consent, assent, or permission may need to be obtained from community, tribal, or family leaders (Nuffield Council on Bioethics, 2002). In all cases, the potential research participant must be approached for consent and must have the right to refuse participation.

3.1.2.6 What to do if the potential participants do not have the legal capacity to consent for themselves

This category of participant is often called “vulnerable people”, and careful consideration must be given

to how recruitment will be conducted (WMA, 2013, 2016). Recruitment of “vulnerable” participants must respect the requirements in the Declaration of Helsinki that all vulnerable groups and individuals should receive specifically considered protection, that the research is responsive to the health needs of this group and cannot be carried out in a non-vulnerable group, and that this group will benefit from the research.

Three types of participant commonly identified as vulnerable are:

- mentally incapacitated adults;
- adults in emergency care situations; and
- minors/children.

In the case of mentally incapacitated adults, a legally authorized representative can provide consent on their behalf. If the participant made legally approved provisions about research participation before they were incapacitated or if they assigned a legal representative, these should be respected. The participant should be involved as much as possible in the decision to participate, and any resistance or objections should be respected.

In the case of research taking place in an emergency clinical situation where consent has not been obtained, requirements will differ by country and may include:

- the local ethics committee explicitly approving the recruitment pathway;
- another medical professional authorizing the involvement of the participant;
- the known wishes or objections of the participant being respected; and
- a maximum time limit being imposed for participant involvement without consent.

Consent should be requested from the participant if the participant regains legal capacity.

In the case of research involving children, they should take part in the consent process in accordance with their age and maturity, and *assent* to

participate (rather than *consent*). Information and consent materials can be designed for different age groups to aid understanding of the research. Any objection from the child should be respected (Hens et al., 2011). The assent process is based on the age and maturity of the child and on any applicable local laws or ethical guidance on the matter. In addition to the assent of the child, the child’s parent(s) or an appropriate legal representative must provide consent on the child’s behalf. It is also good practice to re-contact child participants once they reach the local legal age of maturity, to request consent, if possible (CIOMS, 2002; Hens et al., 2011).

3.1.2.7 Considerations when including samples or data from deceased participants in the biobank

Consent requirements will vary depending on whether the biobank intends to request consent for samples and data from potential participants before their death (for example, for a brain biobank) or request the samples and data after the participants’ death. Local legislation will dictate the applicable consent and legal requirements. Some legal or practical constraints may exist for biobanks accessing medical records after the participants’ death. Uses of the samples and data, collected before or after death, that fall outside the scope of the original consent will require approval by a research ethics committee (Tassé, 2011).

Where samples are to be collected for research after death, local institutional, ethical, and legal guidelines to obtain consent must be followed, and the individual’s wishes expressed before death, if they are known, should be respected. The consent procedure may be built into existing procedures for postmortems or for clinical use of postmortem samples for organ or tissue trans-

plants, which may differ markedly from country to country.

3.1.2.8 The continuing nature of consent

If the participant has given prior written consent, they should always be asked to confirm (verbally and/or tacitly, as appropriate) their agreement to donate samples to the biobank, and they should always have the opportunity to ask questions, before additional sampling (e.g. blood, biopsy, aspirate, bronchial brushings) or data collection is performed. Where possible, the verbal consent should be recorded electronically or noted and stored with the original consent form.

The participant may decline to provide further samples or data at any time. This does not invalidate the consent to use any previous samples or data given to the biobank, unless notice of withdrawal of consent is given.

3.1.2.9 When participants might need to be re-contacted to request new or updated consent

Several situations may arise where the biobank may need to re-contact the participants to request new or updated consent, apart from contact to request additional data and/or samples for the purposes of the same project. These situations may include children reaching the age of maturity and temporarily incapacitated participants regaining legal capacity (see Section 3.1.2.6), and in such cases full informed consent should be requested (Burke and Diekema, 2006). Another situation is when the information provided in the initial consent form and information sheets is modified or updated (e.g. if the scope of the biobank changes). In this case, re-contact of participants to request an updated consent may be required, given the changing conditions of their participation (Wallace et al., 2016). An appropriate research ethics

committee should decide whether re-consent is required or whether a waiver can be applied.

A general guideline is that before re-contact is established, a participant's options with respect to re-contact should be checked, because participants should be given the option not to be re-contacted (see Annex 3).

3.1.2.10 How to approach withdrawal of consent

At any time, participants can withdraw consent for the biobanking and use of their samples or data without giving a reason. It is crucial for the

biobank to present withdrawal options to participants in the consent form or information sheets. This may not mean guaranteeing to destroy all samples and data; for example, the withdrawal options may stipulate that samples and data already released or used in analyses are not retrievable. Examples of withdrawal options include the following.

- “No further use” option: the biobank will destroy all samples and data from the participant and will not contact the participant again.
- “No further contact” option: the biobank will no longer contact the participant directly by any means but can continue to use samples

and data already collected and can continue to access the participant's medical records if necessary.

- “No further access” option: the biobank will not contact the participant or access the participant's medical records but can continue to use samples and data already collected.

The biobank should also clearly communicate to participants when it is impossible to destroy parts of the samples or data. Examples include being unable to destroy:

- samples and data already distributed for research or used in analyses; and
- data needed for audit purposes or already archived.

Key points: informed consent

- Consider local legal or ethical requirements that are applicable to the consent process.
- Distribute the consent materials to the participant in advance whenever possible. The form should be written in a language that is understandable to the participant.
- Give participants adequate time to read the form, understand the information, and consider possible participation.
- The person requesting consent should ensure that the participant fully understands what is required of them.
- The person requesting consent should encourage open discussion with the potential participant and should not coerce them to participate in the project.
- The rights of the participant and the risks and benefits of participating in the project should be explained to potential participants.
- The withdrawal options should be explained.

3.1.3 Data protection, confidentiality, and privacy

This section briefly outlines recommendations about the protection of biobanks' data and about the confidentiality and privacy of the participants' data. Legislation and guidance on these issues vary between countries and, where they exist, may also be complemented by local site requirements.

In the EU, the General Data Protection Regulation (European Commission, 2016) replaces the Data Protection Directive (European Commission, 1995) and unifies data pro-

tection for individuals in the EU. The processing of personal data outside the EU is also an important component of EU privacy and human rights law.

Other examples of privacy and security policies are those of the Confederation of Cancer Biobanks (CCB, 2014) and GA4GH (GA4GH, 2015b).

At a European level, the changing data protection regulations and requirements in relation to the EU-U.S. Privacy Shield should be taken into account. The biobank must develop a strategy and have an IT framework and policies in place for managing

data collected alongside the samples in line with the commitment undertaken with participants.

Methods to ensure data protection, confidentiality, and privacy are discussed in Section 3.3.4 and Section 3.6. The biobank should consider using de-identification methods, such as coding or pseudo-anonymization associated with a procedure to store codes. Explanations of these terms are provided in Section 1 and in Appendix 1 of the privacy and security policy of GA4GH (GA4GH, 2015b).

Examples of particular issues for data protection and privacy for biobanks include the following.

- Access to medical records. When possible, staff members should be bound by a professional code of practice with high standards of ethical behaviour. The participant should be asked for permission to access their medical records and should be informed where these data are held in an encrypted, non-identifiable format at the biobank (CCB, 2014).
- Data protection mechanisms when biobanks share data with other biobanks or provide data for translational research. Privacy and confidentiality of data must be guaranteed, while facilitating access.
- Participants should also be informed, in the informed consent, about what data will be shared and how data will be shared, and how their privacy and the confidentiality of the data will be protected.
- Research involving genetic data and next-generation sequencing data may lead to concerns about (i) whether data can identify individuals and/or family members, and (ii) whether to return results from this type of analysis (see Section 3.1.4).
- The inclusion of medical images in biobanks (e.g. scans and histology slides) poses specific challenges for de-identification, because identifying data are usually embedded within the images, which by themselves may not be identifying. In terms of confidentiality, all staff members with access to confidential data should have a duty of professional secrecy (OECD, 2007). Staff members, consultants, or committee members without such a duty must be asked to sign a confidentiality agreement. Access to personal data should be limited, and access to any data should be restricted to those data needed for the research project or other use. Data can be separated into different databases according to type. The biobank should keep specimen metadata in a linked but separate database from the patients' medical records and demographic information, to keep data safe and confidential. Regular audits of the data systems must be implemented.

Key points: data protection and privacy

- Inform participants about any data protection and privacy issues (e.g. sending information abroad, intention to share data).
- Use a method to protect privacy, such as de-identification, coding, or pseudo-anonymization, and consider how this affects re-contact and return of results.
- Develop a policy or procedure that describes the process of re-identifying participants.
- Coded data and codes should be stored separately.
- Put in place robust data systems and audit trails.
- Manage, limit, and trace rights of access to information systems.
- Limit physical access (e.g. store paper documents in rooms with limited access), and implement electronic security procedures where possible.
- Respect participants' consent options during access, use, and transfer of data.
- Consider what data or combinations of data will not be made available, because of confidentiality or privacy reasons.

3.1.4 Return of results and incidental findings

This section presents the issues with respect to research results: summary results, individual results from baseline assessment, and individual research results. The principal investigator and the biobank have collective responsibility for deciding whether to return research results to participants. The decision-makers should consider the

balance between the duty of care to participants, the ethical and legal requirements to return results, and the logistical and technical ability of the biobank to return results in an appropriate manner. Factors to consider include whether the biobank no longer has contact with the patient, the ease of re-identifying the participants and finding out whether they have chosen to be informed, the potential cost implications of providing re-testing or counselling to

participants, if required, and whose responsibility this is.

One toolkit is the framework on the feedback of health-related findings in research (Medical Research Council and Wellcome Trust, 2014).

3.1.4.1 Generalized, non-individual study results

According to best practices, research results can be published on the biobank website or via a

newsletter (CCB, 2014). These are summary results of research using samples and/or data from the biobank and cannot be connected back to a specific individual.

The participant should be given the option during the consent process to receive these publications, and researchers using samples and data should commit in the MTA to providing the report of research results to the biobank.

3.1.4.2 Individual results from tests conducted during sign-up or registration

Some biobank studies request participants, after they give consent, to undergo initial testing (baseline assessments), such as blood pressure measurements, lung function tests, and vision tests. In addition, biological samples may be routinely tested for infectious diseases, such as HIV, hepatitis B, and hepatitis C, before storage in the biobank. Biobanks should consider whether they will return the results of these tests, and this should be clearly indicated in the participant consent materials. These tests should not be used as incentives for the participants to sign up, and it should be made clear that they are not part of health checks.

3.1.4.3 Individual research results

Individual research results fall into two categories.

- Results that can be anticipated because they are in line with the aims of the research. The method for handling these can be considered during the evaluation of the sample request.
- Incidental findings that are not linked to the aims of the research. The method for returning these to the biobank can be addressed in the MTA.

In both cases, the biobank will need procedures for evaluating the validity of such results, as well as the period of validity, and for returning these results to the participants, including re-identification and re-contact of the participant if the participant has indicated in the consent form that they wish to be re-contacted (UK Biobank Ethics and Governance Council, 2015). The scope of the results to be returned and how they are to be returned should be defined in advance with relevant experts and the ethics committee (Thorogood et al., 2014), taking into account that biobank participants have the right to choose not to know research results. The ideal time to ask about an individual's prefer-

ences is during the consent process. The information sheet and consent form should provide potential study participants with information and give them the opportunity to choose whether they wish to receive individual research results. The protocol must provide a way for participants to later change their preferences.

3.1.4.4 Results of genetic tests and next-generation sequencing

Returning the results of genetic tests or next-generation sequencing should involve offering a clinical-grade validation and making available clinical expertise or genetic counselling. Recommendations about which genetic test results to return are provided, for example, in the American College of Medical Genetics and Genomics (ACMG) recommendations for reporting of incidental findings in clinical exome and genome sequencing (Green et al., 2013) and in the Genomics England project (<https://www.genomicsengland.co.uk/taking-part/results/>).

3.1.4.5 Results of imaging studies and scans

Imaging biobanks are defined by the European Society of Radiology as

Key points: return of results

- The return of research results to the biobank by researchers using samples and/or data should be addressed in the MTA. Return of research results to the participant should be covered in the consent form.
- Individual research results should be validated using clinical techniques before being returned to the participant.
- Individual research results should be returned to the participant only if a relevant clinical support structure can be made available to the participant (e.g. in the case of genetic results, a genetic counsellor should be made available).
- Decisions about whether to return individual research results to participants should consider the balance between the validity of the results, the duty of care to participants, and the logistical and technical ability of the biobank to return results in an appropriate manner.
- Biobank participants should be given the opportunity to choose whether they wish to receive research results, and they should give consent for the return of results.

“organised databases of medical images and associated imaging biomarkers (radiology and beyond) shared among multiple researchers, and linked to other biorepositories” (European Society of Radiology, 2015). Specialized facilities and biobanks that also conduct imaging studies such as scans are particularly likely to discover incidental findings. The Royal College of Radiologists provides guidance on the management of incidental findings detected during research imaging (RCR, 2011).

3.1.4.6 Results about children

If the biobank includes biological samples from children, the biobank needs to evaluate whether it has a stronger responsibility to return results in this case because the participants are children (Hens et al., 2011). It must also consider what action to take if the results become available after the child comes of age, because the original consent was not the child's, and whether the parents have the right to receive all information about the child (see Section 3.1.2.6).

3.1.5 Access to and sharing of samples and data

A catalogue of biological material should be published, to optimize the use of resources and ensure the transparency of biobank activities. Optimally, each sample should be listed, with associated access conditions and consent elements (OECD, 2009).

In some cases, funders may require specific data sharing policies to be designed and implemented (Kaye and Hawkins, 2014; Kosseim et al., 2014). Intended sample and data sharing should be included on the participant information sheets and consent forms (GA4GH, 2015a).

To facilitate data and sample sharing, BBMRI-ERIC has created

one of the largest directories for biobanks in Europe. The directory currently contains more than 6 million samples with associated data, which can be accessed for collaboration (BBMRI-ERIC, 2016).

Researchers requesting access to the biobank's resources should do so by applying to the biobank and following its access policy and access procedures (see Section 3.1.5.1). Furthermore, the biobank should assess and review the type of data requested by the researcher. For example, the biobank cannot, without explicit prior consent, disclose participant-identifiable data to researchers. This should be addressed in any agreement between the researcher and the biobank (such as an MTA or Data Transfer Agreement [DTA]; see Section 3.1.5.5). In all cases, a section stipulating that the researcher may not attempt to re-identify any participants should be included. In general, the policy on disclosing data must consider which identifiers will be removed from the participant's record to ensure that privacy is protected. Particular care should be taken with regard to data that may not directly lead to re-identification but, in combination with other data, could do so.

3.1.5.1 Access to stored materials and data for research purposes

The biobank should develop an access policy and access procedures, in line with its protocol (Section 3.1.1). The policy and procedures should describe the administrative and approvals process for applying for and obtaining access to samples or data, comprising an overview of applicable restrictions and obligations. A procedure should exist to ensure that the applicants are bona fide researchers,

and the policy should be publicly available (CCB, 2014). See Annex 1 for the IARC access policy; other examples include those of the National Cancer Research Institute (NCRI, 2009) and P3G (Harris et al., 2012).

Evaluation of requests should be based on the notion of proportionality, balancing risks against benefits, and ensuring that the intended use follows the biobank's protocol and priorities and the consent provided by the participants (Malette et al., 2013). In general, samples should be shared in a fair, transparent, and equitable manner (Chen and Pang, 2015). In the case of scarce samples, a decision could be made to provide samples to projects more closely aligned with the aims and strategy of the biobank. The researcher should sign an MTA/DTA (see Section 3.1.5.5), which will include the obligations of the researcher, before receiving the samples and/or data.

3.1.5.2 Principles for international specimen exchanges

The legal aspects of sample sharing vary between countries, and an assessment should be made to ensure that the relevant legal regimes are compatible with those of the biobank and the consent. Where applicable, the participant should also have given consent for the transfer of data between countries. Examples of legal requirements are the EU-U.S. Privacy Shield principles, which deal specifically with transfer of data from Europe to the USA (see Section 3.1.2.3), and the new EU General Data Protection Regulation (see Section 3.1.3).

Finally, if there are any doubts in relation to privacy implications when samples or data are to be transferred internationally, a data privacy impact assessment can be performed before such transfer

(GA4GH, 2015b). For further information on the legal requirements related to international sample sharing, researchers can use the Human Sample Exchange Regulation Navigator (hSERN) tool, available at <http://www.hsern.eu/>.

Special attention should be given to the transfer of samples to or from countries with poor or non-existent regulatory frameworks (Chen and Pang, 2015).

3.1.5.3 Collaboration with the private sector

Collaboration with the private sector must adhere to the same requirements and obligations with respect to data and sample sharing. It is important for the possibility of sharing samples and data with the private sector to be specifically mentioned in the informed consent and information sheet (European Commission, 2012a).

3.1.5.4 Intellectual property and ownership

Intellectual property policies vary across institutions, but the biobank should define an intellectual property policy.

Aspects of this policy should be defined in the MTA/DTA (see Section 3.1.5.5), as well as ownership of biological samples.

Key points: data and sample sharing

- As a general rule, no ownership of biological samples exists, and the biobank should assign ownership or custodianship based on national and institutional guidelines.
- The biobank should develop a procedure for sharing samples and data that is in line with its protocol and with the consent provided by the participants.
- The biobank should develop a policy on potential benefit sharing (sharing of benefits received by the biobank through the sharing of samples and/or data) or collaboration with the contributing community.
- The biobank should develop an intellectual property policy.

3.1.5.5 Material Transfer Agreement (MTA)/Data Transfer Agreement (DTA)

An MTA, a DTA, or a similar agreement should be put in place before the transfer of samples and/or data between organizations (ISBER, 2012). An MTA/DTA is a legally binding document that governs the conditions under which the samples and/or data can be used (see Annex 4).

The MTA/DTA outlines the type of samples and/or data to be transferred, the purpose of the transfer, and all restrictions or obligations that relate to the use of the samples and data (NCI, 2011; ISBER, 2012; NCI, 2016). These restrictions and obligations must be in line with the conditions of the informed consent, ethics approval, and biobank governance attached to the samples and/or data. The agreement may include a statement that the samples and data have received appropriate ethics approval and consent.

The agreements should include specific aspects relating to the biobank's policies and provisions that bind the researcher to:

- use the samples and data in line with the biobank access approval given;
- adhere to applicable laws, regulations, and guidance;
- not further distribute the samples or data;
- dispose of, or return, the samples and data after use;
- guarantee confidentiality and data protection;
- not attempt to re-identify participants;
- inform the biobank of any issues with the data or samples;
- provide traceability of samples;
- return research results in the form of individual results, raw data, an interim/final report, relevant publications, or patent applications;
- cite or acknowledge the biobank in publications, patents, or other documents, or include a citation in any published work to a specific publi-

cation describing the biobank; and

- respect intellectual property terms.

An example of an MTA is provided in Annex 4. Other examples include those of Knoppers et al. (2013) (online supplementary material), NCI (NCI, 2016), the National Cancer Research Institute (NCRI, 2009), the Association of Research Managers and Administrators (ARMA, 2016), and Belgian Co-ordinated Collections of Microorganisms (BCCM, 2016).

3.2 General safety precautions required for working in a biobank

The primary, basic requirement of a biobank is general safety. This includes protection of people and of the environment against biological and chemical hazards. The management of these risks should be based on a general implementation of a precautionary principle similar to those used in laboratories and

clinical settings, and should be embodied in a general safety management plan.

3.2.1 General laboratory safety

In addition to biosafety, biobanks must follow strict general safety regulations and procedures in relation to chemical, physical, and electrical safety. The use of liquid gases such as liquid nitrogen (LN_2) for cryopreservation poses a serious source of hazard. Where LN_2 refrigeration is used, an adequate supply of refrigerant must be maintained. The supply maintained on-site should be at least 20% more than the normal refill use, to allow for emergency situations.

Handling LN_2 has serious safety implications. Skin contact with LN_2 can cause severe frostbite.

When bulk storage and piping systems are used, blockage of relief valves and/or overpressure may lead to simultaneous leakage

of LN_2 from several relief valves, causing white-out conditions in a matter of a few seconds. This leads to a drop in visibility to almost zero, and the oxygen level in the area decreases below what is necessary to sustain life. Personnel must evacuate immediately.

Oxygen-level sensors should always be used when LN_2 containers are used in a biobank. LN_2 expands to 650 times its original volume at room temperature, causing a form of explosion hazard if evaporation is restricted. Storage areas must be well ventilated. Plastic and glass containers can easily explode if liquid is trapped when the container is removed from the LN_2 .

Protective safety equipment must be worn when handling LN_2 . Heavy gloves, a face shield, and a protective garment should always be worn (Fig. 2). Protective shoes are also recommended. Safety notices and protocols must be clearly displayed in the biobank area. Appropriate training on the risks of LN_2 , including safe

handling and means of protection, must be given to personnel before they work in a biobank, and should be repeated on a regular basis.

There are also risks associated with the use of chemical fixatives and solvents used in tissue processing. In addition, electrical safety is an important concern. Freezers must be properly wired to adequate sources of electrical supply, and grounded.

Work in a biobank also entails several occupational hazards typical of the laboratory environment. These risks must be taken into account before setting up a biobank, and their prevention must be integrated into all aspects of the SOPs of the biobank.

3.2.2 Biological hazards

Laboratory biosafety requires the implementation of good laboratory practices and procedures as well as the proper use of safety equipment and facilities, to prevent unintentional exposure to microorganisms and toxins, or their accidental release.

All biological specimens should be considered as potentially infectious. They should always be handled with great care to avoid potential exposure. Their collection and processing represents a source of hazard both for the person who is the source of the specimens and for the staff members involved in these processes. It is recommended that potentially infectious samples should be handled under a biological safety hood to minimize exposure of laboratory staff. The risk group of the samples held in a biobank should be determined, and the biobank should comply with the biosafety levels corresponding to the risk group of the samples.

Immunization of biobank staff members is recommended when appropriate vaccines are available. In particular, immunization against hepatitis B virus (HBV) is mandatory

Fig. 2. Equipment for safe handling of liquid nitrogen: (a) individual oxygen detector, (b) knitted gloves, (c) cryogenic gloves, and (d) face shield.



for staff members involved in collecting and processing human blood or tissues. Other significant risks are posed by exposure to hepatitis C virus (HCV) and HIV as well as to the prion that causes Creutzfeldt–Jakob disease. Other pathogens can also represent a serious hazard.

Further sources of biological risk have been identified. Recommendations for laboratory practices in a safe working environment have been provided by the United States Centers for Disease Control and Prevention (CDC) in *Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories* (Miller et al., 2012).

3.2.3 Biosecurity

Laboratory biosecurity describes the protection of, control of, and accountability for valuable biological materials, to prevent their unauthorized access, loss, misuse, theft, or intentional release.

The scope of laboratory biosecurity is broadened by addressing the safekeeping of all valuable biological materials, including not only pathogens and toxins but also scientifically, historically, and economically important biological materials, such as collections and reference strains, pathogens and toxins, vaccines and other pharmaceutical products, food products, genetically modified organisms, non-pathogenic microorganisms, extraterrestrial samples, cellular components, and genetic elements.

Biosecurity can also refer to precautions that should be taken to prevent the use of pathogens or toxins for bioterrorism or biological warfare. Securing pathogens and toxins at research and diagnostic laboratories cannot prevent bioterrorism but can make it more difficult for potential terrorists to divert material from a legitimate facility so as to build a biological weapon (OECD, 2007). In

2006, the World Health Organization developed the publication *Bio-risk Management: Laboratory Biosecurity Guidance*, which defines the scope and applicability of “laboratory biosecurity” recommendations, narrowing them strictly to human, veterinary, and agricultural laboratory environments (WHO, 2006).

Laboratory biosecurity measures should be based on a comprehensive programme of accountability for valuable biological material that includes:

- assessment of biosecurity risks;
- restricted and controlled access;
- containment-in-containment architecture;
- regularly updated inventories with storage locations;
- identification and selection of personnel with access;
- plan of use of valuable biological material;
- clearance and approval processes; and
- documentation of internal and external transfers within and between facilities and of any inactivation and/or disposal of the material.

Institutional laboratory biosecurity protocols should include how to handle breaches in laboratory biosecurity, including:

- incident notification;

- reporting protocols;
- investigation reports; and
- recommendations and remedies.

Adoption of these security requirements is important for biobanks that store pathogenic or toxic biospecimens.

3.3 Infrastructure and storage facilities

The biobank infrastructure and storage system depend on the type of material being stored, the required storage conditions, the anticipated period of storage, the intended use of the materials, and the resources available for purchasing the storage equipment. The storage infrastructure also depends on the available resources and support to the biobank (Mendy et al., 2013). The storage system is fundamental to maintaining high sample quality.

The data and databases related to biospecimen annotation, quality, storage location, and use, including the patients’ clinical and epidemiological information, are important attributes of biobank infrastructure.

The collection, storage, uses, and management of data linked to biospecimens are discussed in Section 3.6 and Section 3.8.2.

Key points: creating a biobank

- Type, number, aliquots, and sizes of biospecimens.
- Storage containers.
- Storage temperature and conditions.
- Frequency of access to biospecimens.
- Requirements for identification of biospecimens.
- Availability of storage space.
- Requirements for temperature monitoring.
- Associated data.
- Financial and operational sustainability.

3.3.1 Storage conditions

Biospecimens should be stored under stabilized conditions to meet the requirements of potential future use in research. In selecting the biospecimen storage temperature, it is essential to consider the type of biospecimen, the intended period of storage, the frequency of use of biospecimens, the biomolecules and analyses of interest, the intended purpose of the sample, and whether the goals include preserving viable cells. Other factors that should be considered include the humidity level, the light intensity in the facilities, access to a continuous power supply, and backup systems in case of freezer breakdowns, loss of power, and other emergencies.

3.3.1.1 Cryopreservation

Cryopreservation is the recommended standard for preservation of human biological samples for a wide range of research applications. The challenge of tissue preservation is to be able to block, or at least slow down, intracellular functions and enzymatic reactions while at the same time preserving the physicochemical structures on which these functions depend.

Cryopreservation is a process in which cells or whole tissues are preserved by cooling to ultra-low subzero temperatures, typically -80°C (freezer) or -196°C (LN_2 phase). At these low temperatures, most biological activity is effectively stopped, including the biochemical reactions that would lead to cell autolysis. However, due to the particular physical properties of water, the process of cryopreservation may damage cells and tissue by thermal stress, dehydration and increase in salt concentration, and formation of water crystals. Specific applications (e.g. proteomics or storage of primary cell cultures) may require more complex cryopreservation procedures. General information is

available on the principles of cryopreservation (Cryo Bio System, 2013) and on the optimal temperature for selected biomarkers and metabolites (Hubel et al., 2014). The process of thawing may also influence cellular structure or metabolite analyses.

Specimen freezing can be performed, for example, by placing the specimen in a sealed (but not airtight) container and immersing the container in the freezing medium. The ideal medium for rapid freezing is isopentane that has been cooled to its freezing point (-160°C). To achieve this, the vessel containing the isopentane should be placed in a container of LN_2 . The freezing point approximately corresponds to the moment when opaque drops begin to appear in the isopentane. Direct contact of the specimen with LN_2 should be avoided because this can damage tissue structure.

3.3.1.2 Other fixation and preservation methods

Formalin or alcohol fixation and paraffin embedding is the best method

for morphological analysis, morphology-related methods, and immunohistochemistry. It may also be used as an alternative method to preserve tissues at relatively low cost when adequate freezing procedures and storage facilities are not available. Paraffin blocks and histological slides may be stored in light- and humidity-controlled facilities at 22°C (Figs. 3 and 4).

Tissue fixed according to strict protocols may be used for DNA extraction. The DNA is usually fragmented but remains suitable for polymerase chain reaction (PCR)-based analysis of short DNA fragments. However, fixed tissue is of limited usefulness for RNA extraction.

RNA/later is a commercial aqueous, non-toxic tissue storage reagent that rapidly permeates tissues to stabilize and protect cellular RNA at room temperature. *RNA/later* eliminates the need to immediately process tissue samples or to freeze samples in LN_2 for later processing. Tissue pieces can be harvested and submerged in *RNA/later* for storage for specific periods without jeopardizing the quality or quantity of RNA obtained after subsequent RNA isolation.

Fig. 3. Paraffin-embedded tissues.



Fig. 4. Histological slides.



PAXgene tissue fixation is increasingly used for tissue preservation. PAXgene tissue systems are formalin-free solutions for the simultaneous preservation of histomorphology and biomolecules and the purification of high-quality RNA, DNA, microRNA (miRNA), proteins, and phosphoproteins from the same sample. Tissue specimens are collected, fixed, and stabilized with the PAXgene tissue fixation and stabilization products. PAXgene-fixed tissue can be processed and embedded in paraffin similarly to formalin-fixed tissue, and biomolecules can be extracted (Gündisch et al., 2014).

3.3.2 Biospecimen storage infrastructure

Two types of storage systems are used for biospecimen storage: ultra-low-temperature (or low-temperature) storage systems and ambient-temperature storage systems. “Ultra-low temperature” can be defined as temperatures below $-80\text{ }^{\circ}\text{C}$ (e.g. LN_2), and “low temperature” as temperatures between $0\text{ }^{\circ}\text{C}$ and $-80\text{ }^{\circ}\text{C}$.

3.3.2.1 Liquid nitrogen storage

LN_2 facilities contain LN_2 in liquid-phase tanks (Fig. 5) and vapour-phase containers (Fig. 6). Cryogenic storage using LN_2 is an effective long-term storage system, because its extreme ultra-low temperatures slow down most biological, chemical, and physical reactions that may cause biospecimens to deteriorate.

LN_2 vapour-phase containers with LN_2 in the base of the tank can maintain samples below T_g (the critical glass-transition temperature, i.e. $-132\text{ }^{\circ}\text{C}$), and submersion in LN_2 guarantees a stable $-196\text{ }^{\circ}\text{C}$ temperature environment for all samples. Vapour-phase storage is preferred over liquid-phase storage, because it avoids some of the safety hazards inherent in liquid-phase storage, including the risk of transmission of contaminating agents (Fig. 6). The design of the tank is critical to maintain a sufficient amount of LN_2 in the vapour phase.

Liquid-phase storage needs less frequent resupply of LN_2 and thus affords better security in case of a crisis in LN_2 supply. Closed LN_2 tanks can maintain samples at below $-130\text{ }^{\circ}\text{C}$ for several weeks without the need to refill the LN_2 tank. The initial investment and the availability and cost of LN_2 can be major drawbacks. Also, safety hazards inherent in the use of LN_2 , such as burning or oxygen deficit risks, should be managed. When LN_2 tanks are used, oxygen-level sensors must be used, and they should be calibrated every few years. The use of

Fig. 5. Liquid nitrogen facility with LN_2 tanks.



Fig. 6. Tank for storage in vapour-phase liquid nitrogen.



protective equipment – in particular, face shields, cryogenic gloves, and individual oxygen detectors – should be mandatory, and this equipment should be easily accessible (Fig. 2). Appropriate training in the safe handling of LN₂ must be provided, and this should be included in an SOP describing the potential health hazards and required safety precautions.

3.3.2.2 Mechanical freezers

Mechanical freezers are used for a variety of storage systems with temperatures ranging from low-temperature to ultra-low-temperature conditions, including $-20\text{ }^{\circ}\text{C}$, $-40\text{ }^{\circ}\text{C}$, $-70\text{ }^{\circ}\text{C}$ to $-80\text{ }^{\circ}\text{C}$, and $-150\text{ }^{\circ}\text{C}$, and come in a wide range of sizes and configurations (Figs. 7 and 8).

Ice crystals may form in biological samples at temperatures between $0\text{ }^{\circ}\text{C}$ and $-40\text{ }^{\circ}\text{C}$, and protein activity may persist until $-70\text{ }^{\circ}\text{C}$ or $-80\text{ }^{\circ}\text{C}$; therefore, freezer temperatures should preferably be below $-80\text{ }^{\circ}\text{C}$. Cascade compressor technologies may produce temperatures

as low as $-140\text{ }^{\circ}\text{C}$. Mechanical freezers, which generally require a lower initial investment than LN₂ tanks and provide easy access to biospecimens, can be installed if appropriate electrical power is available. How-

ever, the compressor technology requires constant electrical power to maintain subzero temperatures, so a backup power system and an emergency response plan are needed. Whether samples warm up significantly during power outages or freezer breakdowns depends on the temperature, type, and volume of the stored biospecimen, the ambient conditions of the environment where the freezers are stored, and the design and maintenance of the freezer.

Ambient temperature and humidity influence temperature stability considerably if doors are left open for prolonged periods, for example for sample loading, or if frost forms in the freezer, racks, or samples. Overheating of compressors may shorten their lives. Mechanical freezers and refrigerators should be positioned with sufficient air flow around the units and preferably in rooms that are air-conditioned or have equipment for extraction of the hot air generated by the compressors. Regular cleaning and

Fig. 7. Freezer facility.



Fig. 8. Freezer racks.



maintenance of freezers should be planned; this should consist, at a minimum, of cleaning filters and removing ice around the door and seals. Freezers should be equipped with alarms set at about 20 °C warmer than the nominal operating temperature of the unit. An independent temperature monitoring system should be in place (Figs. 9 and 10), to prevent freezer failure or

breakdown and/or to alert personnel in case this happens. Some of the freezers (approximately 10%) should be kept empty and cool to be used as a backup system.

3.3.2.3 Refrigerators

Refrigerators are commonly used for samples that can be maintained at ambient temperature. However,

the longevity of biospecimens being stored is enhanced if they are stored below ambient temperature, due to biomolecular degradation that can occur at high ambient temperatures. Storage at 4 °C can be a temporary storage solution as an intermediate step before preparation for ultra-low-temperature storage or before sample processing. For refrigerators, as for mechanical freezers, it is important to maintain and monitor the temperature in the required operating range and to have a backup power system.

3.3.2.4 Ambient-temperature storage

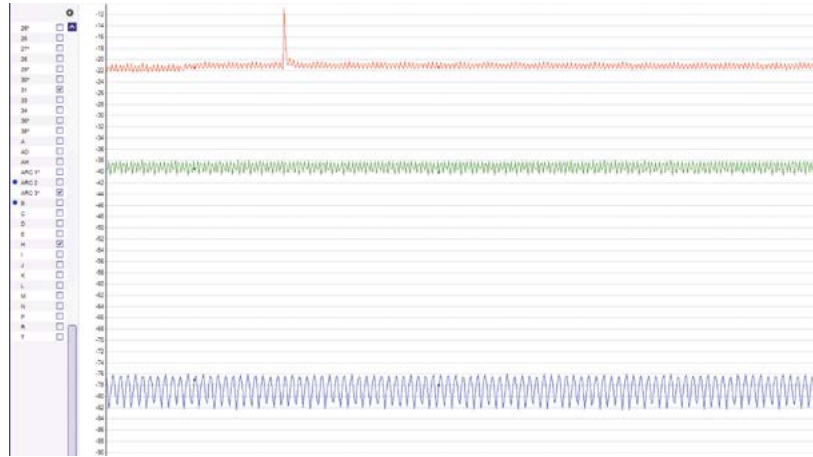
If a biobank does not have mechanical freezers or cryogenic storage equipment, because of practical or financial reasons, then specific biological storage matrices may be used for long-term maintenance of some biological components at room temperature. Formalin-, PAXgene-, or ethanol-fixed, paraffin-embedded tissues and lyophilized samples can be stored at ambient temperatures. Dried samples, such as blood spots on filter paper, can be stored at ambient temperature (Figs. 11 and 12). There are also some new techniques for storage of DNA at ambient temperature, for example in mini-capsules after dehydration. A mini-capsule consists of a glass vial containing the sample, enclosed in a stainless steel shell with a cap. The mini-capsule is sealed by a laser, which welds the junction between the shell and the cap under an anhydrous and anoxic inert atmosphere.

Biological storage matrices should be evaluated before use to ensure that they are appropriate for downstream applications. Temperature, humidity, and oxygen levels should be controlled to avoid mould growth and microbial contamination.

Fig. 9. Temperature monitoring system.



Fig. 10. Graph of temperature log obtained from monitoring system.



3.3.3 Storage services, access, and security

Biobanks should have dedicated storage facilities that are not shared with other activities, for the safety and security of biospecimen collections. Sufficient air conditioning must be provided for air circulation and to maintain the ambient temperature at 22 °C or below, to prevent excess freezer wear and early failure. Rooms that contain LN₂ tanks should be equipped with appropriate air flow systems to avoid the accumulation of N₂ in case of leakage, coupled with an oxygen-level alarm system, to monitor N₂ release from the tanks. In general, storage facilities and equipment should be monitored by appropriate alarm systems (Figs. 13 and 14).

Biobanks should be equipped with a system that adequately limits access to authorized staff members and protects against intrusion by unauthorized individuals (Fig. 15). In principle, only people assigned to biobank activities should have access to the storage facility and biospecimens, and all materials added or withdrawn should be documented. The documentation of sample movement is important for

traceability and for the updating of biobank catalogues.

All biobanks require a constant source of electrical power. Given that the commercial electrical power grid is likely to fail at some point, a backup power system is required. This backup system should operate independently from the grid and from any other facilities. The most common type of backup power is a diesel generator. Such

a system should have the capacity to run for a sufficient time to allow the restoration of the power supply (typically 48–72 hours) and should be tested regularly (Fig. 16). Enough fuel should be available on-site to run the generator for several days. The fuel should also be tested to ensure its quality.

Biobanks with LN₂ facilities should have an LN₂ supply stock

Fig. 11. Room-temperature storage facility.



Fig. 12. Box of samples stored at room temperature.

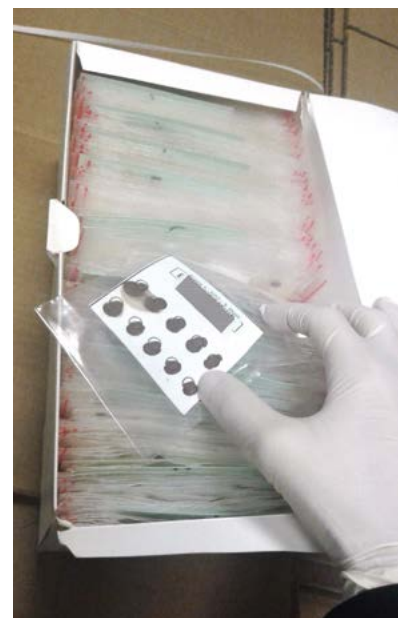


Fig. 13. A tank fitted with a monitoring device, which shows the level of liquid nitrogen inside the tank.



from which to refill the LN₂ tank (Figs. 17 and 18). Adequate backup capacity for low-temperature units must be maintained. The total amount of backup storage required for large biobanks must be determined empirically but will typically be 10% of the total freezer capacity for mechanical freezer storage. Because LN₂ storage is safer than using mechanical freezers, the backup capacity for LN₂ storage could be less than 10% (ISBER, 2012).

Every facility should use basic security systems; these must be monitored and alarms must be responded to 24 hours a day, 7 days a week by people who can take the necessary action to respond to an alarm within a time frame that prevents or minimizes loss or damage to biospecimen collections. Systems should allow for calls to other key staff members from a list of staff telephone numbers if the first person fails to acknowledge the alarm.

Whenever possible, it is recommended to consider splitting stored biospecimen collections into two sets of aliquots, with each set stored in a different location. This strategy

will enable the preservation of a set of samples in the case of adverse events in one location. For multicentre studies, it is recommended that each recruitment centre retain a set of aliquots at the place of collection, with the second set transported to a central location that is accessible to all recruitment centres.

3.3.4 Basic informatics infrastructure

The biobank informatics infrastructure needs to contain hardware and software that are sufficient to address the functional requirements of the biobank, record and store the information acquired during each biobank process (see Section 3.8), and provide an electronic method for records management (see Section 3.6). It is important that the hardware and software infrastructure is designed in such a way that it not only meets these capacity and traceability requirements but also meets the requirements for security, data protection, and privacy (see Section 3.1.3).

One challenge that persists for IT solutions is importing speci-

Fig. 14. Video monitoring in liquid nitrogen facilities.



men-associated clinical data (Section 3.8) that have been input into a separate system. Although it is not essential for the specimen-associated data to be in the same database as the biobank-specific data, it is important for the clinical data to be easily accessible via a link or a regular import. There may be logistic concerns in directly accessing hospital IT systems, and careful attention should be given to this during the planning of the biobank IT infrastructure.

The IT infrastructure should also be part of the QMS, and the records stored in the system should be checked for veracity. QC checks should include the verification of biospecimen locations to assess the concordance between physical storage and database location.

3.3.4.1 IT functionality

The biobank management software must guarantee the management of different functions and data related to biobanking activities (see Section 3.8). It is fundamentally important that there is a method to track each sample throughout the biobank process and to document the actions that have been carried out on the sample.

Fig. 15. Controlled access in a secured room.



Fig. 16. Power generator.



Documentation related to sample collection (informed consent, participant information sheet, sample collection protocol), sample processing, sample sharing (MTA and DTA), and shipment (proof of shipment and delivery) must be appropriately referenced in the IT system (see Section 3.6). The IT system requires a backup process to ensure that all data re-

corded in the IT system are correctly tracked and maintained, and are recoverable in the event of erroneous modifications.

Semantic interoperability, in particular, presents a significant challenge for biobanking and IT support.

The specific location of every stored aliquot relating to a sample should be tracked. The biobank da-

tabase containing this information should be updated in real time as a biospecimen is moved within or out of the biobank.

In addition to IT software to record the information at each point of the biobanking process, there need to be software solutions to document information about monitoring of storage infrastructure and to report alarms about adverse events.

It is also recommended that the biobank software record information about operations and operators. This should include information about the standard and regular measures taken to calibrate and repair biobank instruments.

The management of these functions is fundamental to provide high-quality samples.

3.3.4.2 Software solutions

As biobanking evolves in terms of the types of samples that are collected, archived, and stored and the downstream use of the samples, there continues to be a need to develop informatics tools for the management of biobanks. Different options may be considered depending on the needs, financial resources, and IT resources of the specific biobank. For the rapidly growing field of biobanking, commercial software solutions are increasingly available. Recently, open-source systems have emerged, and some have been selected by European biobanks (Kersting et al., 2015). However, commercial and open-source solutions mainly cover particular aspects and require adaptation to respond to the requirements of the individual biobank.

An alternative to commercial and open-source systems may be the development of a dedicated in-house system, noting that the internal cost of maintaining a development team for modifications and maintenance can be considerable (Voegelé et al.,

Fig. 17. Liquid nitrogen supply stock tank.



Fig. 18. Liquid nitrogen piping.



2010). On a larger scope, a laboratory information management system (LIMS) enables the management not only of the biobank but also of the entire sample life-cycle workflow. Electronic laboratory notebooks are also a solution for the management of procedures performed in a laboratory, and can be used by scientists,

engineers, and technicians (Voegelé et al., 2013).

3.3.4.3 Data management and informatics security

Biobank management systems must permit access to sample data in order to stimulate collaboration, but

they must also guarantee the confidentiality of sample records.

Data security systems should be adequate to ensure confidentiality and safety. Electronic records should be adequately protected through regular backups on appropriate media. Intrusion-proof management systems should include solutions such as dedicated servers, secure networks, firewalls, data encryption, and user authentication through verification of user names and passwords.

All computers used by biobank personnel should be password-protected and have automatic timeout mechanisms. The biobank management software should also be password-protected and should have different user profiles to permit different levels of access. Each biobank staff member should have an individual user ID, to provide complete traceability of all actions performed on biobank data.

The protection of personal information and individual data associated with specimen collection is a fundamental requirement of a biobank. This should be achieved through the use of safe, structured bioinformatics systems. Personal identifiers should be replaced by codes, and all individual data stored in the biobank management system should be protected with the same stringency as patient clinical files. This also applies to data that are considered to be sensitive. Communication to third parties of data files containing personal information and identifiers should be strictly prohibited unless it is required by law or explicit permission to do so was granted. Examples of methods of coding are provided in Appendix 2 of the privacy and security policy of GA4GH (GA4GH, 2015b).

3.3.4.4 Biobank networking infrastructure

The facilitation of scientific networking is an important aspect of

IT infrastructure. Networking can increase biobank use and therefore is an important element of biobank sustainability. Publication of data on the Internet can greatly increase the visibility of the biobank and its ability to participate in biobank networks. It is recommended that a

biobank develop a website to present its operations to the scientific community, in addition to an online catalogue with information on the nature, characteristics, and quality of its biological samples. Networking to facilitate exchange and access to an increased number of samples requires that bio-

banks adhere to standards for use of samples and data to ensure semantic interoperability between different systems and different biobanks, and this in particular presents a significant challenge for biobanking and IT support (see Section 3.8, Section 3.5, and Section 2.1.4).

Key points: IT systems

- IT systems must correspond with biobanking activities and processes.
- IT systems must ensure complete traceability of samples and data.
- Data security systems should be adequate to ensure confidentiality and safety.
- Access to IT systems must be managed so that they can be accessed only by authorized personnel.
- Data and combinations thereof should only be made available based on consent and requirement.
- IT systems should have a method of coding to de-identify individual data to protect privacy.
- IT systems must also include biobank monitoring.
- The biobank management system must permit some level of data publication, such as an online catalogue, to stimulate collaboration.
- Cost, functionality, maintenance, and interoperability must be considered when evaluating the selection of software solutions: commercial, open-source, or developed in-house.

3.3.5 Basic storage disaster recovery – monitoring, backup, and additional storage

Biobanks require a disaster recovery (DR) plan to protect their assets, biological material, and associated data. The ability to respond to a disaster and protect the integrity of the samples and data directly affects their quality.

In its most simple terms, DR entails taking all necessary steps to ensure that, in the event of a disaster, the loss caused by the disaster is kept to an acceptable level and operations can return to normal as smoothly and as quickly as possible. DR encompasses all processes, policies, and procedures for recovery or continuation of infrastructure operation after a natural or human-caused disaster, and must include planning for

key personnel, facilities, and data recovery. DR plans are not a one-size-fits-all solution; in order for DR plans to work, they need to address the needs of the specific biobank.

The best possible DR planning for biological materials and data is to ensure that there are duplicated aliquots stored in two or more locations. The more distinct these locations are in terms of geographical area and reliance on the same utilities (power, generator, LN₂, carbon dioxide [CO₂] supply, ambient-temperature control, and other elements that pertain to the functioning of the biobank storage infrastructure), the better the ability of one of the locations to withstand a particular disaster. Although this strategy will avoid unnecessary loss in case of adverse events in one location, this approach has three difficulties.

- There needs to be enough of the

original specimen to produce two identical aliquots (in the presence of tumour heterogeneity, this is questionable for tumour tissue samples).

- Additional logistics are involved in regular transportation of the fresh and/or frozen samples to ensure that the biobank has the same content at each location.
- Retrieval of samples from the duplicate locations involves increased costs and time delays.

Retrieval of samples from duplicate locations is hampered by increased distances (preferable for the DR plan) and transportation facilities (couriers, transportation infrastructure). Preventive measures such as different methods of storage or reducing the specimen to its basic derivative components, such as nucleic acids, will provide opportunities for innovative storage methods. Also, nucleic acids are more

stable once extracted from tissue, and therefore are more resistant to temperature fluctuations and permit longer response times.

A similar situation relates to biobank data: saving the data contemporaneously at two distinct sites would guarantee the same safeguards to the data. This is potentially more feasible than storing samples in separate locations, because duplicating and transferring data is an easier task and does not necessarily require physical transportation. However, where continual data transfer is not feasible, periodic backups should be carried out, with backups stored off-site to reduce loss of data.

Each biobank infrastructure DR plan should contain an evaluation of the events and elements that can affect the biobank, the probability of these occurring, and the means to address them. These can be either natural events (e.g. earthquakes, hurricanes, storms, floods, fires, plane crashes, excess temperatures and humidity) or human-caused events (e.g. breakdown of a single freezer, breakdown of multiple freezers, power outage or power fluctuations, CO₂ outage, air conditioning breakdown, air extraction breakdown, inaccessible room due to gas leak). Only those elements that affect the biobank, either directly or indirectly, should be considered in the individual plan.

Apart from faults with a single container (caused by blown fuses, battery discharges, blocked refill valves, broken compressors, broken covers or doors, or worn seals), external events will affect each biobank to a different extent.

- Biobanks with -80°C freezers are most affected by electricity supply, CO₂ supply, biobank room temperature, dusty conditions, humidity, and air conditioner faults.
- LN₂ biobanks are most affected by LN₂ supply.

- Automatic LN₂ filling systems are most affected by faulty sensors and faulty transfer pipes.
- Monitoring systems are most affected by electricity supply, Internet connectivity, wireless connections, and telephone lines.

Events such as a power outage or power fluctuations can be low priority if there is a way to mitigate or avoid the problem by providing either an uninterrupted power supply or a backup diesel generator. The backup generator should be able to start automatically, needs to have the capacity to run for a sufficient time to allow the restoration of the power supply (typically 48–72 hours), and should not be affected by the adverse event that caused the power outage.

It is always important to consider the cascading effect of a single event. An example is a fault in the air conditioning system that causes the biobank's ambient temperature to rise. This temperature rise, in turn, causes the mechanical freezers to need CO₂ to maintain their temperature of -80°C . If the CO₂ supply is depleted by the time the ambient temperature returns to an acceptable level, then the temperature of the mechanical freezers will also rise, potentially leading to damage of the samples they contain.

A complete DR plan requires the following steps.

- Categorize the stored samples in order of priority. In case of an emergency, high-priority samples will be moved to an external facility before lower-priority samples.
- Evaluate the acceptable downtime (the time during which the biobank is inaccessible).
- Evaluate the acceptable loss (the number of samples and their associated data that can be lost). The acceptable loss should be considered in terms of delays to research, and by evaluating how much time and money would be

needed to collect the lost material again, considering the availability of such samples and their associated data as well as the effort required by personnel, the equipment to be used, and the consumables. Samples from longitudinal studies acquire more value over time as their associated samples and data accumulate, and therefore the cost of replacing them increases with time.

- Carry out a risk analysis to evaluate the potential disasters, the probability of each type of disastrous event occurring, and the impact each event would have on the biobank. The risk analysis makes it possible to prioritize the events that need to be addressed. Then, based on the resources available, it can be decided how to address each event.
- Calculate the response times in the event of a disaster. Response times are critical because they directly affect the potential loss of samples, and they must be calculated based on the acceptable loss and the time needed to either return to normal functioning or mitigate the problem caused by the adverse event.
- For each type of disaster, calculate a maximum response time to ensure the integrity of the conserved samples, such as either fixing a broken freezer so that it returns to its desired temperature before it has reached critical temperature, or moving the samples to a different location before their quality is compromised. This calculation must take into consideration the different reactions of the containers and the different effects of temperature change on each sample type stored (tissue, blood, plasma, serum, DNA, RNA).
- Assign people to be on call to respond to any alarms at all times (24 hours a day, 7 days a week); it is essential that they are able to

respond and carry out the DR plan within the allocated time.

- Carry out simulation exercises to ensure effective training of the people assigned to respond.
- Specify methods for transporting samples without affecting their quality and integrity, in case the samples need to be moved.
- Ensure that backup facilities are available, in case samples need to be moved from the current biobank or freezer. Adequate backup capacity for low-temperature

units must be maintained (10% is the best practice). The total amount of backup storage required for large biobanks must be determined empirically. Typically, the minimum should be the capacity of a single container (where there are different sizes, this should be calculated based on the capacity of the largest freezer) or, for large biobanks, 10% of the total container capacity (NCI, 2016).

- Prepare a detailed list of actions for each evaluated event. These

lists must be presented in the form of SOPs, so that in the event of a disaster, action can be taken immediately.

The DR plan should be part of the QMS and should be reviewed annually to guarantee that it responds adequately to the biobank's evolution. The DR plan must be tested as extensively as possible using simulated scenarios and should be updated regularly as the biobank infrastructure changes.

Key points: disaster recovery plan

- Categorize the stored samples in order of priority, to facilitate the relocation process if the samples or equipment need to be moved to an external facility in case of an emergency.
- Calculate the acceptable downtime and the response times in the event of a disaster.
- Carry out a risk analysis to evaluate the potential disasters and the acceptable loss.
- List the actions for each evaluated event, and design SOPs as part of the QMS, along with adequate simulation exercises, training, and review.
- Prepare an on-call list of people on standby in case of an emergency.
- Ensure that adequate backup storage capacity is available, in case samples need to be transferred.

3.4 Quality

Biobanks are key for the development of clinically useful biomarkers of disease and disease progression, for discovering and monitoring new drugs, and for understanding the mechanisms of cancer and related diseases. All of these possibilities are underpinned by the availability of high-quality, well-annotated samples of diseased and control tissue, blood, and other biological materials and associated data.

The availability of high-quality samples is also important to demonstrate to funders of biobanks and to the research community that the facility provides a good return on their investments in sample and data collection, which will accelerate progress in cancer research.

The scientific and technical management of the biobank infrastruc-

ture and resources – such as storage facilities, pre-analytical processing tools, trained personnel, robust governance, and policy management – is central to maintaining quality and determines the relevance and success of a biobank.

The key components that can affect the quality of samples and data are presented in Fig. 19.

In general, biobanks should implement systems that specify QC and QA for sample collection, processing, storage, shipment, and disposition. Such systems are essential for maintaining a fit-for-purpose biobank for cancer research. The ISO 15189 standard currently referred to by biobanks (ISO, 2012) is based on ISO/IEC 17025 and ISO 9001, which provide general requirements for the competence of testing and calibration laboratories and for the QMS, respectively. They are not

specific to biobanking processes and procedures. However, in 2015 CEN published a series of Technical Specifications for molecular in vitro diagnostic examinations – Specifications for pre-examination processes, which are relevant for diagnostic laboratories as well as biobanks. See Table 3 for a list of CEN Technical Specifications. It is recommended that these standards are used.

In addition, ISO is developing standards for biobanks and biorepositories. The Technical Committee of ISO 276 (standardization in the field of biotechnology) will include:

- biobanking terms and definitions;
- biobanks and biorepositories;
- analytical methods;
- bioprocessing; and
- data processing, including annotation, analysis, validation, comparability, and data integration (Furuta and Schacter, 2015).

Fig. 19. Overview of the key issues related to quality in biobanking.

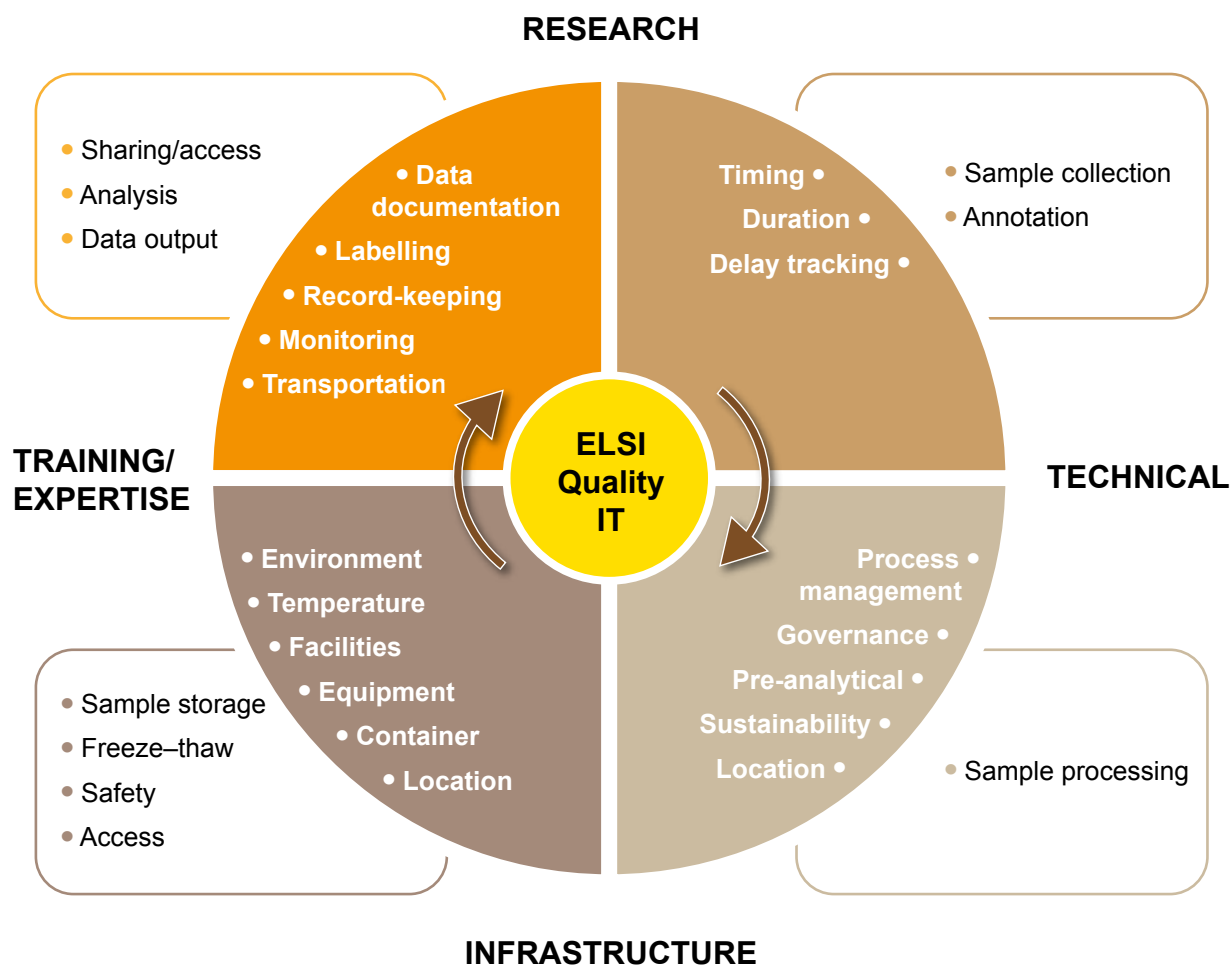


Table 3. CEN Technical Specifications for molecular in vitro diagnostic examinations

Technical Specification	Title
CEN/TS 16826-1:2015	Specifications for pre-examination processes for snap frozen tissue. Part 1: Isolated RNA
CEN/TS 16826-2:2015	Specifications for pre-examination processes for snap frozen tissue. Part 2: Isolated proteins
CEN/TS 16827-1:2015	Specifications for pre-examination processes for FFPE tissue. Part 1: Isolated RNA
CEN/TS 16827-2:2015	Specifications for pre-examination processes for FFPE tissue. Part 2: Isolated proteins
CEN/TS 16827-3:2015	Specifications for pre-examination processes for FFPE tissue. Part 3: Isolated DNA
CEN/TS 16835-1:2015	Specifications for pre-examination processes for venous whole blood. Part 1: Isolated cellular RNA
CEN/TS 16835-2:2015	Specifications for pre-examination processes for venous whole blood. Part 2: Isolated genomic DNA
CEN/TS 16835-3:2015	Specifications for pre-examination processes for venous whole blood. Part 3: Isolated circulating cell free DNA from plasma

CEN, European Committee for Standardization; FFPE, formalin-fixed, paraffin-embedded; TS, Technical Specification.

Biobanks should have appropriate QA and QC programmes with respect to equipment maintenance and repair, staff training, data management and record-keeping, and adherence to principles of good laboratory practice. All biobank operations must be subject to regular audits. The timing, scope, and outcome of these audits should be documented.

3.4.1 Biospecimen quality biomarkers

Biospecimen quality biomarkers are useful to assess the quality of material before it is included in experimental platforms and to avoid the unnecessary use of biospecimens. In 2013, the ISBER Biospecimen Science Working Group

reported on the identification of evidence-based biospecimen QC markers (Betsou et al., 2013). The findings are summarized in Table 4. Although the report provided evidence for several quality biomarkers, their level of applicability and accessibility varies. In Table 4, only markers that scored highly for applicability and accessibility are included. These markers provide QC tools for assessing biospecimens in relation to pre-analytical conditions. NCI's Biorepositories and Biospecimen Research Branch has initiated the Biospecimen Research Network (<http://biospecimens.cancer.gov/researchnetwork/projects/default.asp>), which aims to stimulate original research and disseminate available data in biospecimen science.

3.4.2 Quality of tissue and derivatives

The procurement of tissue, both diseased (neoplastic, pre-neoplastic, and inflammatory) and normal, must always be carried out by, or under the supervision of, a pathologist. This permits a more accurate macroscopic sampling followed by a microscopic confirmation. This is standard QA for tissue procurement (Hainaut et al., 2009).

3.4.2.1 Quality control of tissue (e.g. frozen section)

QC should be done during sampling in the grossing room on surgical samples using the frozen section method. This is done by sampling the area of suspected cancer

Table 4. Identified biospecimen molecular diagnostic biomarkers, with QC scope and evaluation

QC tool	Analyte type	Sample type	QC scope	Applicability grade	Accessibility grade	Delay Consequence	Reference
Transferrin receptor	Protein	Serum	Pre-centrifugation delay	1	1	8 h blood pre-centrifugation delay 90% increase	De Jongh et al. (1997)
K ⁺	Ion	Serum	Pre-centrifugation delay	1	1	1 day pre-centrifugation delay at 4 °C 200% increase 7 day pre-centrifugation delay at 4 °C 500% increase	Heins et al. (1995)
GM-CSF, IL-1α, G-CSF	Protein	EDTA plasma ± PI	Pre-centrifugation delay	1	1	2 h pre-centrifugation delay at RT 11–20-fold increase without PI 7–10-fold increase with PI	Ayache et al. (2006)
sCD40L	Protein	Serum	Exposure to RT	1	1	12 h at 37 °C or 48 h at RT Complete degradation	Lengellé et al. (2008)
Vitamin E	Vitamin	EDTA plasma	Storage conditions	1	1	> 24 months at –20 °C > 90% decrease	Ockè et al. (1995)
MMP-7	Protein	Serum	Freeze-thawing	1	1	30 freeze–thaw cycles Loss of MMP-7	Chaigneau et al. (2007)
DUSP1 expression	RNA	Fresh prostatic tissue	Warm ischaemia time	1	1	Warm ischaemia 14-fold upregulation	Lin et al. (2006)
p-Tyr, ERBB2 (alias HER2; alias Neu)-Tyr1248, PTK2 (alias FAK)	Protein	Breast tissue	Cold ischaemia time	1	1	24 h of cold ischaemia Complete denaturation of phosphorylated epitopes	De Cecco et al. (2009)

±, with or without; EDTA, ethylenediaminetetraacetic acid; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1α, interleukin 1 alpha; K⁺, potassium; MMP-7, matrix metalloproteinase-7; PI, protease inhibitors; QC, quality control; RT, room temperature; Tyr, tyrosine.

Source: Adapted from Betsou et al. (2013), Copyright (2013), with permission from Elsevier.

macroscopically, performing a routine frozen section, preparing a stained slide, and documenting the review data on the sample collection sheet. The following information should be provided, which defines the quality of the tissue sample:

- frozen section performed (yes or no);
- pathologist who performed frozen section review;
- tumour confirmed;
- percentage of tumour cells;
- percentage of stromal and inflammatory cells;
- percentage of surface occupied by necrosis; and
- other comments.

3.4.2.2 Methods for quality control of tissue sections for DNA/RNA extraction

Regardless of whether a frozen section is performed at the time of sampling, microscopic pathology review should be performed on the tissue sections taken for nucleic acid extraction. It is recommended that this is performed every 20 sections of 5 μm , because of the potential heterogeneity in the sample. This is also recommended for sections taken from formalin-fixed, paraffin-embedded (FFPE) blocks.

3.4.3 Quality control of nucleic acids from tissue

The quality of a nucleic acid is based on quantity, concentration, purity, and integrity.

Concentration is calculated for DNA, RNA, and proteins using the ultraviolet (UV) absorbance reading at a wavelength of 260 nm and a conversion factor based on the extinction coefficient for each nucleic acid (A260 of 1.0 = 50 $\mu\text{g}/\text{mL}$ for double-stranded DNA [dsDNA], 40 $\mu\text{g}/\text{mL}$ for RNA, and 33 $\mu\text{g}/\text{mL}$ for single-stranded DNA [ssDNA]).

Purity is calculated from the ratio of the absorbance contributed

by the nucleic acid to the absorbance of the contaminants. Aromatic amino acids absorb light at 280 nm, so absorbance measurements at that wavelength are used to estimate the amount of protein in the sample. Measurements at 230 nm are used to determine the amount of other contaminants that may be present in the samples, such as guanidine thiocyanate, which is common in nucleic acid purification kits. Typical requirements for A260/A280 ratios are 1.8–2.2; A260/A280 of pure DNA is \sim 1.8, and A260/A280 of pure RNA is \sim 2. Requirements for A260/A230 ratios are generally $>$ 1.7. The A260/A230 ratio may also predict sample amplifiability (the ability of the extracted sample to be amplified by PCR).

Acceptable ratios for purity vary with the downstream application. A230 is often constant for nucleic acid purified using a specific kit, whereas the amount of nucleic acid can vary depending on the sample source. Thus, the A260/A230 ratio often decreases when small amounts of nucleic acids are isolated.

Integrity represents intactness or state of degradation. This is often presented as the DNA integrity number (DIN) and the RNA integrity number (RIN). The higher the RIN value, the better the integrity of the RNA. RNA is considered to be of high quality when the RIN value is \geq 7. RNA with RIN values of 5 and 6 may be considered acceptable. Care must be taken when using instruments to determine these values, because the concentration of the sample can affect the resulting value.

The quality of nucleic acid extracted from tissue can vary depending on the sample source and the extraction method applied. Quality requirements can be very different depending on the downstream application. Nucleic acids that are unsuitable for one application may provide perfectly acceptable results in another application.

The qualification process consists of the quantification of dsDNA and the assessment of its suitability for downstream applications, such as high-throughput next-generation sequencing. Microarray experiments may require nucleic acid samples with specific values of concentration, purity, and integrity, whereas quantitative PCR (qPCR)-based assays may accept samples with lower quality scores because the amplicons are small (typically $<$ 100 bp). Correctly interpreting data obtained from quantification and QC analysis is essential.

3.4.3.1 Methods for evaluating quality of nucleic acids from tissue

Spectrophotometers can measure absorbance and provide values for wavelengths of 260 nm, 280 nm, and 230 nm. However, they lack the sensitivity to measure small quantities of DNA. All nucleic acids (dsDNA, RNA, and ssDNA) absorb at 260 nm, and this method cannot distinguish between the various forms of nucleic acid. For example, the amount of genomic DNA (gDNA) present in an RNA preparation or the amount of RNA present in a gDNA sample cannot be determined. These contaminants contribute to the absorbance value, resulting in an overestimation of nucleic acid concentration. In addition, if samples are degraded, single nucleotides will also contribute to the 260 nm reading, and thus the nucleic acid concentration will be overestimated.

Fluorescent dye-based quantification uses dyes that only fluoresce when bound to specific molecules, dsDNA, ssDNA, or RNA, and thus the concentration of the specific molecule can be measured. This makes the measurement more accurate for samples that contain nucleic acid contaminants or samples that are partially degraded.

Although this method provides a more accurate concentration of the sample for the molecule of interest, it does not give an indication of the contamination of the sample.

Gel electrophoresis verifies the integrity of DNA and RNA molecules by separating their fragments based on size and charge and thus estimating the size of DNA and RNA fragments.

The RIN is an algorithm for assigning integrity values to RNA measurements. The integrity of RNA is a major concern for gene expression studies and traditionally has been evaluated using the 28S/18S ribosomal RNA (rRNA) ratio. The RIN algorithm is applied to electrophoretic RNA measurements and is based on a combination of different features that contribute information about the RNA integrity to provide a robust universal measure. If RNA is purified from FFPE samples, the 28S/18S rRNA ratio and the RIN value are not useful for assessing RNA quality.

The DIN determines the level of sample degradation using an algorithm to evaluate the entire electrophoretic trace. The higher the DIN value, the better the integrity of the gDNA sample.

qPCR can be a useful technique in the QC of gDNA for downstream sequencing, because it simultaneously assesses DNA concentration and suitability for PCR amplification. However, this technique is labour-intensive and has higher costs.

Sequential use of spectrophotometric and fluorescence-based methodologies permits the cost-effective assessment of DNA quality for high-throughput downstream applications. This combination also enables the detection of impurities, and thus their removal from samples. This is particularly useful for samples such as FFPE samples that are available in limited amounts.

3.5 Contents of standard operating procedures (SOPs)

Biobanks should develop, document, and regularly update policies and procedures in a standardized written format incorporated into an SOP manual that is readily available to all laboratory personnel. The SOP manual is a key part of the overall QMS of the biobank, is important to the success of biobanking, and is a major contributor to the development of biomedical practice worldwide.

The SOP manual should specifically include:

- procedures for obtaining informed consent and withdrawal of consent from participants;
- records management policies, including access control, a backup system, clinical annotation, and document maintenance and archiving;
- policies and procedures for specimen handling, including supplies, methods, and equipment;
- laboratory procedures for specimen processing (e.g. collection, transportation, processing, aliquoting, tests, storage, and QC);
- procedures for sharing and transferring specimens (access policy, MTA);
- procedures for a business model and cost recovery, when applicable;
- policies and procedures for shipping and receiving specimens;
- QA and QC policies and procedures for supplies, equipment, instruments, reagents, labels, and processes used in sample retrieval and processing;
- procedures for security in biobank facilities;
- policies and procedures related to emergencies and safety, including reporting of staff injuries and exposure to potential pathogens;
- policies and procedures for the investigation, documentation, and

reporting of accidents, errors, complaints, and adverse events;

- policies, procedures, and schedules for equipment inspection, maintenance, repair, and calibration;
- emergency procedures in case of failure of a refrigerator, freezer, or LN₂ tank;
- procedures for disposal of medical waste and other hazardous waste; and
- policies and procedures describing the requirements of recruitment and training programmes for biobank staff.

3.6 Records management

The importance of an adequate records management strategy cannot be overstated.

Documentation related to sample collection, sample processing, sharing of samples (MTA and DTA), and shipment of samples (proof of shipment and delivery) must be appropriately maintained and archived in a traceable and secure manner. A backup system must be implemented to guarantee appropriate maintenance of all documents.

All documents and documentation must be kept centrally and should include:

- the SOP manual;
- quality certifications;
- personnel training records;
- templates of forms and spreadsheets;
- documentation of biobank audits;
- documentation of adverse events;
- instrument calibration records;
- maintenance and repair records;
- signed informed consents;
- signed collaboration agreements;
- sample request forms;
- signed MTAs and DTAs; and
- shipping notes.

Similarly to SOPs, each form should have a unique number and title. All changes made to forms should be noted, dated, and signed to provide a trace of all modifications.

All hard copies of records must be archived in a secure manner, to be accessed only by authorized personnel. All stored records should be stored in a manner that provides easy access for inspection by authorized personnel.

Each container, tank, freezer, refrigerator, or room-temperature storage cabinet should have a unique identifier. The hierarchy of each storage unit should be clearly defined, to enable stored samples to be located easily. A convention should be established for numbering

shelves, racks, and boxes as well as each location within the container.

An IT solution (see Section 3.3.4) can provide a centralized system to maintain traceable records of samples. Where possible, hard copies of records should be scanned into an IT system to provide a backup.

All records should be archived for a period in line with institutional or local regulations, where they exist. Where there are no such regulations, the biobank should de-

cide the period for record retention depending on the type of record. Records pertaining to samples that no longer exist may be destroyed if the records are considered to no longer be valuable. Records pertaining to samples that were withdrawn should be destroyed in a secure manner. Records pertaining to instruments may be destroyed once the instrument has been retired. The destruction of records should be carried out in a manner in line with the security requirements of the record.

Key points: records management system

- Evaluate the available systems: commercial, open-source, or developed in-house.
- Biobanking activities and processes must be documented.
- Data security systems should be adequate to ensure confidentiality and safety.
- Records management should be audited regularly (QA/QC).
- Biobank management systems must also allow access to sample data, to stimulate collaborations.
- Semantic interoperability is an important consideration.
- Systems must ensure full traceability of samples, data, and documentation.
- Documentation must be archived in a traceable and secure manner.

3.7 Specimen collection, processing, and storage

Many types of biological material can be stored for cancer research purposes. The methods used to collect biospecimens will vary depending on what the intended end use is and how the specimens will be processed.

The recommendations presented here are derived from multiple sources, such as international publications and articles (Eiseman et al., 2003), including the biorepository protocols of the Australasian Biospecimen Network. Although this book focuses on cancer research, the research community realizes that samples may also be used in other areas of research; the key issue is the importance of harmonization of techniques and prac-

tices to facilitate multidisciplinary collaboration.

This section provides general advice about the collection of:

- whole blood and derivatives
- solid tissues
- urine
- buccal cells and saliva
- bronchoalveolar lavage
- bone marrow aspirate
- cerebrospinal fluid
- semen
- cervical and urethral swabs
- hair
- nails.

3.7.1 Collection of blood or blood-derived products

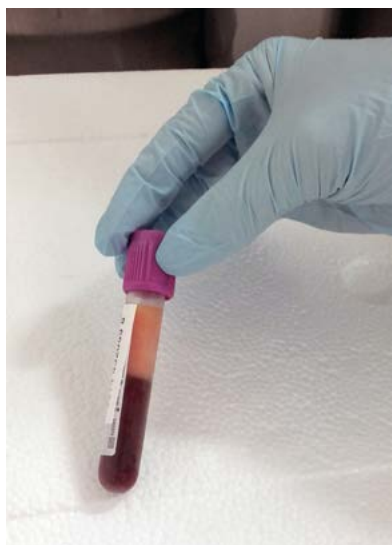
Detailed instructions and protocols for the collection of blood or blood derivatives are provided in Section 4.

3.7.1.1 Blood

The following general guidelines should be considered.

- All blood should be treated as potentially infectious. Blood samples for research purposes should be collected at the same time as routine clinical blood samples, so as to limit discomfort to individuals. Blood should be collected from fasting individuals (i.e. after abstinence from food, alcohol, and caffeine-containing beverages for 8–12 hours).
- Blood should not be collected after prolonged venous occlusion.
- Tubes into which the blood is collected should be clearly labelled (Fig. 20).
- For blood collection, the recommended order of draw is the following

Fig. 20. Blood sample.



(Calam and Cooper, 1982; CLSI, 2007):

1. blood culture tube;
 2. coagulation tube;
 3. serum tube with or without clot activator, with or without gel;
 4. heparin tube with or without plasma separating gel;
 5. ethylenediaminetetraacetic acid (EDTA) tube with or without separating gel;
 6. glycolytic inhibitor.
- For the preparation of plasma, blood may be collected into an EDTA tube, an acid citrate dextrose (ACD) tube, or a lithium heparin tube.
 - Ideally, blood should be processed within 1 hour of collection. After that time, cell viability decreases rapidly, resulting in poor cell structure and degradation of proteins and nucleic acids.
 - Lithium heparin is generally used if cytology studies will be performed, but it is not recommended for proteomics work.
 - PCR was clearly interfered with when heparinized blood (heparin 16 U/mL blood) was used as a source of template DNA (Yokota et al., 1999).
 - Either EDTA or ACD tubes can

be used if DNA will be extracted or lymphoblastoid cell lines will be derived. Lithium heparin is not recommended for establishment of lymphoblastoid cell lines.

- EDTA tubes are recommended if protein studies will be performed. The use of EDTA tubes results in less proteolytic cleavage compared with the use of heparin tubes or ACD tubes.
- For the preparation of plasma, the blood should be centrifuged as soon as possible. For the preparation of serum, the blood should be processed within 1 hour of collection.
- The amount of blood collected should be justified when applying for ethical clearance.
- A reduced volume of blood in a tube containing additives should be recorded to avoid confounding the results.
- The time and date of blood collection and the time of freezing should be recorded, as well as any deviations from the standard processing protocol.
- Blood should be transported at room temperature or on melting ice depending on the particular applications. Samples to be used for proteomics assays should be processed immediately at room temperature, because cool temperatures can activate platelets and release peptides into the sample *ex vivo*.
- Blood spot collection should be considered as an alternative to whole blood for validated techniques when conditions necessitate easier collection and cheap room-temperature storage. Different types of collection cards are available (e.g. Guthrie cards, “fast transient analysis” [FTA] cards, IsoCode cards) (see Section 4).

3.7.1.2 Blood spots

Guthrie cards (Schleicher & Schuell 903 filter paper) are used to collect

heel-stick blood from newborns for metabolic disease screening. The 903 paper is manufactured from 100% pure cotton linters with no wet-strength additives. The critical parameters for collection of newborn screening samples are blood absorbency, serum uptake, and circle size for a specified volume of blood. Blood spots archived for as long as 17 years, sometimes at room temperature, have also provided valuable sources of amplifiable DNA (Makowski et al., 1996) (Fig. 21).

Modified cards (IsoCode cards or FTA cards) have been developed. These consist of filter paper impregnated with a proprietary mix of chemicals that serves to lyse cells, to denature proteins, to prevent growth of bacteria and other microorganisms, and to protect nucleic acids from nucleases, oxidation, and UV damage. Room-temperature transportation of such cards in folders or envelopes (by hand or by mail) has been common for years. The papers protect DNA in the samples for some years under ambient conditions. The main variable is expected to be the quality of the storage atmosphere, particularly the content of acid gases and free-radical-generating pollutants, although FTA paper can protect against such conditions (Smith and Burgoyne, 2004). Sample integrity is optimized when FTA cards are stored in a multi-barrier pouch with a desiccant pack. Whatman Protein Saver Cards are commonly used to collect dried blood spots for molecular and genomic studies and for the isolation of viruses (Mendy et al., 2005) and bacteria (see Section 4).

3.7.1.3 Buffy coat

For DNA testing, if DNA cannot be extracted from blood within 3 days of collection, the buffy coat may be isolated and stored at

Fig. 21. Card with dried blood spots.



-70 °C or below before DNA isolation. Buffy coat specimens that are being used for immortalization by Epstein–Barr virus should be transported frozen on dry ice (solid-phase CO₂). RNA should be isolated from buffy coat within 1–4 hours of specimen collection; alternatively, RNA stabilization solution (e.g. *RNA/later*) should be used (see Section 4).

3.7.2 Collection of solid tissues

Solid tissues for research are collected by biopsy or after surgical excision. Detailed procedures are presented in Section 4.

The following important points should be considered when planning tissue collection for research.

- The collection of samples should be carefully planned with surgeons, clinical staff, and pathologists. Collection of solid tissue for research from surgically excised tissue should always occur in the grossing room unless the standard procedure for clinical care permits collection in the operating theatre or nearby pathology suite.

- The collection of samples for research should never compromise the diagnostic integrity of a specimen. Only tissue that is excess to diagnostic purposes should be collected for research. It is the responsibility of the pathologist to decide this.
- The intact surgical specimen or biopsy sample should be sent to pathology.
- Tissue bank staff members must be present in pathology, to collect, freeze, or fix the tissue as quickly as possible.
- All materials and instruments should be prepared in advance. If a fresh sample is to be obtained, transport medium (RPMI 1640, 10% fetal bovine serum [FBS], 100 U/mL penicillin/streptomycin, 100 U/mL amphotericin) should be prepared. If a sample is to be vitally cryopreserved, cryopreserving solution should be prepared (RPMI 1640, 10% dimethyl sulfoxide [DMSO], 20% FBS).
- A pathologist should supervise the procurement of the tissue for research purposes. The pathologist will examine the sample and, allowing adequate tissue for diagnostic purposes, will remove por-

tions of the tumour and adjacent apparently normal tissue and other areas of interest. Where possible, two or more samples of the tumour tissue should be taken, representing different areas, i.e. different macroscopic patterns in the body of the tumour. Normal tissue can be taken from a non-diseased resected organ, but where the normal tissue is required for use as matched control, it should be taken preferably > 10 mm from the diseased tissue.

- If applicable, involved lymph nodes and metastases will also be collected. Tissues must be sliced with sterile forceps and scalpel blades, and staff members must use sterile gloves. The use of the same scalpel blade for normal and neoplastic areas should be avoided. If this is not possible, normal tissue should be collected before tissue from tumour areas.
- Standard diagnostic processes usually place surgical specimens in formalin after excision. Where fresh, vitally cryopreserved, or fresh frozen samples are required, samples must be transferred as fresh specimens. In this case, fresh specimens should be placed in a closed container in a sterile cloth on wet ice for transportation from surgery to pathology. An alternative, which also permits a delay in the need for immediate processing, is to vacuum-pack the tissue.
- Transfer of specimens on wet ice must be carried out as soon as possible, to minimize the effect of hypoxia on gene expression and degradation of RNA, proteins, and other tissue components. Transfer of vacuum-packed specimens is less time-critical; the samples may be stored for up to 115 hours in a 4 °C refrigerator before and/or after transportation from the operating theatre, until processing. The temperature of the specimen during transfer should be documented.

- It is recommended that surgical specimens or biopsy samples be preserved within 1 hour of excision. However, tissue subject to a delay up to 2 hours should still be collected (Eiseman et al., 2003). Detailed records should be kept of the timing of events from excision (or arterial clamping, in the case of larger specimens) to fixation or freezing.
- All tissue should be treated as potentially infectious; the collection process should be carried out under the most aseptic conditions possible.
- Each specimen collection receptacle must be clearly labelled when multiple samples are being collected for the biobank.
- Fresh tissue required for xenografting or for creation of cultures or cell lines must be placed in transport medium (RPMI 1640, 10% FBS, 100 U/mL penicillin/streptomycin, 100 U/mL amphotericin). If this tissue is to be vitally cryopreserved, it should be placed in freezing medium (RPMI 1640, 10% DMSO, 20% FBS). Because DMSO requires slow freezing, the tissue can be placed into a household -20°C freezer for 30 minutes and then placed into -80°C storage overnight before final storage in LN_2 . A specific system to reduce the temperature of the tissue by 1°C per minute can also be used before the tissue is transferred.
- Tissue required for expression profiling and other molecular profiling, such as whole-genome sequencing or epigenetic studies, must be snap-frozen. Each tissue sample should be placed on card and covered with optimal cutting temperature (OCT) compound before vapour-freezing the sample by holding it over LN_2 . The sample can also be frozen by placing it into a container immersed in freezing medium (e.g. precooled isopentane). Tissue should never

be immersed directly in LN_2 , because of the potential formation of cryo-artefacts. When dry ice or LN_2 is not readily available, tissue collection in RNA $_{\text{later}}$ is a good alternative, provided that this tissue is not required for diagnostic purposes and that permission has been given by the pathologist. Alternatively, PAXgene can be used as a fixative that preserves nucleic acids and morphology for histopathological analyses (Viertler et al., 2012).

- Where possible, it is advisable for a cryostat section to be taken, to prepare a haematoxylin and eosin (H&E)-stained slide for review by the pathologist for confirmation and QC of the tissue sample being conserved. An indication of the cancer cellularity is important for tissue banking because it predetermines the need for microdissection of tissue for nucleic acid extraction in next-generation sequencing.
- FFPE tissue can be used for targeted immunohistochemistry, fluorescence in situ hybridization (FISH), and next-generation sequencing and validation studies. RNA can also be extracted from FFPE tissue for gene fusion studies, next-generation sequencing, or quantitative reverse transcription PCR (RT-PCR). The same procedure as for diagnostic tissue may be followed, with the samples placed in containers of different colours to identify them as samples for research purposes.
- Care should be taken in the evaluation of biopsy material for research, because the sample has a much smaller quantity of tissue and most of it may be needed for diagnostic purposes. When needed for diagnosis, the biopsy sample should follow the standard diagnostic process and be formalin-fixed and paraffin-embedded. After the diagnostic process, any leftover material can be recovered for research.

- Each specimen conservation receptacle (tube) must be clearly labelled before it is placed in the biobank (see Figs. 24–26).

3.7.3 Collection of other specimens

3.7.3.1 Urine

Urine is easy to collect and is a suitable source of proteins, DNA, and metabolites. Urine should be routinely stored at -80°C . Ambient-temperature storage before freezing should be kept to a minimum (see Section 4).

3.7.3.2 Buccal cells

The collection of buccal cells is not difficult and does not require highly trained staff. Buccal cell collection is considered when non-invasive, self-administered, or mailed collection protocols are required for DNA analysis (Steinberg et al., 2002). However, buccal cells will yield only limited amounts of DNA compared with blood. Different methods of self-collection are available, depending on the end-points and the analyses to be performed (Mulot et al., 2005).

Cytobrush

With this method, buccal cells are collected on a sterile cytobrush by twirling it on the inner cheek for 15 seconds. The operation is repeated three times, on the two cheeks. The swabs are separated from the stick with scissors and transferred to a cryotube. The duration of the collection can influence the DNA yield. García-Closas et al. (2001) reported that cytobrushes produce DNA with good quality. However, King et al. (2002) concluded that the mouthwash method of collecting buccal cells is superior for reactions that require long fragments.

Mouthwash

With this method, buccal cells are collected by rinsing the mouth for 10 seconds with 10 mL of sterile water and expectorating the rinse into a 50 mL centrifuge tube. This operation is repeated three times. The effect of lag time of storage at room temperature is observed for mouthwashes, whereas cytobrushes are less sensitive to the lag time at room temperature.

Cytobrushes and mouthwashes are generally considered unsuitable for children, because cytobrushes are abrasive. Mouthwashes require participants to expectorate and may be aspirated or swallowed.

3.7.3.3 Saliva

Saliva is used as a biological fluid for the detection of different biomarkers, such as proteins, drugs, and antibodies. Saliva meets the demand for a non-invasive, accessible, and highly efficient diagnostic medium. The collection of saliva is non-invasive (and thus not painful), and a sample can easily be collected without a need for various devices. Whole saliva is collected by expectoration into a provided tube, whereas for the collection of submandibular saliva and sublingual saliva, different ducts need to be blocked by cotton gauze. For the collection of parotid saliva, a parotid cup should be used (see Section 4).

Treated cards

These cards are treated to inhibit the growth of bacteria and kill viruses, thereby minimizing degradation of nucleic acids. Saliva is expectorated into a sterile cup. The tip of the triangle of treated card is placed into the saliva, which is wicked onto the matrix. The treated card is air-dried and placed in a bag with a desiccant pack. Treated cards correspond to

the lowest efficiency for DNA yield, because of the small quantity of collected saliva. Moreover, some proteins are left in the solution of extracted DNA. Therefore, the DNA cannot be kept for long-term conservation. However, an advantage of this method of saliva collection is its low cost, because of the absence of an extraction step.

3.7.3.4 Bronchoalveolar lavage

The airways, and particularly the alveoli, are covered with a thin layer of epithelial lining fluid, which is a rich source of many different cells and of soluble components of the lung that help protect the lung from infections and preserve its gas-exchange capacity. Bronchoalveolar lavage performed during fibre-optic bronchoscopy is the most common way to obtain samples of epithelial lining fluid (Reynolds, 2000). The cellular and protein composition of the epithelial lining fluid reflects the effects of the external factors that affect the lung, and changes in this composition are of primary importance in the early diagnosis, assessment, and characterization of lung disorders as well as in the search for disease markers (Griese, 1999).

Bronchoalveolar lavage is classically performed by instillation of buffered saline solution divided into three or four aliquots (typically a total volume of 100–150 mL) through a flexible fibre-optic bronchoscope, after local anaesthesia. The first 10 mL should be processed separately and is denoted as bronchial lavage. The rest of the lavage, denoted as bronchoalveolar lavage, should be pooled into a sterile siliconized bottle and immediately transported on ice to the laboratory. At the laboratory, the total volume of the lavage is measured, and cells and proteins are separated by centrifugation. The lavage fluid should be frozen and stored at -80°C until use.

3.7.3.5 Bone marrow aspirate

The following paragraphs on bone marrow aspirate and cerebrospinal fluid are derived from the Australasian Biospecimen Network recommendations (see Table 1) and the publication *Guidelines on Standard Operating Procedures for Microbiology* (Kumari and Ichhpujani, 2000).

Bone marrow is the soft tissue found in the hollow interior of bones. In adults, the marrow in large bones produces new blood cells. There are two types of bone marrow: red marrow (also known as myeloid tissue) and yellow marrow. In cancer research, red bone marrow from the crest of the ilium is typically examined.

Bone marrow should be collected by a doctor who is well trained in this procedure. Bone marrow should be aspirated by sterile percutaneous aspiration into a syringe containing an EDTA anticoagulant, and the specimens should be chilled immediately. Heparin is not recommended as an anticoagulant for molecular testing. If a specimen contains erythrocytes, it should be processed to remove the erythrocytes before freezing. The bone marrow samples should be fresh frozen and stored at -80°C .

3.7.3.6 Cerebrospinal fluid (CSF)

Cerebrospinal fluid (CSF) originates from the blood. The choroid plexuses in the first, second, and third ventricles of the brain are the sites of CSF production. CSF is formed from plasma by the filtering and secretory activities of the choroid plexus and the lateral ventricles. CSF circulates around the brain and the spinal cord. It nourishes the tissues of the central nervous system and helps to protect the brain and the spinal cord from injury. It primarily acts as a water shock absorber. It totally surrounds the brain and the spinal cord, and thus absorbs any blow to the brain. CSF also acts as a carrier

of nutrients and waste products between the blood and the central nervous system.

CSF is a very delicate biological material. Often, only small volumes of CSF are available for analysis, because of the difficulty of collecting CSF, and therefore it should be handled with care. Only a physician or a specially trained nurse should collect the specimen. After collection, the specimen should be transferred into a clean penicillin vial containing about 8 mg of a mixture of EDTA and sodium fluoride in the ratio of 1:2. Centrifuging CSF is recommended before freezing if the sample contains red blood cells or particulate matter. The specimen should be frozen and stored at -80°C or in LN_2 . Do not delay freezing the CSF, because cells are rapidly lysed once the CSF is removed from the body.

3.7.3.7 Semen

Seminal fluid, which is the liquid component of sperm, provides a safe surrounding for spermatozoa. At pH 7.35–7.50, it has buffering properties, protecting spermatozoa from the acidic environment of the vagina. Seminal fluid contains a high concentration of fructose, which is a major nutrient source for spermatozoa during their journey in the female reproductive tract. The complex content of seminal plasma is designed to ensure the successful fertilization of the oocyte by one of the spermatozoa present in the ejaculate. Seminal plasma is a mixture of secretions from several male accessory glands, including the prostate gland, seminal vesicles, epididymis, and Cowper's glands (Pilch and Mann, 2006).

After collection, the fresh ejaculate should immediately be spun down at 4°C to separate the seminal fluid from the spermatozoa. Protease inhibitors should then

Fig. 22. Hair sample.



be added to the sample, to avoid digestion by powerful proteases present in seminal fluid. To ensure complete separation of cell debris or occasional spermatozoa from seminal plasma, the sample can be centrifuged a second time. The sample should be stored at -80°C .

3.7.3.8 Cervical and urethral swabs

The quality of collected cervical and urethral specimens depends on appropriate collection methods. Swabs, brushes, or other collection devices should be placed in a transport medium, or transported dry in a sealed tube and resuspended in the transport medium upon arrival. The transport fluid may either be stored at -70°C or below or immediately centrifuged, and the pellet processed for DNA or RNA extraction (see Section 4).

3.7.3.9 Hair

Currently, hair analysis is used for purposes of assessing environmental exposures, such as exposure to mercury from eating fish. Hair analysis is also used to test for illegal

Fig. 23. Nail clippings.



drug use and to conduct criminal investigations (see Section 4). Hair should be kept in a sealable plastic bag, stored in the dark at room temperature (Fig. 22).

3.7.3.10 Nails

Nail clippings may contain analytes of interest that were deposited during the growth of the nail. Nail specimens can be collected for drug, nutritional, poisons, and toxicity testing (see Section 4) (Fig. 23).

3.8 Specimen annotations and data sets

Data associated with the biological specimens provide added value to the samples and increase the types of research for which the biospecimens can be used. Specimen annotations provide basic information such as sample type, quantity, and current form (how the sample was stabilized and conserved), which can be used to evaluate the use of the sample in a specific assay. Specimen annotation also provides parameters that define the quality of

the specimen and thus the quality of the downstream assay.

For biobanks wishing to share samples in large studies and for research that requires samples from different sources, it is important that, as with all other elements of a biobank, the data are standardized or at least harmonized to permit effective aggregation.

Information to annotate the sample should be collected at each phase of the biobank/biospecimen processes:

- consent;
- donor/patient ID, sample ID;
- collection (technique, date, time);
- processing/stabilization;
- conservation/storage;
- for tissues: organ of origin;
- for tissues: disease features (e.g. tumour, non-neoplastic);
- quality parameters;
- donor/patient-related data;
- distribution/use; and
- returned data.

It is important to determine a minimum data set, because this establishes a basic quality of all samples collected in the biobank (see Table 5). This should not, however, compromise the ability to collect additional data for particular sample sets that may be useful in the future. The minimum data set must be as completely defined as possible, indicating values for each of the fields in the data set, to reduce the heterogeneity of sample-associated data and thus improve its quality.

One potential problem of data values involves different systems that use different date formats: DD/MM/YYYY or MM/DD/YYYY or YYYY/MM/DD. Another problem for sample annotation is unfilled fields. It is important that a value for “not available” is defined, because blank fields can potentially be interpreted as zero and can provide incorrect evaluations when used in research.

During the creation of a data set, it is important that for data that refer

to classification systems, the version to which the value applies is also indicated. As versions change, these values can be correctly interpreted or adjusted. One such example is the staging score used for defining the stage of a cancer. The requirement to indicate the scoring system also applies to values that may be retrieved using different assays. An example of this is the concentration value taken using a spectrophotometer or a fluorescent dye-based quantification. Other fields for which the situation may be similar are units of time (e.g. time to stabilization, time from diagnosis to collection, time from diagnosis to follow-up), which may be recorded in minutes, hours, days, months, or years, as well as units of measurement of size (e.g. millimetres, centimetres) or weight (e.g. nanograms, milligrams).

Systems already exist to address the need to standardize biobank- and sample-associated information.

The SPREC tool, in particular, addresses the pre-analytical data required and contains seven data fields and defined values for the definition of sample type and the processes of collection, stabilization, and storage. There is a SPREC available for fluids and one for solids, to address the different collection and stabilization processes required. However, the SPREC systems will be replaced by CEN norms and ISO standards.

The Biospecimen Reporting for Improved Study Quality (BRISQ) standard covers pre-acquisition, acquisition, stabilization/preservation, storage/transportation, and QA measures (Moore et al., 2011). The elements in the BRISQ list are prioritized into three tiers according to the relative importance of their being reported.

- Tier 1 comprises 15 elements of necessary data, covering all sample types and including the manner in which the specimens were col-

lected, stabilized, and preserved. It also contains clinical data associated with the patient.

- Tier 2 comprises 19 elements of beneficial data, covering patient demographic information, times and temperatures, and methods of enrichment.
- Tier 3 comprises 16 elements of nice-to-have data, pertaining to environmental conditions such as ischaemia, therapy, exposures, disease state, and storage containers and shipping parameters.

Tier 1 is now required for many journals.

MIABIS 2.0 represents the minimum information required to initiate collaborations between biobanks. This standard currently comprises aggregated descriptive data, and not sample-specific data, to permit a harmonized exchange of samples and data among biobanks. The MIABIS standard pertains to descriptive data of a biobank, collection, and study, which include collection types and contact information. It also includes aggregated data such as sex, age range, material type, data categories, and diseases. MIABIS is the only standard to provide indications for this collective type of information. This information is useful when creating biobank catalogues and inventories to provide visibility to available resources.

3.8.1 Annotations on patients/individuals

It is important for the biobank to annotate the consent that is collected for the samples and data that belong to the patient. This information should include whether the consent or a waiver was used to permit the use of the sample or data in research. It is important to indicate the scope of the permission, the type of research that can be performed, information such as what types of entities can access the

sample (public, private), and whether there are geographical restrictions (local, national, international) on shipment of samples and data. In the era of personalized medicine and open access, it is also important to record which participant-related data can be associated with the sample (clinical data, pathological data, follow-up data) and, in particular, whether genetic data can be used and whether these data can be placed in public databases (publication or research). It is vital to indicate whether a donor/patient wishes to be re-contacted for further studies, whether they wish to be informed of incidental findings, and what should be done if any findings have hereditary implications.

For all samples, it is vital to have the diagnosis and pathological data. It is preferable that accepted nomenclature is used for diagnosis and classification systems are used for all pathology data, because they provide standard comparable parameters. One such example is the tumour–node–metastasis (TNM) system for classification of malignant tumours.

Participant-associated data are important, to provide additional value because they permit an extended evaluation of downstream assays. The more information can be collected during the patient's clinical care path, the more valuable the sample becomes. Some of these data categories are:

- demographic information;
- family history;
- environmental exposure;
- lifestyle;
- diagnosis;
- clinical data/medical history;
- complete pathology report, including immunohistochemical and molecular biology markers;
- treatment;
- follow-up/outcome; and
- molecular/genetic characterization.

Not all of these data categories of participant-associated data are required for all studies, and even within a single category, different data fields will be required depending on the type of sample being collected and the intended use of the sample.

3.8.2 Annotations on stored specimens

Obtaining and storing information about the stored specimens – in particular, the pre-analytical variables related to the collection, transportation, ischaemia times, stabilization, and conservation of the specimens – is mandatory in CEN and ISO. The data categories to consider for sample-specific annotations are:

- pre-acquisition;
- collection;
- processing/stabilization;
- conservation/transportation; and
- quality.

3.8.3 General recommendations for data sets

- Wherever possible, the biobank should collect its data from existing clinical databases for patient-related data. This avoids the need for duplicate input and reduces the possibility of human error. If the data are collected through a link between the biobank database and the clinical database, this may also permit tracking of additional clinical data over time.
- Because it is not always possible to set minimum data sets common to multiple sample or disease types, macro fields should be set to indicate the presence of such data (e.g. clinical data, epidemiological data, follow-up data).
- All donor/patient-related data should be associated with each sample collected. This should be done either within the database

system functionality or through a parent ID field that relates initially to the donor data. This avoids repeating each donor data annotation for each sample.

- It is important to have a method to indicate participants for which different sample types are available. This should be done either within the database system functionality or through a field to indicate the availability of other types of samples related to the same case.
- For all classification systems (ontologies) that are used to annotate samples, the version should be indicated.
- All numerical values indicated should have associated units of measurement (e.g. months, days, hours, nanograms, microlitres).
- All null values (not inserted) should have default values that are not zero.
- Values lists for data fields avoid the introduction of error and are preferable to free-text fields.

See Table 5 and Annex 5.

3.8.4 Specimen labelling and aliquoting

Each specimen should be labelled in such a manner that the labelling will survive all potential storage conditions, in particular dry ice and LN₂ and potentially water bath.

Ink used on the label should be resistant to all common laboratory solvents. A minimum requirement is to print labels with a barcode (linear or two-dimensional), thus providing a direct link to database software and preventing human error in identification. However, it is also essential to include human-readable indications of contents in case no barcode reader is available (Figs. 24–26). The barcode template should be documented. The software used for labelling should enable data import and export in standard formats and

Table 5. Example of IARC minimum data set for a study or collection in a biobank

	Attribute	Standard
1	Study details	
1.1	Study ID	MIABIS 2.0
1.2	Study name	MIABIS 2.0
1.3	Description/objective	MIABIS 2.0
1.4	Responsible unit	
1.5	Responsible/principal investigator	MIABIS 2.0
1.6	Sample manager	
1.7	Study design	MIABIS 2.0
1.8	Cancer type	WHO name or ICD-O code
1.9	Other chronic disease	BRISQ
2	Collaborators details	
2.1	Contact person (collaborators) <ul style="list-style-type: none"> – First name – Last name – Telephone number – Email – Contact institution – Contact department – Contact address – Contact country 	MIABIS 2.0
3	Collection details	
3.1	Collection start date	
3.2	Collection end date	
3.3	Collection centres <ul style="list-style-type: none"> – Centre name – Centre country 	
4	Ethical, legal, and social issues (ELSI)	
4.1	Ethical approval <ul style="list-style-type: none"> – Date – Reference 	
4.2	Informed consent	
4.3	Participant information sheet	
4.4	Material Transfer Agreement <ul style="list-style-type: none"> – Date – Reference 	
4.5	Other contract <ul style="list-style-type: none"> – Date – Reference 	
5	Donor/patient-related data	
5.1	Sample ID	
5.2	Parent sample ID (for aliquots and derivatives)	

Table 5. Example of IARC minimum data set for a study or collection in a biobank (continued)

	Attribute	Standard
5.3	Informed consent – YES/NO/NI (implying waiver) – Type of consent – Area of research – Re-contact – Return of results – Access to medical data – Possibility of publishing data – Access to genetic data	
5.4	Sex	
5.5	Age at collection	
5.6	Country and region of origin	
5.7	Basic diagnostic parameters (e.g. for cancer: individual TNM codes where possible; if not, then stage and always grade – for all, the version should be indicated)	
5.8	Associated diagnostic parameters (CA125, CA19-9, etc.)	
5.9	Other diseases	
5.10	Disease status	
6	Biospecimen-related data	
6.1	Biospecimen type	
6.2	Anatomical site: organ of origin or site of blood draw	
6.3	Collection mechanism: how the biospecimens were obtained	
6.4	Type of stabilization: the initial process by which the biospecimens were stabilized during collection	
6.5	Biospecimen size	
6.6	Delay to preservation: – Time between biospecimen collection and processing – Time between biospecimen processing and cryopreservation – Warm ischaemia time for tissue: period between circulatory arrest and beginning of cold storage	SPREC
6.7	Temperature before preservation: – Storage temperature before processing – Storage temperature before cryopreservation	
6.8	Type of long-term preservation: the process by which the biospecimens were sustained after collection	SPREC
6.9	Constitution of preservative: the make-up of any formulation used to maintain the biospecimens in a non-reactive state	
6.10	Storage temperature for short-term storage: the temperature, or temperature range, at which the biospecimens were kept until distribution or analysis	
6.11	Storage temperature for long-term storage	SPREC
6.12	Freeze–thaw cycles: this field is for low-temperature storage and should account for the number of times the sample underwent a freeze–thaw cycle for processing; it should also account for any anomalies to the container containing the samples	

Table 5. Example of IARC minimum data set for a study or collection in a biobank (continued)

	Attribute	Standard
7	Categories of associated data collected	
7.1	Medical history data (e.g. history of other diseases, medications, family history of same cancer to first and second degree, family history of other cancers, family history of other diseases): – Available or not? – Which kind of data? – Where are data kept? – Who manages data?	
7.2	Epidemiological and survey data (e.g. age, sex, exposure, anthropometric data, reproductive history, physical activity, tobacco status, alcohol consumption, occupational history, socioeconomic status, previous illness): – Available or not? – Which kind of data? – Where are data kept? – Who manages data?	
7.3	Clinical data (e.g. clinical diagnosis, clinical presentation, comorbidities, biochemical data, immunophenotypic data, neoadjuvant therapy, disease status of patients, vital status of patients, clinical diagnosis, pathology diagnosis): – Available or not? – Which kind of data? – Where are data kept? – Who manages data?	
7.4	Pathology data (e.g. pathology diagnosis, histological type, TNM, stage, grade, nuclear component, immunohistochemistry): – Available or not? – Which kind of data? – Where are data kept? – Who manages data?	
7.5	Follow-up data (e.g. bioassays, treatment, disease progression, relapse, status – disease-free, alive with disease, dead from disease, dead from other causes): – Available or not? – Which kind of data? – Where are data kept? – Who manages data?	
8	Shipment data saved for each sample	
8.1	Date of deposition	
8.2	Number of biospecimens shipped	
8.3	Shipment conditions	
8.4	Carrier	
8.5	Date of next shipment	
8.6	Number of biospecimens to be shipped	
8.7	Expected carrier	

BRISQ, Biospecimen Reporting for Improved Study Quality (Moore et al., 2011); ICD-O, International Classification of Diseases for Oncology; MIABIS 2.0, Minimum Information about Biobank Data Sharing 2.0 (Brochhausen et al., 2013); SPREC, Sample PREanalytical Code (Lehmann et al., 2012); TNM, tumour–node–metastasis classification of malignant tumours; WHO, World Health Organization.

should be able to link with the biobank management system.

Ideally, all specimens should be labelled with at least two human-readable forms of identification without revealing the identity of the donor. The anonymity of the donor must be guaranteed in all cases. Radio-frequency identification (RFID) is another option but is not in widespread use for biobanking.

Information on the label should include the biobank's unique identifier number, the name of the project, the type of biospecimen, and/or the number of the location within the storage system, with the same information repeated in the barcode if available.

After primary samples are processed, derived products should be stored in appropriate and optimized containers. As technologies for analysing biospecimens improve, smaller volumes of sample are required. Therefore, the volume of aliquots should be adapted to avoid unnecessary freeze–thaw cycles.

A wide range of tubes of different sizes, with or without a preprinted barcode, are now available and affordable. Coloured caps can be used to distinguish between different types of samples and to facilitate the retrieval of samples. More and more analysis platforms are using robots, and sample storage in SBS format containers is also important to consider, to facilitate downstream analyses. Otherwise, specific boxes must be used for appropriate storage of SBS format tubes, allowing

Fig. 24. Printed linear barcode.



space saving in the biobank storage facility. Consideration and attention should be given to the composition of plastic, potential interaction with some analytes, and resistance to ultra-low storage temperatures.

3.9 Specimen shipping

Human biospecimens are considered to be “dangerous goods”, defined by the International Air Transport Association (IATA) as “articles or substances which are capable of posing a risk to health, safety, property or the environment”. According to United Nations regulations, dangerous goods meet the criteria of one or more of nine United Nations hazard classes (DGI, 2016). The relevant class for biological specimens is Class 6, Division 6.2: Infectious substances (IATA, 2015b).

The shipping and dispatch of biospecimens is subject to international regulations. These regulations, applicable to any mode of transport, are based on the recommendations of the Committee of

Experts on the Transport of Dangerous Goods, a committee of the United Nations Economic and Social Council (UNECE, 2015).

The International Civil Aviation Organization (ICAO) Technical Instructions for the Safe Transport of Dangerous Goods by Air (ICAO, 1986) are legally binding international regulations. The Dangerous Goods Regulations incorporate the ICAO provisions and may add further restrictions. The ICAO rules apply on all international flights. For national flights, i.e. flights within one country, national civil aviation authorities apply national legislation. This is usually based on the ICAO provisions but may incorporate variations. State and operator variations are published in the ICAO Technical Instructions and in the IATA Dangerous Goods Regulations (IATA, 2015a; WHO, 2012).

Each person involved in the transportation of biospecimens classified as dangerous goods by IATA should undergo an initial training session followed by a refresher course every 2 years. This training

Fig. 25. Printed two-dimensional barcode.



Fig. 26. Pre-labelled tube with two-dimensional barcode.



is for staff members involved in the preparation of documentation and also for those involved in packaging biospecimens.

3.9.1 Regulations

Infectious substances fall into two categories: Category A and Category B.

Category A comprises any infectious substance that is transported in a form that, when exposure to it occurs, is capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy humans or animals. Category A specimens include, but are not restricted to, specimens contaminated by highly pathogenic viruses (Ebola, Hantaan, Marburg, Lassa, etc.) or cultures of viruses such as dengue, HIV, or HBV. The proper shipping name for such substances is UN 2814: “Infectious substances affecting humans” or UN 2900: “Infectious substances affecting animals only”.

Category B comprises any infectious substance that does not meet the above-mentioned criteria. Most human specimens, such as blood samples, tissues, saliva, exfoliated cells, or urine not contaminated by highly pathogenic viruses, will fall into Category B. The proper shipping name for such substances is UN 3373: “Biological Substance, Category B”.

Biospecimens or derived products that have been specifically treated to neutralize infectious agents, or for which there is a minimal likelihood that pathogens are present, are not subject to these regulations. The proper shipping name for such substances is “Exempt Human (or Animal) Specimens”.

3.9.2 Packaging

The basic triple packaging system applies to all substances. It consists of three layers, as follows (Fig. 27).

Fig. 27. The triple packaging system.



- The *primary receptacle* is a watertight, leakproof receptacle containing the specimen, packaged with enough absorbent material to absorb all fluid in case of breakage.
- The *secondary packaging* is a durable, watertight, leakproof packaging to enclose and protect the primary receptacle. Several primary receptacles may be placed in one secondary packaging, but sufficient additional absorbent material should be used to absorb all fluid in case of breakage.
- The *outer packaging* is the shipping packaging, made of a suitable cushioning material, to protect the contents from outside influences while the package is in transit. An itemized list of contents must be enclosed between the secondary packaging and the outer packaging.

Appropriate insulation should be used. For example, for 8 °C to –20 °C, use gel packs; for –78.5 °C, use dry ice (Fig. 28); and if samples need to be kept at –150 °C, transport them in a dry shipper containing LN₂. Ensure that enough refrigerant is included to allow for a 24-hour delay in shipping.

In-transit temperature monitoring solutions that feature alarms as well as reporting are commercially available.

The triple packaging system also applies to “Exempt Human Specimens”, such as Guthrie cards (which should be transported in watertight plastic bags) and histopathological slides (which need to be cushioned to prevent breakage). In all cases, desiccants should be used for samples that are sensitive to humidity.

3.9.3 Labelling of parcels

All outer packages must bear a United Nations packaging specification

Fig. 28. Dry ice (–78.5 °C).



marking, according to the category in which the specimens fall. For Category A, Packing Instruction P620 applies. For Category B, Packing Instruction P650 applies. Detailed instructions are described in the IATA Dangerous Goods Regulations (IATA, 2015c). All packages must have shipper details and consignee details (name of institute, address, contact name, email, and telephone number).

3.9.4 Constraints

When preparing to transport biospecimens, it is important to consider shipping time, distance, climate, season, method of transportation, and regulations, as well as the type and number of biospecimens to be sent and their intended use. It is also important

to confirm with the recipient before the shipment that someone will be available to receive the samples.

When shipping biospecimens internationally, the sender must be aware of the requirements and regulations in the destination country before initiating the shipment, and must ensure that the consignment adheres to these regulations.

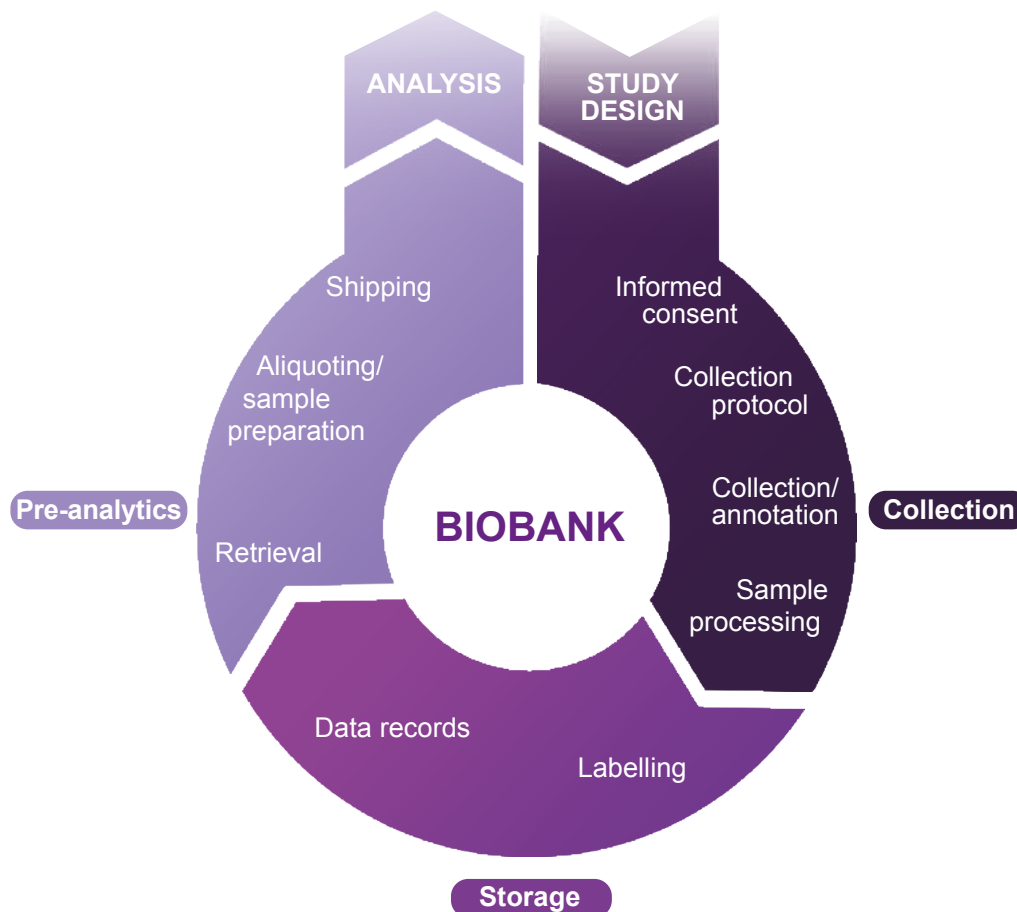
It is important to select an appropriate shipping company. Some companies offer more dedicated services for biospecimens, such as refilling of dry ice, handling of customs paperwork, and step-by-step monitoring and tracking.

3.10 Biobank workflow

Fig. 29 shows the sequence and the flow of information, data, and bio-

specimens, from the study design to final laboratory analyses. This scheme underlines the central role of biobanks as the transfer structure between biospecimen collection and laboratory analysis. It also underlines the fact that, in developing a study protocol, each step in this sequence of events must be clearly defined. The flow of information and biospecimens, as defined by protocols and procedures, will ensure the formation of a collection that contains traceable biospecimens and yields interpretable results. The biobank is an essential source of information and recommendations for the collection of biospecimens and for their annotation, storage, processing, and flow from the participant to the laboratory where they will be analysed.

Fig. 29. Biobank workflow.



Selected protocols

4.1 Processing of blood specimens

If serum and plasma samples are being collected, the blood should be centrifuged as soon as possible after blood collection and separated immediately after centrifuging so that the samples can be frozen as soon as possible. This is critical for time-sensitive samples for protein studies, for example. For the processing of blood specimens, the following protocols are recommended.

4.1.1 Filter paper dried blood spot collection, processing, storage, and shipment

Dried blood spot (DBS) is an easy and inexpensive means of collection and storage of peripheral blood specimens in settings where collection and storage of plasma is not optimal.

DBS can be used for molecular biology techniques and other diagnostic assays. The cost and difficulty of cold chain shipping of plasma samples are greatly reduced by the use of DBS, which can be shipped as non-dangerous goods.

Always wear gloves when handling filter papers, and hold them only by the upper corner, marked out for labelling. Do not allow the card to come into contact with any unclean surface (e.g. bench, base of hood).

The procedure should be performed in accordance with the relevant health and safety practices specific to specimen handling and waste disposal. A minimum level of training is required to perform the procedure.

Reagents and materials required:

- finger prick device (e.g. Unistik 2 device; Fisher Scientific, 22-0227);
- alcohol swab;

- Whatman Protein Saver Card (e.g. Whatman, 903; 10534612);
- gas-impermeable storage bag (e.g. Fisher Scientific, NC9307519);
- desiccant pack (e.g. Whatman, 10548234);
- humidity indicator cards (e.g. Multi-sorb Des Manufacture, MS200032);
- card drying rack (e.g. VWR, 89015-592) (optional; cards can be placed on a dry worktop if a drying rack is not available);
- gloves, preferably powder-free; and
- sample label.

4.1.1.1 Collection of DBS from finger prick

- i. Disinfect the selected site and prick it using a lancet/needle.
- ii. Uniformly saturate the entire circle by quickly and gently touching, not pressing, the puncture site to the filter paper.

- iii. Note: Do not touch the Whatman card at any stage of collection.
- iv. After the collection of five blood spots, clean the site and leave it unbandaged.
- v. Allow the blood spots to air-dry, without the flap covering the spots, in a clean dry place that is protected from rodents or insects and direct sunlight, for at least 4 hours (overnight drying may be needed in areas with higher humidity).
- vi. Do not heat or stack DBS cards or allow them to touch other surfaces during the drying process.
- vii. Tuck in the flap of the card as indicated on the card.
- viii. Clearly label the card with the patient identifier and date, or label it with a prepared barcode label.
- ix. Be sure the DBS card is completely dry before packing.
- x. Insert the DBS card into a gas-impermeable plastic bag containing a desiccant pack and a humidity indicator. Do not store more than one card per bag.
- xi. Ensure that the patient identifier and date (or the prepared barcode label) are on the outside of the bag as well as on the DBS card.
- xii. Seal the plastic bag.
- xiii. Place the sealed bag containing the DBS card in a clean, dry area of the laboratory with no exposure to direct sunlight, free of insects or rodents, and where ambient temperatures will not exceed 30 °C.
- xiv. The room should be temperature- and humidity-controlled (temperature of 20–22 °C and humidity of not more than 22%).
- xv. Check the desiccant pack before shipment of the DBS card and replace it if the colour of the humidity indicator has changed from blue to pink or colourless.
- xvi. Ship the DBS cards at ambient temperature.

4.1.1.2 Preparation of DBS from EDTA, ACD, or heparin tubes

DBS can also be prepared from EDTA, ACD, and heparin blood tubes.

- i. Before starting, mix vacutainers containing anticoagulated blood by inversion.
- ii. Wipe the top of the vacutainer with 70% ethanol before opening the lid.
- iii. Using a micropipette, apply 40 µL of blood onto the circle on the DBS card.
- iv. Air-dry the filter paper thoroughly by following step v above (Section 4.1.1.1), and continue with the rest of the protocol as described above.

4.1.1.3 Shipping of DBS cards

DBS are classified as “Exempt Biological Specimens” according to the ICAO and IATA shipping regulations. DBS bags should be shipped in courier envelopes or boxes under ambient conditions according to the triple packaging system (see Section 3.9.2).

- i. Provide a shipping manifest for all boxes. The shipping manifests must exactly match the label information and the order in the associated shipment, including the global specimen IDs.
- ii. Provide a box map for all boxes. The box maps must exactly match the label information and the order in the associated shipment, including the global specimen IDs.
- iii. Record the courier service and the courier air bill number on the specimen shipment notice.
- iv. Advance notification of shipment must be made to the recipient.

4.1.2 Whole blood

Whole blood is to be prepared from EDTA tubes. The anticoagulated blood can be snap-frozen as it is. If the blood cells are needed intact,

DMSO is needed to keep them alive while freezing.

- i. Dispense 50 µL of DMSO into two 1 mL sterile cryovials.
- ii. Invert the EDTA tube twice, and then add 450 µL of blood to each cryovial.
- iii. Invert the cryovial to mix the whole blood with the DMSO. Note: DMSO is cytotoxic at room temperature; therefore, as soon as it is mixed with blood, it should be placed in a controlled-rate freezer.
- iv. Transfer to –80 °C after at least 4 hours.

4.1.3 Plasma

Plasma collected in EDTA or ACD tubes can be used for bioassays, plasma DNA isolation, proteomic analysis, and biomarker discovery.

- i. Spin the vacutainer (about 9 mL) at 815g for 10 minutes at 4 °C to separate plasma from blood cells.
- ii. After wiping each tube with 70% alcohol, remove about 3 mL of plasma. (The tube can be retained for white blood cell extraction.)
- iii. Transfer to a labelled 15 mL tube, and centrifuge at 2500g for 10 minutes at 4 °C.
- iv. Aliquot plasma into 1 mL labelled cryovials (three or four aliquots).
- v. Place in LN₂ dewar to snap-freeze.
- vi. Store at –80 °C or in LN₂.

The purpose of double-spinning the plasma is to remove all cellular contaminants so that the plasma is suitable for plasma DNA analysis. Therefore, it is extremely important not to disturb the buffy coat after the first spin and any pellet after the second spin.

4.1.4 Platelet-poor plasma

Platelet-poor plasma can be used for the isolation of plasma DNA (from EDTA tubes).

- i. Spin blood at 3200g for 12 minutes at room temperature.
- ii. Pipette off plasma using a plastic Pasteur pipette. Transfer into a tube.
- iii. Spin plasma at 2000g for 10 minutes at 4 °C.
- iv. Aliquot into 1 mL aliquots in labelled cryovials.
- v. Store at -80 °C.
- v. If division of the sample is necessary, at this point pour 25 mL of the sample into another centrifuge tube.
- vi. Spin both tubes at 1200g for 10 minutes.
- vii. Repeat the washing if red blood cells persist.
- viii. Carefully pour off the supernatant.
- ix. Using a swirling motion, remove the pellet with a pipette and transfer it to a labelled cryovial.
- x. Store at -80 °C or in LN₂ until further use.
- vii. Spin at 450g for 10 minutes.
- viii. Pour off the supernatant into a waste container containing chlorine bleach. Add 3 mL of cold freezing mix (10% DMSO, 20% fetal calf serum [FCS], RPMI 1640) and resuspend.
- ix. Dispense the white blood cells into three 1 mL labelled cryovials that have been sitting on ice.
- x. Place on ice. Place vials in a controlled-rate freezer so as to cryopreserve cells under conditions that maintain cell viability. This should be done as soon as possible, because DMSO is toxic at room temperature.
- xi. Transfer on a weekly basis to LN₂ tanks.

4.1.5 Buffy coat cells

The buffy coat is a thin, greyish-white layer of white blood cells (leukocytes and lymphocytes) and platelets covering the top of the packed red blood cells after centrifugation at 450g (from EDTA- or ACD-containing blood tubes).

- i. After having spun the blood, take the buffy coat off with about 100 µL of plasma using a disposable sterile Pasteur pipette; be careful not to lift red blood cells.
- ii. Lyse the remaining red blood cells by addition of red blood cell lysis buffer at room temperature.
- iii. Spin the tube at 450g for 10 minutes at room temperature.
- iv. Resuspend the pellet.
- v. Aliquot as appropriate into labelled cryovials.
- vi. Place in LN₂ to snap-freeze.
- vii. Store in LN₂.

4.1.6 Blood pellets (white blood cells)

Blood pellets can be used for the isolation of DNA (from EDTA or ACD tubes).

- i. Transfer blood from the original tube to a labelled 50 mL tube.
- ii. Fill the tube with Tris-EDTA buffer (formula) and mix vigorously. Place on ice for 5–10 minutes.
- iii. Spin at 1200g for 10 minutes.
- iv. Carefully pour off the supernatant into a waste container containing chlorine bleach. Briefly vortex the pellet and add 50 mL of Tris-EDTA buffer. Shake vigorously.

As an alternative, red blood cells can be lysed by using an ammonium-containing lysis buffer.

4.1.7 White blood cells

White blood cells collected in EDTA or ACD tubes can be used for DNA extraction and the creation of cell lines.

- i. Transfer the remaining blood from the plasma spin to a labelled 50 mL tube containing 10 mL of RPMI 1640.
- ii. After swabbing the lid of this tube with alcohol, aliquot 3 mL of Ficoll into each of two clearly labelled 15 mL tubes.
- iii. Carefully layer 9 mL of diluted blood onto each tube of Ficoll. Treat gently, and do not mix, but spin as soon as possible.
- iv. Spin at 450g for 30 minutes. Note: When centrifuging, do not use the brake.
- v. Remove most of the top layer (RPMI 1640) using a 1 mL Eppendorf tip, and discard about 3–4 mL into a waste container containing chlorine bleach.
- vi. Collect white blood cells with the same Eppendorf tip using a swirling motion to “vacuum up” white blood cells. Do not take too much Ficoll (third layer), because it is toxic to the cells. Place the white blood cells into a labelled 15 mL tube containing 10 mL of RPMI 1640.

Instead of a separation based on Ficoll, a Percoll separation can be used.

4.1.8 Serum

The blood is collected into tubes without addition of anticoagulants. Then, two phases are distinguishable: a solid phase containing fibrin and cells, and a fluid phase containing the serum.

This process should be completed after 30 minutes at room temperature, after which the process described below should start.

- i. Spin blood at 1500g for 10 minutes at room temperature.
- ii. Aliquot 1 mL portions of the supernatant into labelled cryovials.
- iii. Place into LN₂ dewar or dry ice to snap-freeze.
- iv. Transfer to -80 °C freezer or LN₂.

4.2 Processing of solid tissue

Careful and well-documented processing of tissue specimens is crucial to the overall usefulness of the biobank as a resource for scientific research. Detailed records of the first steps in the process of sample handling include the times of anaesthesia administration, ligation of

vessels, and specimen removal from the patient.

These factors are important to assess tissue quality, because they affect the quality of the resulting biomolecules. The most commonly described factor that has an impact on tissue quality is the warm ischaemia time, which is the period from when the blood supply is ligated until the specimen is placed in fixative in the pathology laboratory. Studies have demonstrated that changes in both RNA and protein occur during this time (Dash et al., 2002).

These protocols for collecting and freezing tissue samples were developed within the European Human Frozen Tumour Tissue Bank (TuBaFrost) project (Riegman et al., 2006b) and the Standardisation and Improvement of Generic Pre-analytical Tools and Procedures for In Vitro Diagnostics (SPIDIA) project (Malentacchi et al., 2015).

These recommended protocols contain choices and recommendations for preserving solid tissue, and describe the roles of key people involved in the process. Consult the CEN norms for more detailed information on the processing of snap-frozen tissue and FFPE samples for protein DNA and RNA isolation (CEN/TS 16826-1–2 and CEN/TS 16827-1–3).

4.2.1 Snap-freezing

Snap-freezing is the process by which samples are lowered to temperatures below -70°C very rapidly using dry ice or LN_2 . This method can provide excellent sample integrity and a wide array of options for tissue analysis, including extraction of proteins, RNA, and DNA for use in research diagnosis. Before tissues are stabilized by freezing, the protein, RNA, and DNA profiles can change, and these changes depend on the duration of warm and cold ischaemia and the ambient temperature before

freezing. All the different pre-analytical conditions and durations should be documented.

4.2.1.1 Safety

All procedures should be carried out in accordance with the local codes of practice. Working with LN_2 and isopentane is hazardous; all procedures must comply with local safety rules specific to these chemicals. All tissue must be handled as if it is potentially infectious.

4.2.1.2 Hospital ward

Consent must be obtained from the patient before surgery (if applicable, according to the law and procedures in the country where the samples are being collected).

4.2.1.3 Operating theatre

- i. Deliver the notification of tissue collection (and the consent form, if needed) to the surgeon, or highlight on the operating list.
- ii. The surgeon should:
 - a. complete the pathology form (if possible, in advance);
 - b. perform the operative procedure and record the time of arterial clamping and of excision of the specimen; and
 - c. place the specimen in a labelled sterile pot or bag and put it on ice.
- iii. The operating theatre staff should send the fresh tissue specimen to the pathology department immediately.

4.2.1.4 Histopathology department

- i. Notify the pathologist and the tissue bank research technician (if not already present).
- ii. Check the paperwork and allocate a pathology number to the specimen as routine.

4.2.1.5 Role of the pathologist

- i. Macroscopically describe the specimen as usual.
- ii. Using clean instruments and on a clean surface (sterile foil or clean dissection board), dissect the tissue specimen. Clean or change instruments between dissecting normal tissue and tumour tissue.
- iii. Take representative parts of tissue for routine diagnosis (for fixation and embedding) as a priority, and decide whether there is sufficient material available for the tissue bank.
 - a. Supply the research technician with a tissue sample or samples for biobanking representative parts of the lesion, normal tissue, and pre-malignant conditions.
 - b. Perform QC of frozen tissue and annotation.

4.2.1.6 Role of the technician

- i. Prepare the tissue sample for snap-freezing on a clean surface and using clean instruments; change instruments between preparing normal tissue and tumour tissue. The minimum volume of tissue for snap-freezing is approximately 0.5 cm^3 , although the amount of tissue available will differ depending on the sample site. Smaller fragments should still be snap-frozen and stored in the tissue bank; if there is sufficient material, freeze duplicate samples.
- ii. Pre-cool the freezing medium isopentane (2-methylbutane) until opaque drops begin to appear in the isopentane and the solution becomes misty; this will bring the isopentane towards its freezing point (-160°C), the optimal freezing point for the tissue. Options:
 - a. LN_2 : suspend a vessel of isopentane in LN_2 .
 - b. Dry ice: add dry ice (cardice) to the isopentane until a slush is

- formed, or suspend a vessel of isopentane in dry ice.
- iii. Label cryovials, cryomoulds, or cryostraws with a barcode and/or sequential code (depending on local laboratory practice). Use a waterproof pen with ink that is able to withstand long-term storage at low temperatures. The sequential code is the local inventory code and must not relate to the pathology number or other identifiers. If a barcode is used, readable recognition must also be included to make the sample identifier readable at institutions where there are no barcode readers.
 - iv. Record the local sequential code, the pathology number, the date, the lag time from arterial clamping and excision to freezing, and the type of tissue (the site, and also whether the sample is tumour, normal, and/or pre-malignant) in the inventory book. If a barcode system is in use, the barcode can be scanned into the LIMS and the above-mentioned data recorded.
 - v. Freeze directly in isopentane. Do not remove the tissue from the isopentane until freezing is complete (5 seconds or less, depending on size), but ensure that the sample does not crack. Remove the sample from the isopentane and enclose it in the labelled cryovial. It is good practice to strive to snap-freeze all tissue within 30 minutes of excision from the patient. Tissue subject to a delay of up to 2 hours should still be collected and the delay noted within the local inventory database. Options for freezing:
 - a. Embed the tissue samples in OCT compound and freeze in isopentane, or freeze directly in isopentane. The isopentane used is cooled either by suspension in LN₂ or through addition of dry ice.

- b. Orientate the tissue on a piece of cork and an equally sized piece of Whatman paper soaked in physiological salt solution.
- c. If the cryostraw system is used to introduce a carrot of tissue into the straw, thermally seal each extremity and place in LN₂.

4.2.2 Storage of tissue

Storage of tissue can be done according to different protocols according to the equipment available in the facility. Options for storage:

- i. Transfer the snap-frozen sample from the isopentane to a pre-chilled storage container for transfer to either a locked -80 °C freezer or a LN₂ storage facility in the liquid or vapour phase. For storage for longer than 5 years, LN₂ in the liquid or vapour phase is recommended.
- ii. Place cryostraws in a designated visotube within a goblet (removable LN₂ storage elements) and place in the locked LN₂ repository.
 - a. Store duplicate samples in a different storage facility if this is available.
 - b. Check the backup system for the storage repository – either a backup freezer running constantly or adequate supplies of LN₂.
 - c. Record the storage details in the inventory system, and check earlier data that were entered. At a minimum, the information recorded will include the inventory number (local sequential code), the location, the pathology number, the type of tissue (the site, and also whether the sample is tumour, unaffected/normal, and/or pre-malignant), the lag time between excision and freezing, and the date.

4.2.3 Storage of FFPE blocks and slides

- i. FFPE blocks and sections mounted on slides can be stored at room temperature. Prevent exposure of blocks to sun or extreme temperature variation or humidity.
- ii. Store blocks in moisture-resistant cardboard boxes or plastic storage boxes.
- iii. Transfer details to the computerized database system.
- iv. Update the database when samples are moved or depleted.

4.2.4 Formalin fixation

Formalin fixation is standard practice in most routine histopathology laboratories. The following guidelines address specific issues related to preservation of formalin-fixed specimens in biobanks. Table 6 provides information on the composition of neutral buffered formalin.

- i. Tissue specimens should not be bigger than 3 cm × 2 cm × 0.5 cm.
- ii. Specimens should be fixed in fresh 10% neutral buffered formalin for a minimum of 4 hours and a maximum of 48 hours, after which they should be embedded in paraffin in accordance with conventional techniques.
- iii. All reagents should be DNase- and RNase-free (e.g. prepared using diethylpyrocarbonate [DEPC] water).
- iv. Fixation media, such as Bouin's solution, that contain picric acid should be avoided, because this compound interferes with subsequent PCR analysis of extracted nucleic acids.
- v. Alcohol fixation may be used as an alternative to formalin fixation. For this, tissue is placed into 70% alcohol (diluted with DEPC water) for a minimum of 4 hours. Because of the chemical hazards of formalin, it can be desirable to use alternatives to formalin as a routine

Table 6. Composition of neutral buffered formalin and 70% ethanol

Composition		Total volume
<i>10% neutral buffered formalin (in 40% formaldehyde)</i>		100 mL
100% formaldehyde	37–40 mL	
Na ₂ HPO ₄ (anhydrous)	6.5 g	
NaH ₂ PO ₄	4.0 g	
Distilled water	900 mL	
<i>70% ethanol</i>		
100% absolute alcohol	70 mL of absolute alcohol + 30 mL of water	100 mL
96% ethanol	73 mL of 96% ethanol + 27 mL of water	100 mL

fixative. However, the effect of long-term storage with these alternative fixatives on the desired macromolecules is not always known and should be established empirically.

4.2.5 RNAlater

This substance protects RNA in fresh specimens. It eliminates the need to immediately process or freeze samples.

4.2.5.1 Tissue

Cut the tissue to be smaller than 0.5 cm in at least one dimension, and then submerge the tissue in 5 volumes of RNAlater (e.g. a 0.5 g sample requires about 2.5 mL of RNAlater).

4.2.5.2 Cells

Resuspend the pelleted cells in a small volume of phosphate-buffered saline (PBS) before adding 5–10 volumes of RNAlater.

4.2.5.3 Storage

RNAlater-treated tissue and cell samples can be stored at 4 °C for 1 month, at 25 °C for 1 week, or at –20 °C for an indefinite period. For RNA isola-

tion, simply remove the tissue from RNAlater and process.

4.2.6 Shipment of tissues and slides

FFPE tissues and slides are shipped at ambient temperature in accordance with the established shipment guidelines and protocols of the sending and recipient institutions. Please refer to Section 3.9 for more details.

4.2.7 Quality control for tissue samples

- Ensure that the reagents have not expired and are of the correct composition and volumes.
- Keep high-quality records on all variables related to specimens, FFPE tissues, and slides, including the time of tissue collection, the processing time, and the period of storage before shipment and/or use.

4.2.8 Data to be recorded

- Date and time of tissue collection.
- Number of unprocessed samples, FFPE blocks, and slides prepared.
- Date and time of shipping.
- Any variations or deviations from the

protocol, problems, or issues related to the collection and storage.

4.3 Processing of urine and buccal cells

The following protocols for processing of urine and buccal cells contain recommended procedures.

4.3.1 Urine

- Plastic or glass containers for collection of urine should be clean and dry, should have a 50–3000 mL capacity, a wide mouth, and a leakproof cap, and should be clearly labelled.
- When in transit, urine collections should be maintained on ice or refrigerated.
- Urine should be aliquoted according to the volume needed for analysis or storage.
- Depending on the analyte to be measured, a preservative may be added during collection or before aliquoting.
- Store urine at –80 °C or below in LN₂.

4.3.2 Buccal cells

- A collection kit (containing mouthwash, a 50 mL plastic tube, a

- plastic biohazard bottle, and courier packaging) is mailed or given to the participant, along with an instruction sheet. The participant is to brush their teeth as usual, rinse their mouth out well with water twice, and then wait 2 hours. The participant should not eat or drink anything other than water during this time.
- ii. After 2 hours, 10 mL of commercial mouthwash should be poured into the tube, and then 10 mL of tap water should be added. This diluted mouthwash should be placed into the mouth (without swallowing) and swished around vigorously for 30 seconds.
 - iii. The mouthwash should then be spat back into the plastic tube, and the tube should be sealed tightly.
 - iv. The sample should be sent back to the biobank immediately for processing, or stored at 4 °C until it is sent, but it should be sent within 24 hours.
 - v. When the sample arrives at the laboratory, transfer the mouthwash to 15 mL conical test tubes.
 - vi. Add 35 mL of Tris-EDTA to the mouthwash sample and spin at 450g for 5 minutes.
 - vii. Decant the supernatant and discard.
 - viii. Wash the cells twice, each time with 45 mL of Tris-EDTA.
 - ix. Resuspend the cell pellet in 50 µL of Tris-EDTA and transfer to 2 mL labelled cryovials.
 - x. Store the sample at -80 °C or in LN₂.
- Note: Buccal cells can also be collected with other means, such as brushes.

4.4 Collection and processing of saliva

A research consortium at the University of California, Los Angeles was funded by the United States National Institute of Dental and Craniofacial Research to investigate the human

saliva proteome. The protocol for collection and processing of saliva is derived from the consortium's *Salivary Proteome Handbook Procedures and Protocols* (Hu et al., 2007).

- i. Saliva collection should be done in the morning (aim for 10:00–11:00 am if possible). Ask the subject to refrain from eating, drinking, or oral hygiene procedures for at least 1 hour before the collection.
- ii. The subject should be given drinking water (bottled) and asked to rinse their mouth out well (without drinking the water).
- iii. Five minutes after this oral rinse, the subject should be asked to spit whole saliva into a 50 mL sterile centrifuge tube. The subject should refrain from talking. It is better for the subject to drop their head down and let the saliva run naturally to the front of the mouth, hold this position for a while, and spit into the tube provided. The subject will spit into the collection tube about once a minute for up to 10 minutes. The goal for each whole saliva donation should be about 5 mL. Require that the tube be placed on ice while collecting whole saliva. Remind the subject not to cough up mucus, so that saliva is collected, not phlegm.
- iv. For the collection of submandibular saliva, use 2 × 2-inch cotton gauze to block the opening of each parotid duct. Dry up the floor of the mouth, and block the openings of the sublingual gland (both sides), and have the subject raise their tongue slightly to elevate the opening to the submandibular gland. Begin to collect submandibular saliva by using a sterilized Wolf device. A sterilized and disposable yellow tip (for pipette P200) should be connected into the device and changed after every collection. During the collection, at 2-minute intervals, a few grains of citric acid powder

should be swabbed with a moistened cotton applicator onto the lateral dorsum of the tongue to stimulate the secretion. Aim to collect at least 200 µL of submandibular saliva.

- v. For the collection of sublingual saliva, the protocol is similar to that described above for collection of submandibular saliva. The only difference is that the ductal orifices of the submandibular gland are blocked off. Aim to collect > 100 µL of sublingual saliva every time.
- vi. For the collection of parotid saliva, use a parotid cup to collect the saliva. Parotid cups may be placed bilaterally if the clinical investigator so chooses. This will enable the simultaneous collection from each parotid gland. The citric acid stimulation should be performed as described above. Aim to collect > 1 mL of parotid saliva. The first 0.1 mL of parotid saliva collected should be discarded, to ensure that fresh parotid saliva is obtained.
Note: The collected samples should be kept on ice at all times before processing.
- vii. For sample processing using proteinase inhibitors, to each 100 µL of saliva:
 - a. Add 0.2 µL of proteinase inhibitor cocktail from standard stock solution (Sigma, P8340), and invert gently.
 - b. Add 0.3 µL of sodium orthovanadate (Na₃VO₄) (Sigma, S6508) from standard stock of 400 mM, and invert gently.
- viii. Centrifuge the specimens at 2600g for 15 minutes at 4 °C (if you note that incomplete separation has occurred, increase the spin time to 20 minutes). Then:
 - a. Remove the supernatants from the samples and label them with the term “super”, which stands for the supernatant phase of the saliva.

- b. Taking care not to disturb the pellet and keeping the pellet as is in the original tubes, label the original tubes as “pellet”.
- ix. Freeze the samples at -80°C .

4.5 Processing of cervical cells

In a Pap smear test, a sample of cells is taken from the uterine cervix using a wooden spatula or a brush, smeared onto a slide, and examined under a microscope for abnormal cells (precancer or cancer). This protocol is a selected protocol from diverse collection procedures.

Note the following:

- i. It is best not to take a smear from a woman who is actively menstruating or has symptoms of an acute infection. Slight bleeding is acceptable.
- ii. Pregnancy is not an ideal time for a Pap smear, because it can give misleading results.

4.5.1 Taking the sample of cells

Insert the long tip of the spatula into the cervical os, and rotate the spatula through a full circle (360°). If the cervical broom brush is used, place the tip of the brush into the cervical os, and rotate the brush gently through three 360° circles.

4.5.2 Taking the Pap smear

- i. Smear both sides of the spatula (or the contents of the brush) onto the glass slide with one or two careful swipes. If any abnormalities are seen outside the area

sampled, take a separate specimen and smear it onto another slide.

- ii. Immediately fix each slide. Either use spray fixative, at a right angle to, and at a distance of 20 cm from, the slide, or immerse the slide in a container of 95% ethanol for at least 5 minutes. If the slide is not fixed immediately, the cells will dry and become misshapen; it will then not be possible to read the slide accurately in the laboratory.
- iii. Gently close and remove the speculum.
- iv. Place all used instruments in decontamination solution.

4.5.3 After taking the smear

- i. Label the frosted edge of each slide carefully.
- ii. On the patient record, note and illustrate any features you have noted: visibility of the transformation zone, inflammation, ulcers or other lesions, or abnormal discharge. Note whether other samples were taken, for example Pap smears of other areas, and if the woman has been referred elsewhere, note to whom and when.

4.6 Processing of hair and nails

These protocols are recommended for collecting hair or nail specimens.

4.6.1 Hair

Head hair may be collected as follows.

- i. Along an imaginary line drawn across the middle of the back of

the head from the centre of one ear to the centre of the other, gather a lock of hair at least the thickness of a pencil, and tie it together near the root end (near the scalp) using a small string or a rubber band.

- ii. Cut the hair as close to the scalp as possible without cutting the scalp.
- iii. Maintain the horizontal position of the hairs in the bundle by wrapping the cut section in aluminium foil or plastic wrap.
- iv. Indicate the root end and the tip end by marking the foil or plastic wrap with a permanent marker or with a paper label. **Do not use tape on the hair itself.**
- v. Place the specimen in a clean, dry, labelled paper envelope for shipment to the laboratory. Note whether bleaches, hair dye, or medications (e.g. selenium or minoxidil) were used.

Please note that hair from other sources (pubic, axillary, beard, moustache, chest, etc.) may also be analysed if head hair is not available.

4.6.2 Nails

A clean pair of nail clippers should be used. To clean nail clippers thoroughly, they should be rubbed with alcohol swabs. Nails should be clean of all polish, dirt, and debris. Nail clippings from each finger or toe should be collected and packaged separately in plastic bottles. Each bottle should be labelled with the mass of the nail collected and its source (e.g. right index finger) (NMS Labs and ExperTox).

References

- ABN (2007). Biorepository protocols. Australasian Biospecimen Network. Available from: http://www.iss.it/binary/ribo/cont/ABN_SOPs_Review_Mar07_final.pdf.
- Aleksandrova K, Pischon T, Jenab M, Bueno-de-Mesquita HB, Fedirko V, Norat T, et al. (2014). Combined impact of healthy lifestyle factors on colorectal cancer: a large European cohort study. *BMC Med.* 12(1):168. <http://dx.doi.org/10.1186/s12916-014-0168-4> PMID:25319089
- ARMA (2016). Brunswick Material Transfer Agreement. Cambridge, UK: Association of Research Managers and Administrators. Available from: <https://www.mrc.ac.uk/documents/pdf/brunswick-material-transfer-agreement/>.
- Ayache S, Panelli M, Marincola FM, Stroncek DF (2006). Effects of storage time and exogenous protease inhibitors on plasma protein levels. *Am J Clin Pathol.* 126(2):174–84. <http://dx.doi.org/10.1309/3WM7XJ7RD8BCLNKX> PMID:16891190
- BBMRI-ERIC (2016). BBMRI-ERIC Directory 2.0. Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium. Available from: <http://bbmri-eric.eu/bbmri-eric-directory>.
- BCCM (2016). MOSAICC Micro-organisms sustainable use and access regulation international code of conduct. Belgian Co-ordinated Collections of Micro-organisms. Available from: <http://bccm.belspo.be/projects/mosaicc>.
- Beauchamp TL, Childress JF (2013). Principles of biomedical ethics. 7th edition. Oxford University Press.
- Bergmann MM, Rehm J, Klipstein-Grobusch K, Boeing H, Schütze M, Drogan D, et al. (2013). The association of pattern of lifetime alcohol use and cause of death in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Int J Epidemiol.* 42(6):1772–90. <http://dx.doi.org/10.1093/ije/dyt154> PMID:24415611
- Betsou F, Gunter E, Clements J, DeSouza Y, Goddard KA, Guadagni F, et al. (2013). Identification of evidence-based biospecimen quality-control tools: a report of the International Society for Biological and Environmental Repositories (ISBER) Biospecimen Science Working Group. *J Mol Diagn.* 15(1):3–16. <http://dx.doi.org/10.1016/j.jmoldx.2012.06.008> PMID:23195791
- Bravo E, Calzolari A, De Castro P, Mabile L, Napolitani F, Rossi AM, et al. (2015). Developing a guideline to standardize the citation of bioresources in journal articles (CoBRA). *BMC Med.* 13(1):33. <http://dx.doi.org/10.1186/s12916-015-0266-y> PMID:25855867
- Brochhausen M, Fransson MN, Kanaskar NV, Eriksson M, Merino-Martinez R, Hall RA, et al. (2013). Developing a semantically rich ontology for the biobank-administration domain. *J Biomed Semantics.* 4(1):23. <http://dx.doi.org/10.1186/2041-1480-4-23> PMID:24103726
- Burke W, Diekema DS (2006). Ethical issues arising from the participation of children in genetic research. *J Pediatr.* 149 (1 Suppl):S34–8. <http://dx.doi.org/10.1016/j.jpeds.2006.04.049> PMID:16829241
- Calam RR, Cooper MH (1982). Recommended “order of draw” for collecting blood specimens into additive-containing tubes. *Clin Chem.* 28(6):1399. PMID:7074955
- Cambron-Thomsen A, Thorisson GA, Mabile L; BRIF Workshop Group (2011). The role of a Bioresource Research Impact Factor as an incentive to share human bioresources. *Nat Genet.* 43(6):503–4. <http://dx.doi.org/10.1038/ng.831> PMID:21614086
- CCB (2014). Biobank quality standard: collecting, storing and providing human biological material and data for research. London, UK: National Cancer Research Institute Confederation of Cancer Biobanks. Available from: <http://ccb.ncri.org.uk/wp-content/uploads/2014/03/Biobank-quality-standard-Version-1.pdf>.
- CEN (2015). European Committee for Standardization (CEN) norms. Available from: <https://standards.cen.eu/index.html>.
- Chaigneau C, Cabioch T, Beaumont K, Betsou F (2007). Serum biobank certification and the establishment of quality controls for biological fluids: examples of serum biomarker stability after temperature variation. *Clin Chem Lab Med.* 45(10):1390–5. <http://dx.doi.org/10.1515/CCLM.2007.160> PMID:17635068
- Chen H, Pang T (2015). A call for global governance of biobanks. *Bull World Health Organ.* 93(2):113–7. <http://dx.doi.org/10.2471/BLT.14.138420> PMID:25883404
- CIOMS (2002). International ethical guidelines for biomedical research involving human subjects. Geneva, Switzerland: Council for International Organizations of Medical Sciences and World Health Organization. Available from: www.cioms.ch/publications/layout_guide2002.pdf.

- CLSI (2005). Collection, transport, preparation, and storage of specimens for molecular methods; approved guideline. CLSI document MM13-A, Vol. 25, No. 31. Wayne (PA), USA: Clinical and Laboratory Standards Institute. Available from: <http://shop.clsi.org/molecular-methods-documents/MM13.html>.
- CLSI (2007). Procedures for the collection of diagnostic blood specimens by venipuncture; approved standard – sixth edition. CLSI document GP41-A6, Vol. 27, No. 26. Wayne (PA), USA: Clinical and Laboratory Standards Institute. Available from: http://shop.clsi.org/c.1253739/site/Sample_pdf/GP41A6_sample.pdf.
- Council of Europe (2006). Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin. Available from: <https://wcd.coe.int/ViewDoc.jsp?id=977859&BackColorInternet=9999CC&BackColorIntranet=FFBB55&BackColorLogged=FFAC75>.
- Crowe FL, Key TJ, Appleby PN, Overvad K, Schmidt EB, Egeberg R, et al. (2012). Dietary fibre intake and ischaemic heart disease mortality: the European Prospective Investigation into Cancer and Nutrition-Heart study. *Eur J Clin Nutr*. 66(8):950–6. <http://dx.doi.org/10.1038/ejcn.2012.51> PMID:22617277
- Cryo Bio System (2013). Fundamentals of cryobiology. Available from: http://www.cryobiosystem-imv.com/media/fundamentals_of_cryobiology_037984100_1259_18112013.pdf.
- Dash A, Maine IP, Varambally S, Shen R, Chinnaiyan AM, Rubin MA (2002). Changes in differential gene expression because of warm ischemia time of radical prostatectomy specimens. *Am J Pathol*. 161(5):1743–8. [http://dx.doi.org/10.1016/S0002-9440\(10\)64451-3](http://dx.doi.org/10.1016/S0002-9440(10)64451-3) PMID:12414521
- De Cecco L, Musella V, Veneroni S, Cappelletti V, Bongarzone I, Callari M, et al. (2009). Impact of biospecimens handling on biomarker research in breast cancer. *BMC Cancer*. 9(1):409. <http://dx.doi.org/10.1186/1471-2407-9-409> PMID:19930681
- De Jongh R, Vranken J, Vundelinckx G, Bosmans E, Maes M, Heylen R (1997). The effects of anticoagulation and processing on assays of IL-6, sIL-6R, sIL-2R and soluble transferrin receptor. *Cytokine*. 9(9):696–701. <http://dx.doi.org/10.1006/cyto.1997.0217> PMID:9325019
- DGI (2016). The 9 classes of dangerous goods. Dangerous Goods International. Available from: <http://www.dgiglobal.com/classes>.
- Eiseman E, Bloom G, Brower J, Clancy N, Olmsted SS (2003). Case studies of existing human tissue repositories: “best practices” for a biospecimen resource for the genomic and proteomic era. Santa Monica (CA), USA: RAND Corporation. Available from: http://www.rand.org/pubs/monographs/2004/RAND_MG120.pdf.
- ESMO (2010). Improving rare cancer care in Europe – recommendations on stakeholder actions and public policies. European Society for Medical Oncology. Available from: http://www.rarecancerseurope.org/content/download/16802/296577/file/ESMO_Rare_Cancers_recommendations_2010.pdf.
- European Commission (2012a). Biobanks for Europe: a challenge for governance. Directorate-General for Research and Innovation. Brussels, Belgium: European Commission. Available from: https://ec.europa.eu/research/swafs/pdf/pub_archive/biobanks-for-europe_en.pdf.
- European Commission (1995). Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Official Journal L 281/31–50. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML>.
- European Commission (2012b). Proposal for a Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation). Brussels, Belgium: European Commission. Available from: <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A52012PC0011>
- European Commission (2016). Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Official Journal L 119/1–88. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.119.01.0001.01.ENG.
- European Society of Radiology (2015). ESR position paper on imaging biobanks. *Insights Imaging*. 6(4):403–10. <http://dx.doi.org/10.1007/s13244-015-0409-x> PMID:25999018
- Furuta K, Schacter B (2015). Report on status of ISO276/WG2 on biobanks and bioresources: international standards for biobanking. *Biopreserv Biobank*. 13(6):452–3. <http://dx.doi.org/10.1089/bio.2015.29041.kf> PMID:26697915
- GA4GH (2016). Global Alliance for Genomics and Health: about the Global Alliance. Available from: <http://genomicsandhealth.org/about-global-alliance>.
- GA4GH (2015a). Global Alliance for Genomics and Health: consent policy. Available from: <https://genomicsandhealth.org/files/public/Consent%20Policy%20%28Final%20-%2027%20May%202015%29.pdf>.
- GA4GH (2015b). Global Alliance for Genomics and Health: privacy and security policy. Available from: [https://genomicsandhealth.org/files/public/Privacy%20and%20Security%20Policy%20\(Final%20-%2026%20May%202015\).pdf](https://genomicsandhealth.org/files/public/Privacy%20and%20Security%20Policy%20(Final%20-%2026%20May%202015).pdf).

- García-Closas M, Egan KM, Abruzzo J, Newcomb PA, Titus-Ernstoff L, Franklin T, et al. (2001). Collection of genomic DNA from adults in epidemiological studies by buccal cytobrush and mouthwash. *Cancer Epidemiol Biomarkers Prev.* 10(6):687–96. PMID:11401920
- Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al.; American College of Medical Genetics and Genomics (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med.* 15(7):565–74. <http://dx.doi.org/10.1038/gim.2013.73> PMID:23788249
- Griese M (1999). Pulmonary surfactant in health and human lung diseases: state of the art. *Eur Respir J.* 13(6):1455–76. <http://dx.doi.org/10.1183/09031936.99.13614779> PMID:10445627
- Gündisch S, Slotta-Huspenina J, Verderio P, Ciniselli CM, Pizzamiglio S, Schott C, et al. (2014). Evaluation of colon cancer histomorphology: a comparison between formalin and PAXgene tissue fixation by an international ring trial. *Virchows Arch.* 465(5):509–19. <http://dx.doi.org/10.1007/s00428-014-1624-4> PMID:25085759
- H3Africa (2013). H3Africa guidelines for community engagement. Developed by the H3Africa Working Group on Ethics and Regulatory Issues for the Human Heredity and Health (H3Africa) Consortium. Available from: http://www.h3africa.org/images/GuidelinesPolicyDocs/CE%20Guidelines_Final.pdf.
- Hainaut P, Caboux E, Bevilacqua G, Bosman F, Dassel T, Hoefler H, et al. (2009). Pathology as the cornerstone of human tissue banking: European consensus expert group report. *Biopreserv Biobank.* 7(3):157–60. <http://dx.doi.org/10.1089/bio.2010.7303> PMID:24835883
- Hall JA, Daidone MG, Peters GJ, Harbeck N, Lacombe D, Sleijfer S (2011). Integrating collection of biospecimens in clinical trials: the approach of the European Organization for Research and Treatment of Cancer. *Biopreserv Biobank.* 9(2):181–6. <http://dx.doi.org/10.1089/bio.2011.0003> PMID:24846265
- Harris JR, Burton P, Knoppers BM, Lindpaintner K, Bledsoe M, Brookes AJ, et al. (2012). Toward a roadmap in global biobanking for health. *Eur J Hum Genet.* 20(11):1105–11. <http://dx.doi.org/10.1038/ejhg.2012.96> PMID:22713808
- Heins M, Heil W, Withold W (1995). Storage of serum or whole blood samples? Effects of time and temperature on 22 serum analytes. *Eur J Clin Chem Clin Biochem.* 33(4):231–8. PMID:7626695
- Hens K, Lévesque E, Dierickx K (2011). Children and biobanks: a review of the ethical and legal discussion. *Hum Genet.* 130(3):403–13. <http://dx.doi.org/10.1007/s00439-011-1031-8> PMID:21660506
- Hu S, Loo JA, Wong DT (2007). Human saliva proteome analysis. *Ann N Y Acad Sci.* 1098(1):323–9. <http://dx.doi.org/10.1196/annals.1384.015> PMID:17435138
- Hubel A, Spindler R, Skubitz AP (2014). Storage of human biospecimens: selection of the optimal storage temperature. *Biopreserv Biobank.* 12(3):165–75. <http://dx.doi.org/10.1089/bio.2013.0084> PMID:24918763
- HUPO (2015). Human Proteome Organization: about HUPO. Available from: <https://www.hupo.org/about-hupo/>.
- IATA (2015a). Dangerous Goods Regulations (DGR). Montreal, Canada: International Air Transport Association. Available from: <http://www.iata.org/publications/dgr/Pages/index.aspx>.
- IATA (2015b). IATA classification: Division 6.2 – Infectious substances. Montreal, Canada: International Air Transport Association. Available from: <https://www.iata.org/whatwedo/cargo/dgr/Documents/infectious-substance-classification-DGR56-en.pdf>.
- IATA (2015c). Packing instructions – Class 6 – Toxic and infectious substances. Montreal, Canada: International Air Transport Association. Available from: <https://www.iata.org/whatwedo/cargo/dgr/Documents/packing-instruction-650-DGR56-en.pdf>.
- ICAO (1986). Technical instructions for the safe transport of dangerous goods by air. Montreal, Canada: International Civil Aviation Organization. Available from: <http://www.icao.int/safety/DangerousGoods/Pages/technical-instructions.aspx>.
- ISBER (2012). 2012 Best practices for repositories: collection, storage, retrieval, and distribution of biological materials for research. International Society for Biological and Environmental Repositories. *Biopreserv Biobank.* 10(2):79–161. <http://dx.doi.org/10.1089/bio.2012.1022> PMID:24844904
- ISO (2012). ISO 15189:2012. Medical laboratories – Requirements for quality and competence. Geneva, Switzerland: International Organization for Standardization. Available from: http://www.iso.org/iso/catalogue_detail?csnumber=56115.
- Kaye J, Hawkins N (2014). Data sharing policy design for consortia: challenges for sustainability. *Genome Med.* 6(1):4. <http://dx.doi.org/10.1186/gm523> PMID:24475754
- Kersting M, Prokein J, Bernemann I, Drobek D, Illig T (2015). IT systems for biobanking: a brief overview. Hannover, Germany: Hannover United Biobank, Hannover Medical School. Available from: http://www.markus-kersting.de/wp-content/uploads/2014/12/Poster_Biobank_Systeme_HUB_2014_12_01_mk_b.pdf.
- King IB, Satia-Abouta J, Thornquist MD, Bigler J, Patterson RE, Kristal AR, et al. (2002). Buccal cell DNA yield, quality, and collection costs: comparison of methods for large-scale studies. *Cancer Epidemiol Biomarkers Prev.* 11(10 Pt 1):1130–3. PMID:12376522
- Knoppers BM, Chisholm RL, Kaye J, Cox D, Thorogood A, Burton P, et al.; P3G International Steering Committee (2013). A P3G generic access agreement for population genomic studies. *Nat Biotechnol.* 31(5):384–5. <http://dx.doi.org/10.1038/nbt.2567> PMID:23657386

- Kon OL (2001). Tissue banking for biomedical research. Commissioned paper for the Human Genetics Subcommittee of the Bioethics Advisory Committee. National Cancer Centre Singapore. Available from: <http://www.bioethics-singapore.org/images/uploadfile/52533%20PMHT%20AppendixB-Dr%20Kon.pdf>.
- Kosseim P, Dove ES, Baggaley C, Meslin EM, Cate FH, Kaye J, et al. (2014). Building a data sharing model for global genomic research. *Genome Biol.* 15(8):430. <http://dx.doi.org/10.1186/s13059-014-0430-2> PMID:25221857
- Kumari S, Ichhpujani RL (2000). Guidelines on standard operating procedures for microbiology. New Delhi, India: World Health Organization Regional Office for South-East Asia. Available from: http://apps.searo.who.int/PDS_DOCS/B0217.pdf.
- Laurie G (2011). Reflexive governance in biobanking: on the value of policy led approaches and the need to recognise the limits of law. *Hum Genet.* 130(3):347–56. <http://dx.doi.org/10.1007/s00439-011-1066-x> PMID:21766192
- Lehmann S, Guadagni F, Moore H, Ashton G, Barnes M, Benson E, et al. (2012). Standard preanalytical coding for biospecimens: review and implementation of the Sample PREanalytical Code (SPREC). *Biopreserv Biobank.* 10(4):366–74. <http://dx.doi.org/10.1089/bio.2012.0012> PMID:24849886
- Lengellé J, Panopoulos E, Betsou F (2008). Soluble CD40 ligand as a biomarker for storage-related preanalytic variations of human serum. *Cytokine.* 44(2):275–82. <http://dx.doi.org/10.1016/j.cyt.2008.08.010> PMID:18851919
- Lin DW, Coleman IM, Hawley S, Huang CY, Dumpit R, Gifford D, et al. (2006). Influence of surgical manipulation on prostate gene expression: implications for molecular correlates of treatment effects and disease prognosis. *J Clin Oncol.* 24(23):3763–70. <http://dx.doi.org/10.1200/JCO.2005.05.1458> PMID:16822846
- Mager SR, Oomen MH, Morente MM, Ratcliffe C, Knox K, Kerr DJ, et al. (2007). Standard operating procedure for the collection of fresh frozen tissue samples. *Eur J Cancer.* 43(5):828–34. <http://dx.doi.org/10.1016/j.ejca.2007.01.002> PMID:17329097
- Makowski GS, Davis EL, Hopfer SM (1996). The effect of storage on Guthrie cards: implications for deoxyribonucleic acid amplification. *Ann Clin Lab Sci.* 26(5):458–69. PMID:8879364
- Malentacchi F, Pizzamiglio S, Verderio P, Pazzagli M, Orlando C, Ciniselli CM, et al. (2015). Influence of storage conditions and extraction methods on the quantity and quality of circulating cell-free DNA (ccfDNA): the SPIDIA-DNAplax External Quality Assessment experience. *Clin Chem Lab Med.* 53(12):1935–42. <http://dx.doi.org/10.1515/cclm-2014-1161> PMID:25883202
- Mallette, A., Tassé AM, Knoppers BM (2013). P3G model framework for biobank governance. Public Population Project in Genomics and Society. Available from: http://www.p3g.org/system/files/biobank_toolkit_documents/P3G%20Model%20Framework%20for%20Biobank%20Governance%20FINAL%20%281%29_0.pdf.
- Matharoo-Ball B, Thomson BJ (2014). Nottingham Health Science Biobank: a sustainable bioresource. *Biopreserv Biobank.* 12(5):312–6. <http://dx.doi.org/10.1089/bio.2014.0056> PMID:25340939
- Mayrhofer MT, Holub P, Wutte A, Litton JE (2016). BBMRI-ERIC: the novel gateway to biobanks: from humans to humans. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitschutz.* 59(3):379–84. <http://dx.doi.org/10.1007/s00103-015-2301-8> PMID:26860601
- Medical Research Council and Wellcome Trust (2014). Framework on the feedback of health-related findings in research. Available from: <https://www.mrc.ac.uk/documents/pdf/mrc-wellcome-trust-framework-on-the-feedback-of-health-related-findings-in-researchpdf>.
- Mendy M, Kirk GD, van der Sande M, Jeng-Barry A, Lesi OA, Hainaut P, et al. (2005). Hepatitis B surface antigenaemia and alpha-fetoprotein detection from dried blood spots: applications to field-based studies and to clinical care in hepatitis B virus endemic areas. *J Viral Hepat.* 12(6):642–7. <http://dx.doi.org/10.1111/j.1365-2893.2005.00641.x> PMID:16255766
- Mendy M, Lawlor R, Van Keppel AL, Riegman P, Betsou F, Cohen O (2013). Biosampling and biobanking. In: Rebbeck TR, editor. Handbook for cancer research in Africa. Brazzaville, Republic of the Congo: World Health Organization Regional Office for Africa; pp 77–94. Available from: <http://apps.who.int/iris/bitstream/10665/100065/1/9789290232216.pdf>.
- Miller JM, Astles R, Baszler T, Chapin K, Carey R, Garcia L, et al.; Biosafety Blue Ribbon Panel; Centers for Disease Control and Prevention (CDC) (2012). Guidelines for safe work practices in human and animal medical diagnostic laboratories. Recommendations of a CDC-convened, Biosafety Blue Ribbon Panel. *MMWR Suppl.* 61(1):1–102. PMID:22217667
- Moore HM, Kelly AB, Jewell SD, McShane LM, Clark DP, Greenspan R, et al. (2011). Biospecimen reporting for improved study quality (BRISQ). *Cancer Cytopathol.* 119(2):92–101. <http://dx.doi.org/10.1002/cncy.20147> PMID:21433001
- Morente MM, Mager R, Alonso S, Pezzella F, Spatz A, Knox K, et al. (2006). TuBaFrost 2: standardising tissue collection and quality control procedures for a European virtual frozen tissue bank network. *Eur J Cancer.* 42(16):2684–91. <http://dx.doi.org/10.1016/j.ejca.2006.04.029> PMID:17027255
- MRC (2014). Human tissue and biological samples for use in research: operational and ethical guidelines. United Kingdom Medical Research Council. Available from: <http://www.mrc.ac.uk/publications/browse/human-tissue-and-biological-samples-for-use-in-research/>.

- Mulot C, Stücker I, Clavel J, Beaune P, Lorient MA (2005). Collection of human genomic DNA from buccal cells for genetics studies: comparison between cytobrush, mouthwash, and treated card. *J Biomed Biotechnol.* 2005(3):291–6. <http://dx.doi.org/10.1155/JBB.2005.291> PMID:16192688
- NCI (2011). Informed consent template for cancer treatment trials. United States National Cancer Institute. Available from: <https://www.rtog.org/LinkClick.aspx?fileticket=H5dVynC5MVA%3D&tabid=347>.
- NCI (2016). NCI best practices for biospecimen resources. Biorepositories and Biospecimen Research Branch, United States National Cancer Institute. Available from: <http://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf>.
- NCRI (2009). Samples and data for research: template for access policy development. London, UK: National Cancer Research Institute. Available from: <http://www.ncri.org.uk/wp-content/uploads/2013/09/Initiatives-Biobanking-2-Access-template.pdf>.
- Norlin L, Fransson MN, Eriksson M, Merino-Martinez R, Anderberg M, Kurtovic S, et al. (2012). A minimum data set for sharing biobank samples, information, and data: MIABIS. *Biopreserv Biobank.* 10(4):343–8. <http://dx.doi.org/10.1089/bio.2012.0003> PMID:24849882
- Nuffield Council on Bioethics (2002). The ethics of research related to healthcare in developing countries. Available from: <http://nuffieldbioethics.org/wp-content/uploads/2014/07/Ethics-of-research-related-to-healthcare-in-developing-countries-1.pdf>.
- Ockè MC, Schrijver J, Obermann-de Boer GL, Bloemberg BP, Haenen GR, Kromhout D (1995). Stability of blood (pro)vitamins during four years of storage at -20 degrees C: consequences for epidemiologic research. *J Clin Epidemiol.* 48(8):1077–85. [http://dx.doi.org/10.1016/0895-4356\(94\)00232-F](http://dx.doi.org/10.1016/0895-4356(94)00232-F) PMID:7775995
- OECD (2001). Biological resource centres: underpinning the future of life sciences and biotechnology. Paris, France: Organisation for Economic Co-operation and Development. Available from: <https://www.oecd.org/sti/biotech/2487422.pdf>.
- OECD (2007). OECD best practice guidelines for biological resource centres. Paris, France: Organisation for Economic Co-operation and Development. Available from: <http://www.oecd.org/sti/biotech/38777417.pdf>.
- OECD (2009). OECD guidelines on human biobanks and genetic research databases. Paris, France: Organisation for Economic Co-operation and Development. Available from: <https://www.oecd.org/sti/biotech/44054609.pdf>.
- P3G (2016). Public Population Project in Genomics and Society: about P3G. Available from: <http://www.p3g.org/about-p3g>.
- Pilch B, Mann M (2006). Large-scale and high-confidence proteomic analysis of human seminal plasma. *Genome Biol.* 7(5):R40. <http://dx.doi.org/10.1186/gb-2006-7-5-r40> PMID:16709260
- Precision Medicine Initiative Working Group (2015). The Precision Medicine Initiative Cohort Program – building a research foundation for 21st century medicine. Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH. United States National Institutes of Health. Available from: <https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-working-group-report-20150917-2.pdf>.
- RCR (2011). Management of incidental findings detected during research imaging. London, UK: The Royal College of Radiologists. Available from: https://www.rcr.ac.uk/sites/default/files/publication/BFCR%2811%298_ethics.pdf.
- Reynolds HY (2000). Use of bronchoalveolar lavage in humans – past necessity and future imperative. *Lung.* 178(5):271–93. <http://dx.doi.org/10.1007/s004080000032> PMID:11147312
- Riegman PH, Dinjens WN, Oomen MH, Spatz A, Ratcliffe C, Knox K, et al. (2006a). TuBaFrost 1: uniting local frozen tumour banks into a European network: an overview. *Eur J Cancer.* 42(16):2678–83. <http://dx.doi.org/10.1016/j.ejca.2006.04.031> PMID:17027254
- Riegman PH, Oomen MH, Dinjens WN, Oosterhuis JW, Lam KH, Spatz A, et al. (2006b). TuBaFrost: European virtual tumor tissue banking. *Adv Exp Med Biol.* 587:65–74. http://dx.doi.org/10.1007/978-1-4020-5133-3_6 PMID:17163156
- Rohrmann S, Linseisen J, Nöthlings U, Overvad K, Egeberg R, Tjønneland A, et al. (2013). Meat and fish consumption and risk of pancreatic cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 132(3):617–24. <http://dx.doi.org/10.1002/ijc.27637> PMID:22610753
- Smith LM, Burgoyne LA (2004). Collecting, archiving and processing DNA from wildlife samples using FTA databasing paper. *BMC Ecol.* 4(1):4. <http://dx.doi.org/10.1186/1472-6785-4-4> PMID:15072582
- Steinberg K, Beck J, Nickerson D, Garcia-Closas M, Gallagher M, Caggana M, et al. (2002). DNA banking for epidemiologic studies: a review of current practices. *Epidemiology.* 13(3):246–54. <http://dx.doi.org/10.1097/00001648-200205000-00003> PMID:11964924
- Tassé AM (2011). The return of results of deceased research participants. *J Law Med Ethics.* 39(4):621–30. <http://dx.doi.org/10.1111/j.1748-720X.2011.00629.x> PMID:22084848
- Thorogood A, Joly Y, Knoppers BM, Nilsson T, Metrakos P, Lazaris A, et al. (2014). An implementation framework for the feedback of individual research results and incidental findings in research. *BMC Med Ethics.* 15:88. <http://dx.doi.org/10.1186/1472-6939-15-88> PMID:25539799

- UK Biobank Ethics and Governance Council (2016). Ethics and governance framework. Available from: <http://egcukbiobank.org.uk/Ethics-and-governance-framework>.
- UK Biobank Ethics and Governance Council (2015). Feedback of health related findings: foreground principles and background perspectives. London, UK: Wellcome Trust. Available from: http://egcukbiobank.org.uk/sites/default/files/UKBEGC_FeedbackReport.pdf.
- UK Biobank Ethics and Governance Council (2009). Workshop report: involving publics in biobank research and governance. London, UK: Wellcome Trust. Available from: <http://egcukbiobank.org.uk/sites/default/files/meetings/EGC%20workshop%20report.pdf>.
- UNECE (2015). United Nations recommendations on the transport of dangerous goods – model regulations, 19th revised edition. United Nations Economic Commission for Europe. Available from: http://www.unece.org/trans/danger/publi/unrec/rev19/19files_e.html.
- van Ommen GJ, Törnwall O, Bréchet C, Dagher G, Galli J, Hveem K, et al. (2015). BBMRI-ERIC as a resource for pharmaceutical and life science industries: the development of biobank-based Expert Centres. *Eur J Hum Genet.* 23(7):893–900. <http://dx.doi.org/10.1038/ejhg.2014.235> PMID:25407005
- Vaught J, Kelly A, Hewitt R (2009). A review of international biobanks and networks: success factors and key benchmarks. *Biopreserv Biobank.* 7(3):143–50. <http://dx.doi.org/10.1089/bio.2010.0003> PMID:24835880
- Vaught J, Rogers J, Carolin T, Compton C (2011). Biobankonomics: developing a sustainable business model approach for the formation of a human tissue biobank. *J Natl Cancer Inst Monogr.* 2011(42):24–31. <http://dx.doi.org/10.1093/jncimonographs/lgr009> PMID:21672892
- Viertler C, Groelz D, Gündisch S, Kashofer K, Reischauer B, Riegman PH, et al. (2012). A new technology for stabilization of biomolecules in tissues for combined histological and molecular analyses. *J Mol Diagn.* 14(5):458–66. <http://dx.doi.org/10.1016/j.jmoldx.2012.05.002> PMID:22749745
- Voegele C, Alteyrac L, Caboux E, Smans M, Lesueur F, Le Calvez-Kelm F, et al. (2010). A sample storage management system for biobanks. *Bioinformatics.* 26(21):2798–800. <http://dx.doi.org/10.1093/bioinformatics/btq502> PMID:20807837
- Voegele C, Bouchereau B, Robinot N, McKay J, Damięcki P, Alteyrac L (2013). A universal open-source Electronic Laboratory Notebook. *Bioinformatics.* 29(13):1710–2. <http://dx.doi.org/10.1093/bioinformatics/btt253> PMID:23645817
- Wallace SE, Gournay EG, Laurie G, Shoush O, Wright J (2016). Respecting autonomy over time: policy and empirical evidence on re-consent in longitudinal biomedical research. *Bioethics.* 30(3):210–7. <http://dx.doi.org/10.1111/bioe.12165> PMID:25960157
- WHO (2006). Biorisk management: laboratory biosecurity guidance. Geneva, Switzerland: World Health Organization. Available from: www.who.int/csr/resources/publications/bio_safety/WHO_CDS_EPR_2006_6.pdf.
- WHO (2005). Guidance on regulations for the transport of infectious substances. Geneva, Switzerland: World Health Organization. Available from: http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2005_22r%20.pdf.
- WHO (2012). Guidance on regulations for the transport of infectious substances 2013–2014. Applicable as from 1 January 2013. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/78075/1/WHO_HSE_GCR_2012.12_eng.pdf.
- WHO (2015). Guidance on regulations for the transport of infectious substances 2015–2016. Applicable as from 1 January 2015. Geneva, Switzerland: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/149288/1/WHO_HSE_GCR_2015.2_eng.pdf.
- WMA (2013). WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. World Medical Association. Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- WMA (2016). WMA Declaration of Taipei on ethical considerations regarding health databases and biobanks. World Medication Association. Available from: <http://www.wma.net/en/30publications/10policies/d1/>.
- Yokota M, Tatsumi N, Nathalang O, Yamada T, Tsuda I (1999). Effects of heparin on polymerase chain reaction for blood white cells. *J Clin Lab Anal.* 13(3):133–40. [http://dx.doi.org/10.1002/\(SICI\)1098-2825\(1999\)13:3<133::AID-JCLA8>3.0.CO;2-0](http://dx.doi.org/10.1002/(SICI)1098-2825(1999)13:3<133::AID-JCLA8>3.0.CO;2-0) PMID:10323479
- Yuille M, van Ommen GJ, Bréchet C, Cambon-Thomsen A, Dagher G, Landegren U, et al. (2008). Biobanking for Europe. *Brief Bioinform.* 9(1):14–24. <http://dx.doi.org/10.1093/bib/bbm050> PMID:17959611

IARC policy on access to human biological materials

A1.1 Definitions

- 1.1 The IARC Biobank (IBB): the IBB is a centralized biological resource storage facility for samples collected from studies conducted worldwide by IARC in collaboration with international partners (<http://ibb.iarc.fr/>).
- 1.2 The Laboratory Services and Biobank Group (LSB): LSB is responsible for the management of the IBB. The Group also provides services in pre-analytical sample processing and shipment.
- 1.3 Biological resources: include human tissues, cells, biological fluids/derived products, and associated sample quality data.
- 1.4 Sample collections: include biological resources based on common characteristics (e.g. sera from individuals from a population-based study; a clinical collection of breast cancer tissues).
- 1.5 Associated data: include anonymized data associated with biological samples, sample annotations, and data on sample quality.
- 1.6 Steering committee for multicentre studies: the steering committee has a coordinating role for a particular study, with responsibilities for coordinating research activities, including with regard to use of the study's biological resources.
- 1.7 IARC Principal Investigator (PI): the PI is the IARC scientist who is responsible for the sample collection at IARC.
- 1.8 IARC Custodian (CU): the CU is the IARC scientist to whom the responsibility for the sample collection was assigned after the departure of the original IARC PI.
- 1.9 Biobank Steering Committee (BSC): the BSC is the committee that oversees the biobanking activities at IARC.
- 1.10 Biobank Application sub-Committee (BAC): the BAC is the sub-Committee appointed by the BSC to assist in the handling of requests for human sample access.
- 1.11 IARC Ethics Committee (IEC): the role of the IEC is to provide ethical evaluation of all IARC projects within its competence (<http://ethics.iarc.fr/>).

- 1.12 Requestor: the requestor is a scientist affiliated with a public research institution or organization based in any country who is applying to access IARC sample collections for the purpose of research.
- 1.13 User: the user is a requestor who has received the necessary approvals to access IARC samples.
- 1.14 Material Transfer Agreement (MTA): the MTA is an agreement developed and signed between IARC and the host institute of the requestor, which governs the terms and conditions under which the parties will collaborate.
- 1.15 Study results: all laboratory results obtained from the use of IARC samples.

A1.2 Sample access: principles and policies

A1.2.1 Introduction

The IARC Biobank (IBB) comprises one of the largest and most varied collections of cancer-related samples in the world. The IBB is publicly funded by IARC Participating States and research grants and hosts more than 50 different studies, led or coordinated by IARC scientists.

Over the years, IARC has developed or coordinated a considerable number of large molecular epidemiological studies involving specimen collections. These studies are extremely diverse in their size, design, and governance and in the type of biomarker analyses involved. Study designs include case series, prevalence studies, case–control studies, and cohort studies. Most of the samples in the IBB are body fluids, including plasma, serum, and urine as well as extracted DNA samples.

A table of biospecimens stored at IARC is available on the IBB website (http://ibb.iarc.fr/docs/collection_table.pdf). The table provides details of sample origin, primary study design, key words describing the collection, and the name of the IARC PI/CU to contact for further information by potential requestors.

The IBB includes, as part of its governance structure, the Biobank Steering Committee (BSC) and the IARC Ethics Committee (IEC). The BSC oversees the IBB and provides advice to the Director in terms of the strategic development of IARC biobank activities. The IEC provides ethical guidance and evaluates all IARC projects within its competence.

A1.2.2 Guiding principles

The mission of IARC includes promoting cancer research internationally. As a publicly funded international organization with a mandate for collaborative research, IARC wishes to ensure that biospecimens stored within the Agency are being put to the best possible use. Within this context, the samples stored at IARC are available for research projects consistent with IARC's scientific goals and the IARC/WHO legal and ethical standard practices.

The principle of access means that samples and data entrusted to the Agency should be put to best possible scientific use taking into account the best interest of the participants and for public benefit. In particular, IARC PIs and CUs are encouraged to identify new potential uses and users of the resources and to make cancer researchers worldwide aware of these progressions in scientific research.

Access to and use of IBB biological samples are governed by the following principles:

- As an overarching principle, the biological samples stored under the Agency's custodianship in the IBB remain the property of the national collaborating centre as the original source, unless otherwise specified under a separate agreement. Consequently, access to IBB biological samples for third parties will only be granted by IARC after consultation and agreement with the relevant national centre and the IARC PI/CU as applicable.
- Applications by requestors for access to IARC's biological samples will be required to follow the sample request procedure described below.
- The confidentiality and data protection principles of IARC also apply to the IBB by maintaining participants' confidentiality and anonymity; the rights, privacy, and consent of participants must be protected and respected at all times.

- IBB biological samples will be made available for use in a timely and responsible manner taking into account the need to ensure data validity and sample integrity.
- IBB biological samples can only be used for research and non-profit purposes.
- All extensions to the use of human biological material beyond the aims and objectives for which samples were initially collected and provided, subject to the above-mentioned overarching principle, must also be approved by the IEC and be in line with the medium- and long-term objectives of IARC.
- To ensure ongoing enrichment of the IARC biological sample collections, users will be required to provide IARC with the results arising from specific analyses (including biological sample analysis, derived variables, etc.) carried out using the data and/or samples provided by the IBB, unless otherwise specified in a previous agreement.
- Management for access purposes will be cost-neutral to the IBB; requestors will contribute to the cost of sample retrieval, pre-analytical processing, and shipment according to standard costs published by the IBB.
- IARC reserves the right to refuse any request without a necessity to provide justification for decisions made, although appropriate feedback will normally be provided regarding a refusal for access.

A1.3 Limits on the use of IBB biological samples

IBB biological samples can only be used for research and non-profit purposes by investigators affiliated with public sector research organizations. Access may be denied for certain specific reasons, for example:

- The available sample volume is insufficient for delivery of samples without compromising the future scientific value of the collection.
- The project overlaps with ongoing or planned projects or analyses, leading to unnecessary duplication of work and a waste of materials and other resources.
- The scientific quality of the project is considered inadequate. Scientific quality and ability to administer the project will be more specifically considered by the IARC PI/CU and the IEC. The applicant will have to show evidence of expertise, resources, and financing for the successful completion of the project.
- There are ethical or legal issues with the proposal, including, for example, when the proposed use is not consistent with the specified purpose of the specimen collection in the original informed consent.
- The proposed project is in contradiction with IARC's mission and goals towards public health or against the above-mentioned guiding principles.

A1.4 Procedure for accessing IARC biological resources and monitoring

A1.4.1 Sample request procedure

Access to IARC biological samples is a six-step procedure, summarized in Fig. A1.1.

Step 1: Requests for accessing IARC biospecimens should be initially directed to the IARC Biobank (ibb@iarc.fr). The requestor will be required to complete a Project Application Form (CIRC 66 11/2013) and a Partner Profile Form (CIRC 67 11/2013) to provide information on project, requestor, and requesting institute.

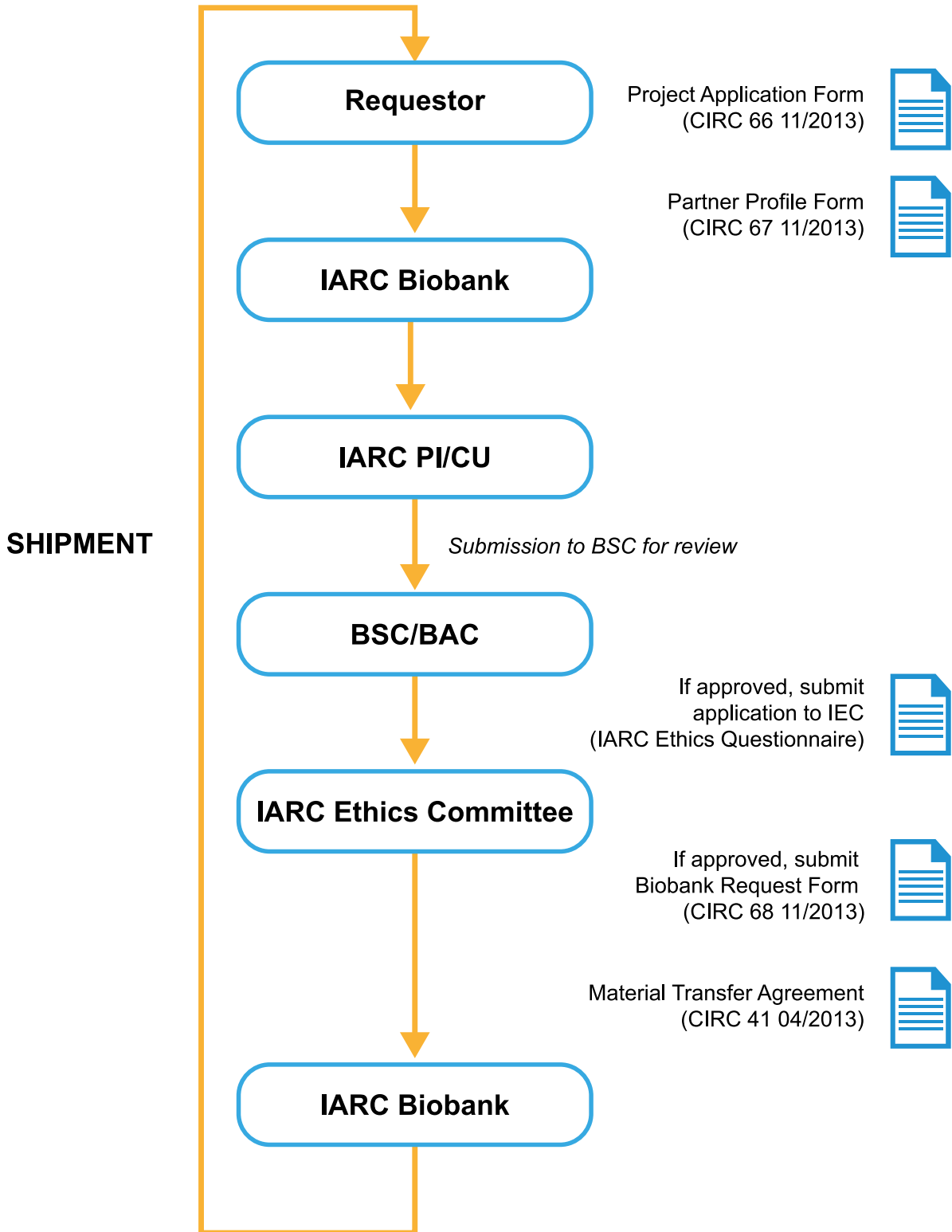
Step 2: After review of the Project Application Form and Partner Profile Form, the IARC Biobank submits the request to the IARC PI/CU, to assist in the handling of the request.

Step 3: The IARC PI/CU will carry out an initial review of the request for recommendation to the BSC/BAC.

- In the case of multicentre studies with already defined procedures, the IARC PI/CU will contact the steering committee of the study, when there is one in place (e.g. the steering committee for the European Prospective Investigation into Cancer and Nutrition [EPIC] study). The relevant steering committee will review the request according to its established protocol and provide feedback through the IARC PI/CU.

Step 4: Once the request has been approved by the BSC/BAC, or the relevant steering committee when applicable, the requestor is informed. The IARC Ethics Questionnaire must then be submitted to the IEC for ethical approval.

Fig. A1.1. Sample request procedure. BAC, Biobank Application sub-Committee; BSC, Biobank Steering Committee; CU, IARC custodian; IEC, IARC Ethics Committee; PI, IARC principal investigator.



Step 5: Subject to ethical approval by the IEC, a Biobank Request Form (CIRC 68 11/2013) must be completed by the requestor and sent to the IARC Biobank, together with all required supporting documents; these will enable the IARC Biobank to prepare the requested samples and the related MTA (using form CIRC 41 04/2013).

Step 6: Upon receipt of the signed MTA and payment of relevant sample access charges, the IARC Biobank will proceed with shipment of the samples for the project.

A1.4.2 Monitoring and follow-up

In order for the IARC Biobank to monitor use of IARC biological resources, the requestor will be required to submit a Project Progress Report (using form CIRC 69 11/2013) on a 6-monthly basis after samples have been sent.

A1.5 Responsibilities of the requestor/requesting institution

In submitting requests to access IARC biological resources, requestors have the following responsibilities.

A1.5.1 Requesting and receiving

Requestors should:

- be affiliated to a recognized academic or other public research organization;
- follow the sample request procedure described above, and accept the provisions and general principles contained in the present policy;
- pay all sample access charges as invoiced by the IARC Biobank; and
- comply with any request to discard sample(s) if notified by IARC that subject(s) have withdrawn permission for the use of donated sample(s).

A1.5.2 During the study

Requestors should:

- accept and undertake research in the context of the ownership of samples and data as stipulated in the IARC MTA (CIRC 41 04/2013);
- provide plans for publication of the study results in peer-reviewed journals within 1 year of reception of the samples (or provide clear justification for the requirement of a longer period);
- report on progress made within the project (using form CIRC 69 11/2013), every 6 months until the study has been completed and remaining samples, if any, have been destroyed or returned to IARC (as is stipulated in the MTA); and
- ensure compliance with the terms and conditions of the MTA; users found to be in breach of the MTA will be denied future access to the IARC biological resources.

A1.5.3 At the end of the study

Requestors should:

- report on the outcome of the study upon completion, including publications (using form CIRC 69 11/2013);
- return any unused samples to IARC, unless otherwise stated in the MTA (CIRC 41 04/2013); and
- provide IARC with a copy of the results generated within the project through use of the IARC biological resources (raw data or other relevant format agreed upon with IARC) within 6 months of publication.

A1.6 Acknowledgement in publications

Full acknowledgement of the sources of all biological resources must be included in any publications that arise from access to and use of the IBB resources. All publications must include at a minimum the following acknowledgement: "The research was made possible using the data/samples provided by the IARC Biobank." In addition, where applicable, the acknowledgements must refer to the original sample source centre as well as the source of funding. Specific authorship rules may apply in some instances; these will be agreed upon on a case-by-case basis.

A1.7 Reference documents

- 7.1 IARC Policy on Access to Human Biological Materials (IARC/Access Policy/Group-BSC/EN/11/2013): <http://ibb.iarc.fr/docs/iarc-policy-access.pdf>
- 7.2 Project Application Form (CIRC 66 11/2013): http://ibb.iarc.fr/docs/IBB_ProjectForm.dot
- 7.3 Partner Profile Form (CIRC 67 11/2013): http://ibb.iarc.fr/docs/IBB_PartnerForm.dot
- 7.4 IARC Ethics Questionnaire: <http://ethics.iarc.fr/Submission/index.php>
- 7.5 Biobank Request Form (CIRC 68 11/2013): http://ibb.iarc.fr/docs/IBB_RequestForm.dot
- 7.6 MTA Form (CIRC 41 04/2013): <http://ibb.iarc.fr/access/index.php>
- 7.7 Project Progress Report Form (CIRC 69 11/2013): http://ibb.iarc.fr/docs/IBB_ReportForm.dot

Guidelines for informed consent

These guidelines are made up of the following three sections: design decisions; guidance for broad consent participant information sheets and consent forms; and links to biobank-specific templates for participant information sheets and consent forms.

A2.1 Design decisions

This section contains useful points to consider when designing participant information sheets and consent forms for biobanks.

A2.1.1 Where do I start?

The templates for participant information sheets and consent forms listed in Section A2.3 are a good place to start to get an idea of the general contents of participant information sheets and consent forms.

A2.1.2 Will I provide the participant information sheet and the consent form as separate documents?

It is common practice to provide these documents separately, and this may be the most practical solution for biobanks in terms of the storage and distribution of these documents. However, in clinical trials that involve biobanking, the two documents are often combined, which ensures that the participant information sheet and the consent form used are stored together.

A2.1.3 Will I require that the participants initial or tick the boxes on the consent form?

It is recommended that biobanks follow best practice in clinical trials, which requires that participants initial the boxes on the consent form. It is worth making this requirement clear on the consent form itself.

A2.1.4 Will I provide opt-in/opt-out statements on the consent form?

The most critical thing to consider before providing opt-in/opt-out statements is whether the biobank can support this. For example, allowing the participant to opt out of research that involves animals but not being able to enforce this when distributing samples will cause problems for the biobank. The most common problem is that the biobank database does not record the participant's decisions, resulting in a time-consuming search for the consent form each time a sample is distributed. If opt-in/opt-out statements are provided, add two boxes, marked with "yes" and "no", to the consent form so that it is clear that these statements are optional. See the information on dynamic consent in Table A2.2 for examples of possible opt-in/opt-out statements.

A2.1.5 Should I consider what might happen to the samples in the future?

It is very important that when the participant information sheets and consent forms are being developed, the biobank should carefully consider the possible future use of the samples and data, so that the biobank can inform the participant at the outset and will not need to re-contact them for further permissions. Some examples of areas to consider are: issues that are potentially ethically or legally challenging, such as transfer of samples or data across national borders or use of samples and data by commercial researchers (see the recommendations in Section 3.1.2.3); return of results and incidental findings (see Section 3.1.4); access to and sharing of samples and data (see Section 3.1.5); when participants might need to be re-contacted; and whether the participants need to receive information or give consent via an interpreter. If an interpreter is needed, lines may need to be added to the consent form to allow the interpreter to sign the form.

A2.2 Guidance for broad consent participant information sheets and consent forms

Table A2.1 provides information on the headings that would be expected on a biobank participant information sheet aiming for a broad consent approach. The optional sections apply only to specific types of biobanks or specific types of research being conducted.

Table A2.1. Sections for inclusion on a biobank participant information sheet, indicating whether these are optional or mandatory; the initial statements or questions can be used as titles in the participant information sheet

Section	Mandatory or optional?
Why are human tissues and body fluids vital for research?	Mandatory
What is the purpose of the biobank? Answering questions such as: • What is the aim of the biobank? • Is the biobank disease-specific? • Is unspecified future research (secondary use) planned?	Mandatory
Who has approved the research?	Mandatory
Why am I being invited?	Mandatory
What will happen if I agree to participate? Answering questions such as: • Is access to medical or other health-related records planned?	Mandatory
Will my samples be used in genetic research?	Mandatory
What are the benefits and risks of taking part?	Mandatory
Who will have access to my samples and data? Answering questions such as: • Can the samples and/or data be transferred to/used by/shared with other researchers/biobanks/institutions? – Is this individual-level/aggregated/genetic data? – Will the samples be shared? • Can the samples and/or data be transferred to/used by/shared with researchers in other countries? • Will the data be included in a public database? • Can the samples be accessed by commercial organizations?	Mandatory

Table A2.1. Sections for inclusion on a biobank participant information sheet, indicating whether these are optional or mandatory; the initial statements or questions can be used as titles in the participant information sheet (continued)

Section	Mandatory or optional?
How will my samples and data be stored? Answering questions such as: • What are the privacy/data protection mechanisms?	Mandatory
How long will my samples and data be stored?	Mandatory
Will I find out results of the research? Answering questions such as: • Will any results (general or individual) be returned to the participant? • How will any return of results take place? • What options does the participant have?	Mandatory
What if I change my mind? Answering questions such as: • What withdrawal options are there? • What happens to samples and/or data after withdrawal?	Mandatory
Contact details for the biobank	Mandatory
Will my cells or tissue be used for research involving animals?	Optional
Will my cells or tissue be used to create cell lines?	Optional
Will my cells or tissue be used for research linked to reproduction?	Optional
Can I donate cells or tissues after death?	Optional
Will I receive any compensation for being involved?	Optional
Detailed explanations about tissue, cells, and DNA: Human cells and tissues DNA and genes How cells and tissue are collected Use of human tissue and fluids for medical education and audit Details for specific types of tissues or donors (e.g. stem cells, healthy donors)	Optional
Detailed information about biobank governance Answering questions such as: • What type of committee reviews applications for access to biobank samples and/or data, and who serves on this committee? • What type of contracts must those accessing the biobank samples and/or data complete (e.g. Material Transfer Agreements)? • How is the biobank governed?	Optional
Detailed information for postmortem donors	Optional
Information about whether samples and/or data are collected from vulnerable persons or populations and how that works Answering questions such as: • Can samples and/or data be used after children participating in the study become adults?	Optional
Preferences for re-contact (see Table A2.2)	Optional

Table A2.2 provides information on the consent statements that might be expected on a biobank consent form aiming for a broad consent approach. Some of these consent options may be required by the legal system in a particular country, for example the need to gain specific consent to access medical records. In addition, legal requirements may mean that consent is needed to transfer samples or data across national borders if this may occur in the biobank. Opt-in/opt-out statements should be included only when these are recordable, actionable by the biobank, and practicable.

Table A2.2. Items for consideration on a biobank consent form, including options that may be provided as consent statements and possible opt-in/opt-out statements

Area	Example of statement on consent form (<i>italic means that text must be adapted</i>)
The participant confirms that they have read and understood a particular participant information sheet	I have read and understood the information pamphlet [<i>version/date</i>]. I have had the opportunity to consider the information it contains and to ask all the questions I had. I have obtained satisfactory answers to my questions.
The participant confirms that they have had the risks and benefits of participation explained to them	The risks and benefits of my participation have been explained to me.
The participant understands that participation in the research is voluntary	I understand that my participation is voluntary. I am free to withdraw at any time, without giving any reason.
Use of samples and data by commercial researchers	I understand that some of these research projects may be carried out by commercial organizations and that I will not benefit financially if this research leads to new treatments or medical tests.
Use of samples for genetic research	These samples may be used for genetic research.
Access to medical records	I give permission for information about me, provided by me or found in my medical and other health-related records, to be supplied to and stored by [<i>name of biobank</i>] for research purposes. <i>or</i> I give permission for access to my medical and other health-related records, and for long-term storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).
Contacting general practitioner for information	My general practitioner can be contacted for information relevant to my condition and current treatment.
<i>Possible opt-in/opt-out statements (to be used when these are recordable, actionable by the biobank, and practicable)</i>	
Re-contacting participants to ask for further information or about participation in new studies	We may like to re-contact you in the future to ask for further samples or information that may be of use to researchers, or for further permissions relating to the use of the samples and information you have already donated. I agree that [<i>name of biobank</i>] may re-contact me in the future to ask me to provide additional samples or information related to [<i>name of biobank</i>] or to invite me to participate in a new study. I understand that this does not oblige me to provide the samples or to participate in further research.
Re-contacting participant with information arising from the study The text included here in the consent form will depend on the biobank's policy in relation to return of study results	<i>These are the areas where permission may be requested, if relevant:</i> <i>A. Agreement or opt-in/opt-out to receiving general research project results, for example in the form of a newsletter or email.</i> <i>B. Agreement or opt-in/opt-out to receiving the results of any physical examination conducted as part of the sample or data collection, in which case also briefly explain the circumstances under which this may take place and the mechanisms by which it would be achieved.</i> <i>C. Agreement or opt-in/opt-out to receiving the results of any tests for infectious diseases conducted on the samples. Briefly explain the related circumstances and mechanisms, as in B.</i> <i>D. Agreement or opt-in/opt-out to receiving individual-level research results or other incidental findings arising from the research. Briefly explain the related circumstances and mechanisms, as in B.</i>
Transfer of samples or data across national borders	Do you give permission for samples to be sent to centres outside [<i>name of country</i>]?
Experiments involving animals	Do you give permission for your samples to be used in experiments using [<i>animal type, e.g. rodents (rats or mice)</i>]?
Creation of cell lines from the tissue	These samples may be used to create cell lines.

A2.3 Links to biobank-specific templates for participant information sheets and consent forms

The documents and links listed below can be used as reference materials to produce biobank participant information sheets and consent forms.

1. World Health Organization (WHO):
 - WHO Informed Consent Form Templates: http://www.who.int/rpc/research_ethics/informed_consent/en/
 - WHO Informed Consent Form Template for Consent for Storage and Future Use of Unused Samples: http://www.who.int/entity/rpc/research_ethics/Informed%20consent%20for%20sample%20storage.doc?ua=1
2. Public Population Project in Genomics and Society (P3G):
 - P3G-IPAC Generic Clauses/Agreements Database, to assist researchers in building documents: <http://www.p3g.org/resources/ipac>
 - P3G Generic Information Pamphlet and Consent Form (2014): http://www.p3g.org/system/files/biobank_toolkit_documents/P3G%20Generic%20Info%20Pamphlet%20and%20Consent%20Form%20for%20Biobanks_0.pdf
3. Global Alliance for Genomics and Health (GA4GH):
 - Consent tools in relation to international data sharing: <http://www.p3g.org/sites/default/files/site/default/files/GA4GH-Consent%20Tools-FINAL%20%281%29.pdf>
4. Human Heredity and Health in Africa (H3Africa):
 - H3Africa Guidelines for Informed Consent (2013), guidance for designing consent materials for genomic research in African contexts: http://h3africa.org/images/FinalPoliciesDocuments/H3A%20WG%20Guidelines%20Informed%20Consent_FINAL_01082013.pdf
5. Beskow LM, Friedman JY, Hardy NC, Lin L, Weinfurt KP (2010). Developing a simplified consent form for biobanking. PLoS One. 5(10):e13302. <http://dx.doi.org/10.1371/journal.pone.0013302>
6. Strategic Tissue Repository Alliances Through Unified Methods (STRATUM) project:
 - Consent Models Work Package tools, including a two-page combined participant information sheet and consent form template and an in-depth biobank participant information sheet template: <http://stratumbiobanking.org/consent.html>
7. UK Biobank:
 - Consent form: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Consent_form.pdf
 - Participant information sheet: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Participant_information_leaflet.pdf?phpMyAdmin=trmKQIYdjjnQlgJ%2CfAzikMhEnx6
8. Children's Cancer and Leukaemia Group (CCLG):
 - Information sheets for involving children in biobank research: <http://www.cclg.org.uk/tissue-bank/information-for-patients>

Template consent form for biobanking

This template is based on Public Population Project in Genomics and Society (P3G) database resources.

General considerations

- The information brochure and consent form should be clear, in plain language, easy to read, and written in large fonts (size may vary according to the target population). The date of the version of the form should be identified in the footer, and pages should be numbered “Page x of y”. In the information pamphlet, the term “you” should be used to refer to potential participants. In the consent form, the term “I” should be used.
- Researchers should follow a culturally sensitive process of providing information to obtain participants’ consent. In particular, in some communities, obtaining the agreement of local community leadership for the proposed research is mandatory and this agreement should be sought before the preparation of consent forms and before obtaining the consent of any participant from that community. In addition, the degree of autonomy that individuals have may vary between cultures. In preparing for the consent process, the researcher must therefore consider applicable norms and traditions.
- Other considerations may be specific to certain populations (e.g. research involving children, vulnerable populations), and additional requirements may apply to the consent process. Researchers should ensure that all such specific requirements are taken into account when preparing consent materials.

The following text presents generic template language in the preparation of biobanking consent forms for adult participants (*italic means that text must be adapted*).

[Insert logo and letterhead of biobank]

INFORMATION PAMPHLET AND CONSENT FORM FOR PARTICIPANTS
[Name of biobank/Title of study]

[Name of Principal Investigator]

[Name of organization]

[Names of funders and sponsors]

[Contact information]

Preamble

We are inviting you to take part in the creation of a resource for research called [identify biobank/title of study]. Your participation is voluntary. Before you decide whether or not to participate and sign the consent form, please take your time to read this information pamphlet. This document may contain information or words that you do not understand. Please ask us if there is something you do not understand, or if you would like more information. It is important that you fully comprehend what participation in this project entails.

1. Nature and objectives of the study

[Describe the study purpose, in addition to the current and future scope of research.]

The [identify biobank/title of study] is a resource that contains biological materials, such as DNA samples, in addition to health/lifestyle information and personal information (data) on a large number of people over time. It has been set up so that it can be used in the future as a resource for researchers undertaking a wide range of medical research.

Optional clauses

- If applicable, provide specific information as to “large number of people involved”;
- If applicable, specify types of future “medical research” (e.g. specific disease/research area).

This [biobank/study] has two main aims. The first aim is to gain a better understanding of the interactions between genes, the environment, and our lifestyle that influence our health or cause diseases. The second aim is to use this understanding to develop new drugs, genetic tests, and treatments, and to create public health strategies that will benefit everyone.

Your participation in this project involves you giving broad consent. This means that you allow your personal information and samples to be used for a variety of future medical research approved by an ethics committee, but which cannot be specified at the present time.

Optional clauses

- If applicable, specify types of medical research that will use the biobank (e.g. specific disease/research area). If other types of research are indicated, add: “Some future types of research may require your specific consent.”
- If data linkage is planned, add: “Your personal data will have to be regularly updated by being linked to your medical record and other sources of administrative health information. If, after reading this information pamphlet, you do not agree to any of these aspects, you should not take part.”

2. Prospective participants

[Outline the total number of expected participants, and explain why the individual was selected to participate.]

The [biobank/study] involves the participation of [number] people between [age] and [age] years of age from [region].

You have been chosen from [identify database, registry, etc.] to be invited to participate.

Optional clauses

- If applicable, specify targeted disease or specific illness.
- If applicable, add: “You are being asked to participate because you are a patient at [name of hospital/institution]” or “You have been identified by your personal doctor as someone who is in the correct age bracket and meets the relevant criteria to participate.”

However, please note that you should not participate if [enumerate exclusion criteria].

3. Researchers and institutions conducting the study

[This section should also disclose any conflicts of interest.]

The [biobank/study] is a research effort led by [identify institution(s)]. This institution is responsible for the practical aspects, such as data collection and secure storage of samples and data. It will be the point of contact for you, and for the researchers who use the biobank. The person who has overall responsibility for the management of the biobank is [name of executive director]. If you need to contact the biobank for any reason, please telephone [name] at [telephone number], email [email address], or write to [mailing address].

The [biobank/study] is supported by [identify institution(s)] and is funded by [name(s) of sponsor(s)/government agency]. The [name of study] has received approval from [name of research ethics committee].

4. What does participation involve?

[Outline study procedures; what participants are expected to do throughout the course of the study; include types of information being gathered (samples and data); amount of information being gathered; tests to be performed (manner of acquiring samples); questionnaires; length of time; location, etc.]

If you choose to participate, you will be asked to:

- (1) Undergo a physical assessment, which involves you:
 - attending an appointment at [insert location], which will last approximately [insert duration of appointment];
 - providing a [insert sample type (e.g. blood, urine, saliva)] sample of [insert amount/measures of samples taken], which the biobank will store;
 - answering a questionnaire on [insert topics (e.g. your health and lifestyle, family, and medical history)] that will take approximately [insert length of time]; and
 - allowing our staff members to perform basic measurements, including [insert measurement types (e.g. measuring your weight, height, and blood pressure)].

The physical assessment will be conducted by [qualified health professionals (e.g. nurses, physicians)]. In total, it should take approximately [insert duration of entire assessment].

- (2) Allow your samples and data to be stored and used in coded form by researchers for many years [if applicable, specify length of time].

Optional clauses

- If applicable, add: “Allow your personal information contained in your administrative health records to be accessed now and in the future.”
- If applicable, add: “We may continue to access these records even if you become unable to make decisions for yourself or after your death.”

5. Study risks

[List possible disadvantages or risks (e.g. discomfort, malaise, stress, transportation costs, time).]

Your participation entails few risks. The physical assessment involves little risk. The taking of a blood sample for DNA analysis may cause some bleeding, bruising, dizziness, and/or discomfort. You should be aware that certain physical measurements that will be taken [e.g. *your weight*] and/or some of the questions you will be asked in the questionnaire may be personal in nature. The storage of your samples and the extraction of DNA involve minimal risk, because rigorous security measures are in place (as described below) and all samples will be kept in a high-security facility.

Unless required by law or a court order, access to this information will not be offered to third parties such as employers, insurance companies, or family members. Only authorized staff members will have access to your information. For requests for access by researchers, they will not be given any information that would allow them to identify you. The utmost care will be taken to ensure the confidentiality of all data.

6. Potential study benefits

You will not directly benefit by taking part in this study, because the most important health benefits will be realized many years from now. Rather, your participation will contribute to the advancement of scientific knowledge and help future generations, because your participation is expected to improve our understanding of genetic and non-genetic factors that affect the health of the population.

However, any immediate, life-threatening condition will be reported to you immediately so that you can obtain emergency care.

7. Privacy and confidentiality

[Specify who will have access to the participants' personal information and the types of information.]

The information in your file could include your past and present medical history, in addition to information about your life and test results from examinations and procedures done during this study. Your file could also contain information such as your name, sex, date of birth, and ethnic origin.

All information collected about you will remain confidential. No one will have access to your directly identifying information, that is information that identifies you through specific identifiers such as your name, your social insurance number, and your personal health number.

To protect your privacy, your information will be coded. “Coded” means that your information has been stripped of any direct or indirect identifiers, which are replaced by a numerical code. A list that links the coded information with your identity will be kept secure, to allow for your re-identification in certain circumstances. Your unique code will enable us to link the information from different data sets to you, but at the same time, will enable us to keep your identity confidential when we give your data to other researchers to use.

While study information could be printed in journals or shared with other people at scientific meetings or for teaching purposes, it will not be possible to identify you. Your identity will be kept confidential. All data will be presented as group data, rather than individual data.

Also, specific rules regulate access to your data and samples by researchers. Researchers will not have access to any of your personal information.

8. Access to your data and samples

Only approved research studies can gain access to your coded data and samples, in order to protect your privacy. An approved researcher can be from *[outline the approved users as per access policy (e.g. academia, a charitable organization, a private company, or a public institution)]*. All projects must be approved by the *[identify the access committee]*, who will essentially review whether the proposed study has received prior scientific and ethical approval by the relevant committees, and that the study fits within the purpose of the biobank and meets other general requirements.

Researchers have to sign agreements that control their access to data and samples, and they are not permitted to disclose or transfer data or samples to anyone else or to use them for purposes other than those agreed to. Researchers must also agree that they will not attempt to re-identify you from your data and samples and should immediately report any re-identification of participants to the biobank.

We also expect to receive access requests from overseas researchers and international collaborators. These researchers must follow the same procedures as all other researchers. All access is subject to the strictest scientific and ethical scrutiny, as described above.

When transferred samples are no longer needed for the purpose for which they were given to researchers, researchers must *[return them to the biobank or destroy them]*. Researchers must also return their research results to the biobank, so that those results are available for other researchers to use in the future. This facilitates future research and enriches the database of the *[name of biobank]*.

9. Storage of your data and samples

[Specify where the data and samples will be stored (location) and how long they will be stored.]

Your data and samples will be stored in a database at *[name of institution/hospital and location]*. This is a secure facility, meeting international security and safety standards for laboratories. Also, in order to keep your information confidential, numerous safeguards are in place. In particular, we will:

- remove personal identifiers such as your name or date of birth from your samples and records;
- assign codes to your samples and records;
- keep your personal details separate from your data and samples;
- use stringent security measures to prevent unauthorized use, including strict access controls, computer security and data encryption techniques, confidentiality agreements, and staff training;
- hold information in secure databases, which can be accessed only by the authorized staff members and by approved researchers, who will only have access to coded information; and
- have a decoding step that will allow us to re-link your personal details with your samples and information, should you want to withdraw from the study or in order to make sure that the database records are correct.

Your samples and data will be kept for a period of *[identify period of conservation (e.g. number of years)]*. After this period, your samples and data will be *[destroyed or transferred]*, unless an ethics committee decides otherwise.

Optional clause

If samples and data are transferred at the end of the period of conservation, specify where the data and samples will be transferred *[name of biobank]*.

10. Withdrawing from the study

[Indicate treatment (planned use and storage procedures) of already collected data/samples.]

You may choose whether or not you wish to take part in this study. If you choose to take part now, you can change your mind later and withdraw, meaning stop participating at any time and for any reason.

You can withdraw by *[indicate ways for participant to signal their withdrawal (e.g. by telephone, by email, by mail, and whom to contact)]*. You will receive a letter confirming your withdrawal.

If you withdraw, your identifiable samples and the data derived from your samples and other personal information will be destroyed if possible. Data that are already being used for research cannot be destroyed or removed.

The code that enables us to re-link your samples and personal information will be deleted so that no further information about you will be collected. Only your signed consent form and a copy of the letter confirming your withdrawal will be kept as a record of your wishes. Such a withdrawal will prevent information about you from contributing to further research and analyses.

11. Return of research results

[Outline the biobank's policy as to returning results, including the results from the laboratory assessment and physical assessment, general research results, individual research results, and incidental findings. If the biobank's policy is to return individual results, indicate who has the obligation of returning these results and for how long.]

(a) Results from laboratory assessment and initial physical assessment

You can choose to immediately receive the results of your physical assessment, such as *[specify results that can be returned]*, from your *[type of assessment (e.g. BMI, ECG, blood pressure)]*. These results will be provided with the appropriate explanations (e.g. your measurements alongside “standard measures”). You can decide whether you want these measurements sent to you or not.* If, during the physical assessment, we find something that we feel should be explored further, we will advise you to see your personal doctor, because the assessment is not a clinical check-up.

Optional clause

* If applicable, add: “You can ask that they be sent to your personal doctor.”

(b) General research results

General research results, meaning aggregate results derived from the analysis of the data and samples of research participants, will also be made available to participants, researchers, and any other people who might be interested through *[state format (e.g. website, newsletter)]*. This is done to make data more readily available to researchers and encourage medical advances. Such data will not have any identifiers that will enable anyone to link the data to you. You can access these results through the biobank *[specify how/where participants can find these results]*.

(c) Individual research results and incidental findings

Individual research results are results discovered during the course of research that concern you and have potential health or reproductive consequences.

Incidental findings are unforeseen findings about you that have potential health or reproductive consequences. Although they were discovered during the course of research, they are outside of the study objectives.

Alternative clauses

Alternative clause 1: “We will not return any individual research results or incidental findings to you”;
or

Alternative clause 2: “With your consent, we will return individual research results or incidental findings to you when they are scientifically valid, they are clinically significant, and there is a recognized therapeutic or preventive measure or way of changing the clinical course of the disease or condition. These results will be returned to you by [e.g. the Principal Investigator, a qualified health professional] for a period of [number of years]. After this period, the biobank will no longer return individual research results to you.”

12. Re-contact

With your permission, we may re-contact you to invite you to update your questionnaire or to provide additional samples or to be involved in new research projects by other researchers that could require additional physical assessments, tests, and questions.

13. Compensation

[Include travel expenses and the procedure for reimbursement.]

Alternative clauses

- If compensation is not offered, add: “Your participation is on a voluntary basis. You will not be compensated for your participation.”
- If compensation is offered, add: “Your participation is on a voluntary basis. However, as compensation you will receive [specific amount] for [type of visit (e.g. a visit to the clinic or a home visit)], travel expenses, and other inconveniences related to your participation.”

14. Possible commercialization

[Explain the potential uses of data and samples, including the development of intellectual property and commercial uses.]

[Identify biobank or specific committee] has been set up as the [guardian/owner/custodian] of the database and sample collection. The use of your data and samples might someday lead to the commercialization of a medical or genetic test or product. This may be done by a university or hospital, a commercial company, or both working in partnership. This means that researchers, including, potentially, commercial companies, may benefit financially. You will not derive any personal financial advantage from this commercialization.

15. Closure of the biobank

[Explain what will happen upon the closure of the biobank, whether the closure is scheduled or unplanned.]

If the [name of biobank] were to close for whatever reason, [see Alternative clauses].

Alternative clauses

Alternative clause 1: “all of the research results and information will be put into an archive that will be overseen by the [identify committee]”;

Alternative clause 2: “all of the samples and data will be destroyed”;

Alternative clause 3: “all of the samples and data will be transferred to [identify existing biobank]”.

16. Your questions or concerns

If you have any questions or concerns, please contact *[insert name of person]* free of charge at *[insert telephone number]* or by mail/email at *[insert mailing address and/or email address]*.

If you wish to make a complaint about any aspect of this study at any time, please contact *[insert name of person]* free of charge at *[insert telephone number]* or by mail/email at *[insert mailing address and/or email address]*. We take all comments seriously and will get back to you as soon as possible.

Thank you for considering taking part in this study!

[Insert logo and letterhead of biobank]

PARTICIPANT CONSENT FORM
[Name of biobank/Title of study]

Name of biobank: [insert name of biobank]

Investigator(s): [insert name(s) of investigator(s)]

Sponsor(s): [insert name(s) of sponsor(s)]

The goal of the [biobank/study] is [provide a brief summary of goal].

BY SIGNING THIS CONSENT FORM, I AGREE TO PARTICIPATE IN THE [BIOBANK/STUDY] AND DECLARE THAT:

- ▶ I have read and understood the information pamphlet [version/date]. I have had the opportunity to consider the information it contains and to ask all the questions I had. I have obtained satisfactory answers to my questions.
- ▶ The risks and benefits of my participation have been explained to me.
- ▶ I understand that my participation is voluntary. I am free to withdraw at any time, without giving any reason. This can be done by contacting [insert name] at [insert telephone number, email address, and/or mailing address]. I will receive a letter confirming my withdrawal.
- ▶ I understand that I will not receive any personal financial benefit from any possible commercialization of a test or product developed by using my data and samples.
- ▶ I understand that my participation does not entail any direct personal benefit. However, any immediate, life-threatening condition will be reported to me immediately so that I can obtain emergency care.
- ▶ I understand that upon closure of the biobank, my data and samples will be [specify policy for closure: archived, destroyed, or transferred to another biobank].
- ▶ I understand that unless access is required by law, only approved researchers will have access to my coded data and samples. Access is subject to ethics approval and oversight.
- ▶ I understand that general research results, meaning aggregate results, will be made available to participants, researchers, and other people who might be interested through [specify format (e.g. website, newsletter)] in order to make data more readily available and encourage medical advances.

I AGREE TO:

- ▶ Undergo a physical assessment, including:
 - attending an appointment at [insert location], which will last approximately [insert duration of appointment];
 - providing a [insert sample type (e.g. blood, urine, saliva)] sample of [insert amount/measures of samples taken], which the biobank will store;
 - answering a questionnaire about [insert topics (e.g. my health and lifestyle, family, and medical history)]; and
 - allowing staff members to perform basic clinical measurements, including [insert measurement types (e.g. measuring my weight, height, and blood pressure)].
- ▶ Allow my coded data and samples of [insert sample type (e.g. blood, cells, DNA, urine, saliva)] to be used for various research purposes approved by the relevant research ethics committee.

Optional clause

If specific disease/research area: "Allow my coded data and samples of [*insert sample type (e.g. blood, cells, DNA, urine, saliva)*] to be used for [*specify disease/research area*] approved by the relevant ethics committee. My approval will be required for other types of research."

- Have my data and samples stored at [*specify storage location*] for [*specify period of conservation*]. All data and samples will be kept in a secure facility overseen by [*insert name of individual or committee*].
- Allow my data contained in administrative health records to be examined now and in the future. My records and samples will continue to be accessed even if I become unable to make decisions for myself or if I die.

Alternative clause

If applicable: "Allow my data contained in administrative health records to be examined now and in the future. If I die, my records and samples will no longer be used."

RETURN OF RESULTS

(a) Results from laboratory assessment and initial physical assessment

Optional clauses

- I wish to receive the measurements or other results taken during the physical assessment and laboratory tests.

YES NO

[OR]

- I wish to have the measurements or other results taken during the physical assessment and laboratory tests sent to my doctor.

YES NO

(b) Individual research results and incidental findings

Alternative clauses

Alternative 1:

- I understand that I will not receive any individual research results or incidental findings.

Alternative 2:

- I agree to have individual research results and incidental findings returned to me when these results are scientifically valid, have clinical significance, and are actionable (there is a recognized therapeutic or preventive measure or way of changing the clinical course of the disease or condition).

YES NO

RE-CONTACT

- I agree to be re-contacted by [*identify biobank/study*] to update my data (questionnaires or physical measures) or to provide additional data/samples.

YES NO

- I agree to be re-contacted by [*identify biobank/study*] to participate in new research projects conducted by other researchers that could require additional physical assessments, tests, questions, or samples.

YES NO

CONFIRMATION BY INVESTIGATOR OR HIS/HER DESIGNEE

I described the [*identify biobank/study*], including the conditions of participation, to the participant. I explained the contents of the information pamphlet and consent form to the participant. Any questions were answered. I explained that participation was voluntary.

Investigator/Designee name Signed Date

Optional clause

TRANSLATOR INFORMATION (if applicable)

I was present during the meeting between [*name of investigator/designee*] and the participant. I translated, for the participant, the consent form and all information presented regarding the research project.

Translator name Signed Date

PARTICIPANT INFORMATION

I AGREE TO PARTICIPATE IN [*BIOBANK/STUDY*] AND WILL RECEIVE A COPY OF THIS CONSENT FORM AFTER I SIGN IT.

Name

Signed Date

THANK YOU FOR PARTICIPATING! FOR MORE INFORMATION, PLEASE CONTACT: [*insert website, name of person to contact, telephone number, email address*].

To file a complaint regarding your participation, please contact: [*insert name of person to contact, telephone number, email address, and mailing address*].

Template Material/Data Transfer Agreement (MTA/DTA)

This template is based on the IARC MTA template. The text presents generic template language (*italic means that text must be adapted*).

[Insert logo of Providing Institute]

MATERIAL AND DATA TRANSFER AGREEMENT – MTA/DTA

MTA/DTA Reference Number: *[to be provided by [insert name of Providing Institute]]*

Subject to the terms and conditions of this Agreement, the *[insert name of Providing Institute]* hereby agrees to provide, and the Receiving Institute hereby agrees to accept, the Materials and Information specified below for such Purposes of Use and subject to such Restrictions on Use as specified below.

In this Agreement, the following expressions shall have the following meanings:

1. “Providing Institute”:

[Insert name and full address of Providing Institute]

Contact: *[insert name and contact details (including email address) of Providing Institute’s Principal Investigator]*

2. “Receiving Institute”:

[Insert name and full address of Receiving Institute]

Contact: *[insert name and contact details (including email address) of Receiving Institute’s Principal Investigator]*

3. “Materials”:

[Insert precise description of Materials], held by [insert name of Providing Institute], and made available to the Receiving Institute hereunder in a quantity of [insert quantity to be provided by Providing Institute].

4. “Information”:

Any information, unpublished or otherwise, owned by [insert name of Providing Institute] and communicated to the Receiving Institute by [insert name of Providing Institute] during the term of this Agreement relating to the Materials, their production, properties, and/or experimental results observed using the Materials or any derivatives therefrom.

5. “Purposes of Use”:

The Materials and Information are provided for the following purposes, as more fully described in Appendix 2 (the “Research Project”):

[Insert a brief description of the purposes for which the Materials, and products incorporating or developed with the Materials, may be used.] [Add reference to a specific grant, etc. when appropriate.]

6. “Restrictions on Use”:

The Materials and Information shall not be used for any purpose other than the Purposes of Use.

In particular, the Materials and Information shall not be used for [insert any specific restrictions on use].

7. “Term of Agreement”:

This Agreement shall remain in full force and effect as from the date of its signature by both parties for a duration of [specify duration/may be based on project duration].

8. “Materials Charges”:

PLEASE KEEP THE APPLICABLE CLAUSE (1) AND DELETE THE REST.

8.1 **As per price list** The cost of sample retrieval, processing – including DNA extraction – packaging, and shipment will be charged by [insert name of Providing Institute] to the Receiving Institute at the latest rate [indicate where rate will be made available for informational purposes].

or

8.1 **As per agreed unit price** The cost of sample retrieval, processing – including DNA extraction – packaging, and shipment will be charged by [insert name of Providing Institute] to the Receiving Institute at the following agreed rate: [list unit price].

or

8.1 **Lump sum amount** The cost of sample retrieval, processing – including DNA extraction – packaging, and shipment will be charged by [insert name of Providing Institute] to the Receiving Institute for the total lump sum amount of [amount and currency in words].

or

8.1 **Free of charge** The sample retrieval, processing – including DNA extraction – packaging, and shipment will be provided free of charge.

9. “General Conditions”:

The General Conditions attached hereto under Appendix 1 form an integral part of this Agreement.

This Agreement is duly signed on behalf of the parties as follows:

Signed for and on behalf of *[Providing Institute]*:

Signed for and on behalf of Receiving Institute:

[Providing Institute] Responsible Scientist

Receiving Institute Responsible Scientist

Name

Name

Title

Title

[Providing Institute] Authorized Official

Receiving Institute Authorized Official

Name

Name

Title

Title

Date

Date

APPENDIX 1 – GENERAL CONDITIONS

1. Use

- 1.1 The Materials and Information are supplied by *[insert name of Providing Institute]* to the Receiving Institute solely for the Purposes of Use and subject to the Restrictions on Use as set out herein.
- 1.2 The Materials and Information shall not be used in human subjects, in clinical trials, or for diagnostic purposes involving human subjects without the written consent of *[insert name of Providing Institute]*.
- 1.3 Other than for and within the Purposes of Use, and as specifically described in Appendix 2, the Materials and Information shall not be transferred, offered for sale, or otherwise used without the prior written agreement of *[insert name of Providing Institute]*.
- 1.4 The Receiving Institute shall allow only parties who have a need to know for the Purposes of Use and who are bound by similar obligations of confidentiality and Restrictions on Use as contained in this Agreement to have access to the Materials and Information.
- 1.5 The Receiving Institute shall require any party handling and/or using the Materials and Information to comply with all relevant laws, rules, and regulations applicable to the use of such Materials and Information.

2. Confidentiality

- 2.1 The Information may incorporate confidential information of *[insert name of Providing Institute]*. Accordingly, if and to the extent that any such Information is clearly marked as “confidential”, the Receiving Institute shall during the Term of this Agreement and for a period of *[insert number of years]* years following its termination treat such Information as confidential and only disclose it under like obligations of confidentiality and Restrictions on Use as those contained herein. The Receiving Institute shall be deemed to have fulfilled its obligations if it exercises at least the same degree of care in maintaining confidentiality as it would in protecting its own confidential information.
- 2.2 The above-mentioned obligations of confidentiality shall not apply to Information which:
 - (i) can be shown to have been known to the Receiving Institute at the time of its acquisition from *[insert name of Providing Institute]*; or
 - (ii) is acquired from a third party, not in breach of any confidentiality obligation to *[insert name of Providing Institute]*; or
 - (iii) is independently devised or arrived at by, on behalf of, or for the Receiving Institute without access to the Information; or
 - (iv) enters the public domain otherwise than by breach of the undertakings set out in this Agreement.
- 2.3 In some cases, the Information may also incorporate confidential information pertaining to research participants having provided the Materials. The Materials provided to the Receiving Institute have been *[coded or anonymized (provide description of data treatment here)]*. If the Receiving Institute inadvertently receives information that identifies individual research participants, the Receiving Institute will take all reasonable and appropriate steps to protect the privacy and confidentiality of such information. This may require immediate destruction of the information on request of *[insert name of Providing Institute]*. The Receiving Institute agrees to make no intentional attempt to re-identify research participants through linkage of data or otherwise. The Receiving Institute will immediately report any identification of research participants to *[insert name of Providing Institute]*.

3. Rights

- 3.1 Except for the rights explicitly granted hereunder, nothing contained in this Agreement shall be construed as conveying any rights under any patents or other intellectual property which either party may have or may hereafter obtain.

3.2 [Insert name of Providing Institute] shall retain ownership of the Materials and Information and shall have the unrestricted right to use, assign, or distribute the Materials and Information to any third parties for any other purposes. The Receiving Institute acknowledges and agrees that nothing contained in this Agreement shall be deemed to grant to the Receiving Institute any intellectual property rights in any of the Materials or Information provided hereunder.

3.3 The Receiving Institute must not make intellectual property claims on Materials or Information derived directly from [insert name of Providing Institute]. However, the importance of downstream inventions made with [insert name of Providing Institute] Materials is recognized; patents on such inventions are permitted. In doing so, the Receiving Institute agrees to implement licensing policies that will not obstruct further research. The Receiving Institute will own all results, data, and inventions which arise under the Research Project described in Appendix 2.

OPTIONAL ADDITIONAL CLAUSE: The Receiving Institute does, however, grant to [insert name of Providing Institute] a perpetual, non-cancellable, royalty-free, worldwide license, with right to sublicense, to use study results for all purposes.

4. Return of Individual-Level Results

OPTIONAL CLAUSES:

4.1 **No return of individual-level results:** Individual Research Results and Incidental Findings will not be returned to [insert name of Providing Institute].

or

4.1 **Return of individual-level results:** Participants in [insert name of Providing Institute] have consented to the return of Individual Research Results and Incidental Findings that are clinically significant, analytically valid, and actionable (i.e. treatable or preventable). If in the course of their research the Receiving Institute comes across such findings, they must be returned to the [insert name of Providing Institute].

5. Publications

5.1 Upon completion of the Research Project, the Receiving Institute will send to [insert name of Providing Institute] [specify: reports, enriched data, etc.]. The Receiving Institute must endeavour to publish results in an academic journal or in an open access database. The Receiving Institute agrees to acknowledge [insert name of Providing Institute] in any publication or presentation on work derived in whole or in part from the Materials and to supply [insert name of Providing Institute] with a copy or web address of any publication.

6. Warranties and Liabilities

6.1 [Insert name of Providing Institute] makes no warranty of the fitness of the Materials for any particular purpose or any other warranty, either express or implied. However, to the best of [insert name of Providing Institute]'s knowledge, the use of the Materials and/or Information within the Purposes of Use shall not infringe on the proprietary rights of any third party.

6.2 [Insert name of Providing Institute] will not be liable for damages related to the provision of Materials to the Receiving Institute. This includes but is not limited to damages in relation to inaccuracies, lack of comprehensiveness, or use of the Information and Materials and/or Information, or any delay or break in supply by [insert name of Providing Institute]. The Receiving Institute acknowledges that [insert name of Providing Institute] makes no guarantee that the Materials and/or Information are free of contamination from viruses, latent viral genomes, or other infectious agents. The Receiving Institute agrees to treat the Materials as if they were not free from contamination, to ensure that appropriate biosafety training is provided to research personnel, and to implement appropriate biohazard containment measures.

6.3 The Receiving Institute agrees that, except as may explicitly be provided in this Agreement, *[insert name of Providing Institute]* has no control over the use that is made of the Materials or the Information by the Receiving Institute in accordance with the terms of this Agreement. Consequently, the Receiving Institute agrees that *[insert name of Providing Institute]* shall not be liable for such use.

7. Amendment, Extension, and Termination

7.1 Any amendment to this Agreement, including extension of the Term of Agreement, shall be valid only by written amendment executed by the duly authorized officers of both parties.

7.2 Notwithstanding the conditions set forth in this Agreement, in particular the Purposes of Use, Restrictions on Use, and Confidentiality obligations, either party may terminate this Agreement with sixty (60) days prior written notice to the other party.

7.3 When the Research Project is completed or this Agreement is terminated, whichever comes first, any unused Materials will either be destroyed in compliance with all applicable statutes and regulations or will be returned to *[insert name of Providing Institute]* by the Receiving Institute upon *[insert name of Providing Institute]*'s request.

8. Miscellaneous

8.1 Nothing in this Agreement shall be interpreted as establishing a partnership between the parties or establishing one party as the agent of the other or conferring a right on one party to bind the other, except as may be specifically set out herein.

8.2 Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The parties shall accept the arbitral award as final.

8.3 This Agreement sets forth the entire understanding between the parties and supersedes any prior agreements, written or verbal.

APPENDIX 2 – RESEARCH PROJECT

[Provide description of project/work to be performed using the Materials and/or Information.]

Biobank, collection, study, and sample minimum data set and associated standards

Table A5.1 lists the minimum data set, which reduces the heterogeneity of sample-associated data and thus improves its quality. Such standardization enables biobanks to share samples in large studies and for research that requires samples from different sources.

Table A5.1. Minimum data set and associated standard available in BRISQ, SPREC, and MIABIS

Type of data set	Data field	Explanation of data field	BRISQ Tier 1	SPREC	MIABIS
Collection or study or biobank	ID	The unique ID or acronym of the study	NA	NA	Text value
Study or biobank	Acronym	Short name	NA	NA	Text
Collection or study or biobank	Name	Name of the study in English	NA	NA	Text
Collection or study or biobank	Description	Description of the study aim; recommendation maximum, 2000 characters	NA	NA	Text
Study	Principal investigator	Name of the person responsible for the study (e.g. the principal investigator)	NA	NA	Text
Collection or study	Sex	Sex of individuals can be one or more values	NA	NA	One or more values
Collection or study	Age low	Age of youngest donor	NA	NA	Number
Collection or study	Age high	Age of oldest donor	NA	NA	Number
Collection or study	Age unit	Unit of age	NA	NA	Value can be in years, months, weeks, or days

Table A5.1. Minimum data set and associated standard available in BRISQ, SPREC, and MIABIS (continued)

Type of data set	Data field	Explanation of data field	BRISQ Tier 1	SPREC	MIABIS
Collection or study	Data categories	Type of data that is associated with the collection or study	NA	NA	List of Yes/No values; also including whether biological samples are collected
Collection or study	Material type	Can be several values defining type of specimen	NA	NA	List of fluid or solid NCI definitions
Collection	Storage temperature	—	NA	NA	List of value ranges
Collection	Collection type	The type of collection; can have several values	NA	NA	List of collection types: case-control, cohort, longitudinal, etc.
Collection	Disease	Main disease of interest; can be more than one	NA	NA	Five subfields: ontology, ontology version, ontology code, ontology description, and free text
Collection or study or biobank	Contact information	Contact information for the contact person	NA	NA	Eight subfields for contact name and contact information (telephone, email, and address)
Study	Study design	Design of the study	NA	NA	List of collection types: case-control, cohort, longitudinal, etc.
Study	Total number of participants	Number of participants recruited	NA	NA	Number
Study	Total number of sample donors	Number of participants who provided samples	NA	NA	Number
Study	Inclusion criteria	Parameters to determine type of donor	NA	NA	List of values
Biobank	Biobank URL	Internet address of the biobank	NA	NA	http address
Biobank	Biobank juristic person	Person or entity legally responsible	NA	NA	Text value with name of juristic person
Biobank	Biobank country	Country of the biobank	NA	NA	ISO standard letter code
Sample	Sample ID	Unique ID or acronym of the study	NA	NA	Text identifier or barcode
Sample	Parent sample ID	Specimen from which the sample was derived; only for aliquots or derivatives	NA	NA	Text identifier or barcode
Sample	Type of sample	Biological definition of the sample	Called "biospecimen type"; solid tissue, whole blood, serum, cells, etc.	Value list; different list and codes for solid and liquid	Called "material type"; list of fluid or solid NCI definitions
Sample	Type of primary container	How the specimen was collected	Called "type of stabilization"; for fluids, analogous to SPREC, but for solids, SPREC calls this field "type of collection"	Value list; for solids, the field is called "type of collection" and the values are different	NA

Table A5.1. Minimum data set and associated standard available in BRISQ, SPREC, and MIABIS (continued)

Type of data set	Data field	Explanation of data field	BRISQ Tier 1	SPREC	MIABIS
Sample	Pre-centrifugation delay	Time between collection and processing in hours	NA	Value list	NA
Sample	Centrifugation	Centrifugation speed (in <i>g</i>) and temperature	NA	Value list	NA
Sample	Second centrifugation	Centrifugation speed (in <i>g</i>) and temperature	NA	Value list	NA
Sample	Post-centrifugation delay	Time between centrifugation and storage in hours	NA	Value list	NA
Sample	Long-term storage	Container and temperature	NA	Value list	Called “storage temperature”; uses SPREC values and has additional value LN ₂
Sample	Type of collection	Biopsy, surgical, FNA, etc.	Called “collection mechanism”	Value list	NA
Sample	Warm ischaemia time	Ranges in minutes	NA	Value list	NA
Sample	Cold ischaemia time	Ranges in minutes	NA	Value list	NA
Sample	Fixation type	OCT compound, RNA <i>later</i> , etc.	Called “constitution and concentration of preservative”; indicates formulations to maintain a non-reactive state, but in BRISQ, also refers to fluid samples	Value list; in SPREC, only refers to solid samples	NA
Sample	Fixation time	Value ranges mostly in hours	NA	Value list	NA
Sample	Long-term preservation	Type of preservation	Can include formalin fixation, freezing, and indication of temperature	Called “long-term storage”, combining this value and the values of “storage temperature” in a single value list	NA
Sample	Storage temperature	Temperature	A temperature or range	Called “long-term storage”, combining this value and the values of “storage temperature” in a single value list	NA
Sample	Sampled time	Time of sampling	NA	NA	The time when the sample was taken
Sample	Anatomical site	The part of the body from which the sample was taken	Organ of origin or site of blood draw	NA	Five values: name, version of ontology, anatomical code, description, and free text
Sample	Biospecimen disease status	For tissue, the pathological status of the specific sample	Normal, diseased, normal adjacent	NA	NA

Table A5.1. Minimum data set and associated standard available in BRISQ, SPREC, and MIABIS (continued)

Type of data set	Data field	Explanation of data field	BRISQ Tier 1	SPREC	MIABIS
Sample	Clinical characteristics	—	Available medical information	NA	NA
Sample	Vital status	—	Alive or deceased	NA	NA
Sample	Clinical diagnosis	Clinical information	Clinical evaluation based on anamnesis and physical examination	NA	NA
Sample	Pathological diagnosis	Pathological information	Macroscopic and microscopic pathological evaluation	NA	NA
Sample	Collection mechanism	How the sample was taken; helps define also whether before or after treatment	FNA, pre-operative blood draw, etc.	NA	NA
Sample	Storage duration	Field recording the length of time that the sample has been stored	Time between acquisition and use	NA	NA
Sample	Shipping temperature	The temperature that is maintained during transportation	Temperature maintained during shipping	NA	NA
Sample	Composition assessment and selection	Criteria used for use; this field is mainly only after use in a specific research study	Criteria used for selection	NA	NA

BRISQ, Biospecimen Reporting for Improved Study Quality; FNA, fine-needle aspiration; ISO, International Organization for Standardization; LN₂, liquid nitrogen; MIABIS, Minimum Information about Biobank Data Sharing; NA, not applicable; NCI, United States National Cancer Institute; OCT, optimal cutting temperature; SPREC, Sample PREanalytical Code.

Disclosures of interests

Dr Joakim Dillner reports that his unit at the Karolinska Institutet benefited from research funding from Sanofi Pasteur MSD and from Merck in 2014.

Dr Jan-Eric Litton reports holding intellectual property rights to the biobank lexicon Minimum Information about Biobank Data Sharing (MIABIS).

Dr Kurt Zatloukal reports having received personal consultancy fees from AstraZeneca and Daiichi Sankyo, support for travel from GlaxoSmithKline, and support from Daiichi Sankyo, Qiagen, and Siemens as an R&D partner. Dr Zatloukal is a European Committee for Standardization (CEN)/International Organization for Standardization (ISO) Technical Committee member.



© R. Dray/IARC

ISBN 978-92-832-2464-8