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COMMITTEE ON BIOETHICS
(DH-BIO)

Compilation of replies
to the public consultation concerning the Working document on on research on biological materials of human origin

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GENERAL COMMENTS ON THE WHOLE TEXT

BIOBANKS

3C-R, réseau français de biobanques

Club 3C-R is a network of 95 Biological Resource Centres (or biobanks), including 85 in the field of human health. Its members are therefore highly attentive to recommendations on research using biological materials of human origin.
The members of Club 3C-R, who are very involved in the storage of residual biological materials for future research, consent management and governance of collections, wished to provide feedback in the form of "comments" relevant to the daily functioning of biobanks and to submit a number of "proposals" concerning the articles' wording (drafting amendments are shown in blue in this document to facilitate their identification).
The main substantive proposals concern:

1. The addition of an article (at the beginning of Chapter V) so as to recognise the key role played by Biological Resource Centres, or biobanks, in managing biological materials used for research purposes in the field of human health. These BRCs are recognised in international documents[1] that could serve as a basis for certain of the recommendation's provisions
2. The definition of the recommendation's scope, so as to dispel any ambiguity
3. Specific issues regarding the management and use of coded biological materials
4. Conditions relating to the secondary uses of biological materials

The BRCs and research teams active in the human health field have been consulted to obtain their views on the proposal. Seven teams participated actively in the examination of the draft revised Recommendation 2006 (4) and constituted the drafting group that drew up this document.

24 teams also participated in the validation group and support these comments and proposals.

Biobanking and BioMolecular resources research infrastructure BBMRI-ERIC

Proposal for textual harmonisation:
Why not using the terms « human biological resources » as the pooling of human biological samples and associated (personal) data, according to the work done by the OECD on this matter? Also the term “samples” is preferred to “materials” and we recommend using the term “biobank” as it has been defined or inspiring from the definition provided in the EU Commission Implementing Decision (2013/701/EU) fixing the status of BBMRI-ERIC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:320:0063:0080:EN:PDF): “Biobanks (and Biomolecular Resources Centres)’ means collections, repositories and distribution centres of all types of human biological samples, such as blood, tissues, cells or DNA and/or related data such as associated clinical and research data, as well as biomolecular resources, including model- and micro-organisms that might contribute to the understanding of the physiology and diseases of humans”.
This would give more consistency to the European framework and would allow clarifying the scope and the rules that would become thus much more operational.

[1] OECD Best Practice Guidelines for BRCs: 2007

Comment about the content:
Overall there is significant room for national interpretation and while many of the subjects could be clearer – and we would like them to be clearer - it is not certain that consensus could ever be reached, at least not without ending up with recommendations which are the most restrictive and complicated. Best to leave it flexible and let member states write their own laws or regulatory texts.
This commendable proposal to guarantee the patient's rights does however not take into account existing mechanisms with the same purpose. E.g. in several countries like Belgium, France, ethical committees, established by law, control the creation of biobanks, the storage of samples and their use in any study. It would be wise to leave enough room for those existing mechanisms to be kept and strengthened and look into these existing mechanisms for inspiration. These guidelines should therefore give a general framework that can be implemented on the national level using the mechanisms that are already in place.

The focus of the draft is not just about research, but also about collecting and storing samples for the purposes of future research, whose exact nature is not necessarily known at the time of collection/storage. The role of biobanks and the role of researchers in a specific project are different, and each provision should be checked against this background. Thus, biobank governance and use for research/approval of research plans are different.

The recommendation should reflect rights to privacy as well as rights of access to preventive health care and the right to benefit from medical treatment:
The preamble rightly states the significance of protecting private life. However it should also explicitly address the rights of each citizen to prevention and medical treatment. In agreement with the European Convention for the Protection of Human Rights and Fundamental Freedoms, the Social Charters adopted by the Union and by the Council of Europe, the Charter of Fundamental Rights of the European Union (2010/C 83/02) emphasizes the right of each individual to integrity within the fields of medicine and biology, implying a free and informed consent according to the procedures laid down by law (Article 3). Article 8 grants the individual the right to the protection of personal data concerning him or her, implying that processing of such data requires consent of the person concerned or some other legitimate basis laid down by law. These and other rights in the charter may be motivated by a fundamental respect of each individual's autonomy and right to have control of matters related to oneself, e.g. the processing of personal data and the use of biological samples of human origin. In addition to these autonomy rights the Charter of Fundamental Rights of the European Union also lays down rights of each individual to social security benefits and social services in cases of illness (Article 34) and the rights of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices (Article 35). As described, the charter of the European Union recognizes both the autonomy right and the right to health care and social services in cases of illness as fundamental individual rights, notwithstanding that there may also be societal and public health related interests concerned.
The development of a quality health care and the safeguarding of a high level of excellence in health care depends on the persistence of biomedical research also based on residual material. This aspect must be highlighted in communications to the public and legislation. So the patient can understand the importance of his/her contribution occurring in a legal and ethical framework for the use of biological samples and associated data. Also, samples and data have been entrusted to the researcher/biobank/institution. Thereof, their responsibility to use the samples for the development of medicines and better healthcare could be deduced.
Regarding privacy:
Does the use of anonymised samples safeguard human dignity? Why build up a strict procedure for collection and use of identifiable samples, but keep it light/non-existent when anonymised? Is the recommendation mostly about data protection? Then it is unnecessary, as we have already very strict data protection regimes at European level, and reference to

EU and CoE such texts could be made explicitly. We however acknowledge that such a recommendation can be used in other countries than the European ones.

Proposal for a clear table/chapter of key terms definitions:
Some of the terms used may be read/"interpreted" in different manner (i.e. human sample resource, anonymised, coded etc) and, since this is a recommendation could be taken into consideration also from other than European geographic areas, where "wording use" may be quite different, we suggest to add a very short table / chapter with the definition of main terms used in the document. We know that no absolute definitions exist but it is good practice in legislation on European and international level to introduce some key terms by such a table of definitions ("For the purposes of this recommendation…").
Specific/contextual comments about this crucial issue can be found throughout this contribution.
This table should be aligned with existing documents in Europe, e.g. the Oviedo Convention and relevant protocols, EU legislation such as the Directive 95/46/EC, and at least include the following terms:

- "pseudonymised" (instead of "coded"),
- "biological material" or other chosen term (see supra proposals about human biological resources and the term "samples")
- "collection of biological material" or other chosen term (see supra proposals about "biobank"),
- "removal of biological material",
- "family",
- "same group of individuals",
- "persons concerned",
- "consent" (freely given)
- "authorisation".

Dutch National Tissue bank Portal BBMRI-NL

As the project manager of the Dutch National Tissuebank Portal (BBMRI-NL project) I have gained knowledge and experience on how archived pathology samples in the Netherlands obtained in the clinical context of a diagnostic process are being used for research purposes. …

I would like to take you along the process of storage and use of residual tissue left over after a diagnostic process.

Let's say a patient enters a hospital because of suspected bowel/colorectal cancer. A doctor performs an endoscopy, takes a biopsy, which shows that a tumor is present.
The patient is informed and advised to have the tumor removed. The patient agrees and has the operation. After removal (by a surgeon), the resection specimen is investigated by the Pathology department for assessment of the procedure, determination of tumor extent and running molecular tests for further therapy (if needed). Pathologists select tissue pieces from the specimen (10 to 15 will do) and these are processed in the lab either to formalin fixed paraffin embedded blocks (FFPE blocks) or other means to preserve the tissue for diagnostic use. Ultrathin slides from these blocks allow microscopic assessment for diagnosis. The findings are communicated via the doctor to the patient. Subsequently the FFPE blocks and slides are stored and archived at the Pathology department. This is done *primarily* for future diagnostic re-use purposes for the patient himself (primary use) or his relatives. In cases of metastasis, it can be compared to the primary tumor and, if needed, further tests can be done on the stored primary tumor slides.
But besides this primary re-use for diagnostic follow-up, the FFPE blocks can also be used for scientific research, quality control or educational purposes. This so called *secondary or*

further use is of huge importance for research. Secondary use of these FFPE blocks is always retrospective research. Which implies that we do not know beforehand if the tissue blocks will or will not be used for research purposes.

In the Netherlands it is estimated that there are more than 60 million FFPE samples stored from more than 11 million patients. These FFPE blocks are being used daily by many researchers. It is difficult to estimate an exact amount of how many tissue blocks are being used, because this is not (yet) registered nationally. But with my experience and knowledge I think an estimate of > 50.000 FFPE blocks are used yearly by researchers nationally.

EUROPEAN, MIDDLE EASTERN AND AFRICAN SOCIETY FOR BIOPRESERVATION AND BIOBANKING (ESBB)

Although the concept of "ownership" of biological materials of human origin is still subject to an intense debate within the international community(6-7), the ESBB Working Group recommends some clarification in the form of concrete examples, of who are the "owners" or "custodians" of samples stored in a biobank. Given that several legislations in Europe consider and govern the ownership of human biological materials differently - ranging from custodianship (Dutch, Spanish law on biobanks) to property models (Portuguese law on biobanks) - it would be helpful for all persons engaged in biobanking (either private or public) to know which prototype may be applied within the EU jurisdiction.

2) Information and Consent
Clarification of consent models available within the European and non-European regulatory landscape (including Middle Eastern, Asia, North and South America) is recommended, to help understanding of which kind of information and consent may be adopted for research utilizing human biological materials.

From this perspective, the "opt-out" system for *residual samples and secondary use* of human biological materials should also be described.

With specific regard to *leftover materials* (remaining after diagnostic, clinical or research utilization) which have to be employed for clinical trials, the need for informed consent of the concerned patient could be waived when those samples are not individually identifiable. This approach is currently supported by the FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable. (8)

3) Commercial products derived from research using human biological materials
Clarification about the regulation of commercial products derived from research using human biological materials is recommended to clarify which benefit sharing approach is supported in this DH-BIO Working Document. In particular, it is recommended to make clear that under the European jurisdiction donors are not entitled to receive any form of financial compensation deriving from the development of commercial products based on the use of donated biological materials for research.

4) Privacy Protection
Although the protection of privacy is the subject of the Convention on Protection of Personal Data (N°108) of Council of Europe(9) as well as of the EU Directive 45/96 (10), that are presently under revision, clarifications about the regulation of the privacy of concerned people in relation to the research biobanking processes are recommended. In particular, careful attention should be paid to the restrictions foreseen in the General Data Protection Regulation proposal (11) with regard to the effects that the final approval of this legal

document could have on the research field, including, among the others, the inhibition of many medical research activities.

5) Characterisation of biological materials
We recommend clarification of the scope of these Recommendations with regard to the kind of human biological materials (e.g., blood, tissues, DNA, stem cells, etc.) covered. For example, it needs to be made clear whether the scope includes specimens residual to newborn screening programmes, and whether it includes pluripotent stem cells (iPSCs) which are bioresources of increasing relevance.

6) Relation between the Recommendation on research on biological materials of human origin and existing regulations covering the same field
The DH-BIO Working Document does not take into account existing mechanisms with the same purpose. For example, in several countries like Belgium, ethics committees, established by law, control the creation of biobanks, the storage of samples and their use in any study. It would be advantageous to leave enough room for those existing mechanisms to be kept and strengthened and maybe look into these existing mechanisms for inspiration. The guidelines, like the Recommendation Rec(2006)4 on research on biological materials of human origin, should therefore give a general framework that can be implemented on the national level using the mechanisms that are already in place.

Swedish National Council of Biobanks (NBR)

In summary, we believe that these recommendations take well into account the individual donors rights to privacy. We do believe that the individual's right to adequate prevention, diagnosis and treatment should be more visible in the recommendation.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Whilst I understand that the focus of this review is on articles 12, 13, 14, 17, 20, 21, 22, 23 and 24, I believe there remain significant issues with the way the preceding articles are drafted that confuse the scope of this document and also how research should be conducted using human biological samples. I have outlined my concerns below.

In summary I believe that the present document may serve to confuse researchers and regulators about what is permitted and may have the unintended risk of significantly impeding vital medical research in the absence of significant risk to individuals.

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

The four Deans of the Faculties of Health and Medical Sciences in Denmark (Aarhus University, University of Southern Denmark, Aalborg University and Copenhagen University) have each asked a group of their most prominent experts – within the many aspects associated with the establishment and utilization of biobanks – to give their inputs. The eight members of this expert group are located either at the universities and/or the university hospitals. Based on their comments, we have formulated the present response.

The response applies to residual biological material, i.e. the collection, storage and subsequent use of human biological materials and associated personal data for *future*

research purposes. Included is the use of biological materials that were previously obtained for other purposes, i.e. diagnostic material contained in a clinical biobank or scientific materials obtained in a previous research project.

The response is divided into two parts:
1. Comments relevant to "*The Danish legislation*" within the area, pp. 1-3
2. Remarks to the "*Working document on research on biological materials of human origin*", pp. 3-7

1. Comments relevant to *"The Danish legislation"* within the area

The Danish legislation does not recognize a *broad consent* to future research obtained from the donor at the time of obtaining the biological material, irrespective of the kind of information provided to the donor beforehand. Instead, an *informed consent* has to be obtained from the donor at the time of usage of the material in a concrete research project which has been approved by a Danish Research Ethics Committee. In special circumstances, the Danish Research Ethics Committee may grant exemption from the requirement of informed consent. Exemptions may be given if the research project does not impose any risk or strain on the donor, or if the obtainment of consent is disproportionately difficult (e.g. in case of a very large number of participants) or impossible (e.g. a death donor).

The Danish legislation provides a number of problems and restrictions concerning the usage for research purposes of biological material that has been obtained in a clinical setting during diagnosis/treatment or has been obtained in a concrete research project as surplus material for future research:

- Even if the donor may wish to consent to a broad range of future usages of their biological material, it is not possible to obtain such consent at the time of collecting the sample.
- The task of tracing the donors and obtaining an informed consent for a concrete research project at a later time point could be huge, for example for biological materials collected in a clinical setting years before the intended use.
- If an informed consent cannot be obtained, research usage of the biological material may be very restricted unless granted an exemption from the consent requirement.
- Use of biological material in research projects which includes comprehensive genome mapping (NGS) – or other techniques entailing risk of incidental significant health findings – demands special requirements to the information and consent.

In principle, we do support the legal recognition of a broad consent to future research usage obtained at the time of collection of the materials, as suggested in the recommendation DH-BIO/INF (2014), including information to the person as stipulated in Chapter III, article 11, paragraph 1. However, as the specific nature of a future research project is unknown and any future use cannot be foreseen at the time when the material is collected and the consent obtained, special precautions have to be taken in terms of recognition of a broad consent for biomedical research.

Our support to the concept of a broad consent relies on the implementation of three essential issues:

a. The Research Ethics Committee must play a central role in safeguarding the patients' rights.
b. Openness about collection, storage and usage, i.e. information to the donor at the time of collection and information to the donor/the public about biobank activities.

c. Emphasis on protection of personal data during collection, storage, and – in particular – during usage in research to sustain public trust and support to research activities.

The following conditions must apply:

- Specifically for biological materials for future research obtained in a previous research project – whether as *surplus* material after termination of the specific project or collected as *extra* material for the purpose of future research: for use in a new research project, the research ethics committee must specifically evaluate whether:
  - the donor was informed that extra/surplus material would be stored for future research,
  - the donor has consented to such storage for future research,
  - there may exist an ethically relevant difference between the original and the new research project which calls for a re-consent. Research projects with the possibility to produce results of consequence for the donor requires re-consenting, *unless* the donor has specifically declined being re-contacted for that purpose.

- If obtained from a patient within a clinical context: usage of the material in future research projects may be both *within the field of the patient's disease/condition* and in other fields, which must be stated in the information to the patient.
- A national system for opting-out must be at place, i.e. a registry for donors who want their biological material being used only for their own treatment/diagnosis. The registry must be consulted by the biobank custodians before any disclosure of material that has been stored for future research purposes, whether obtained in a previous research project or in a clinical setting.
- In genomic mapping or similar research projects the handling of significant, incidental health findings within the project should be described. Feedback to the patient of such findings should be provided *if* the findings are validated and there is a possibility for treatment or prevention of a disease, *unless* the donor has specifically declined such feedback. Therefore, the consent form – whether broad or informed – should inform the donor of the potential for using the biologic material for genomic research and furthermore grant the donor the possibilities of declining such use and of declining any feedback of results.
- Chapter III, article 11, paragraph 2: It must be specifically emphasized that:
  - any research project must be approved by a research ethics committee,
  - a research project with the potential to produce results of consequence for the donor requires re-consenting, *unless* the donor has specifically declined being re-contacted for that purpose.
- Large biobanks/population biobanks should be obliged to inform the donors about the specific research activities being conducted using material from the biobank. The information could be posted on biobank webpages and in newsletters.
- Data protection: in terms of recognition of a broad consent to future research it is highly important to sustain public trust in health research. Focus on:
  - development and implementation of appropriate research infrastructures to ensure protection of personal data not only during collection and handling/storage in biobanks but also during research usage.
  - concrete instructions to researchers on how to handle/store/disclose personal data to ensure compliance with national and international legislation.
  - control of institutions and research projects by national bodies to ensure compliance with data protection rules.

2. Remarks to the *"Working document on research on biological materials of human origin"*

The working document appears somewhat unstructured with removal-storage-use mixed up for persons able to consent and persons not able to consent. Removal-storage-use should rather be described separately for persons able to consent and then for persons not able to consent.

The distinction between *residual* material and *extra* material, whether obtained in a clinical context or during a previous research project, is not always clear.

Karolinska Institutet, Sweden

The recommendations by the Bioethics Committee rightly emphasize the right of autonomy of each European citizen from which follows duties of governments, public authorities, universities and private organisations to protect privacy and restrict access to personal sensitive data. However, the recommendations do not, in our view, fully reflect significant rights of each European citizen to health and prevention of illness to be made available through research. In particular we would like to emphasize that, considering both autonomy rights and rights to health care, broad consent should be the optimal procedure for prospective sampling while opt out or no re-consent after decision by an ethical review board should be selected for previously collected samples. Sampling for children should be recommended following similar concerns to benefit children as recently recommended concerning clinical trials. Specifications of types of research to be approved by the research subject may often not be in the best interest of the subject.

The recommendation should reflect rights to privacy as well as rights of access to preventive health care and the right to benefit from medical treatment

The preamble rightly states the significance of protecting private life. However it should also explicitly address the rights of each citizen to prevention and medical treatment. The Charter of Fundamental Rights of the European Union (2010/C 83/02) emphasizes the right of each individual to integrity within the fields of medicine and biology, implying a free and informed consent according to the procedures laid down by law (Article 3). Article 8 in this charter grants the individual the right to the protection of personal data concerning him or her, implying that processing of such data requires consent of the person concerned or some other legitimate basis laid down by law. These articles are in agreement with the European Convention for the Protection of Human Rights and Fundamental Freedoms, the Social Charters adopted by the Union and by the Council of Europe.

These and other rights in the charter may be motivated by a fundamental respect of each individual's autonomy and right to have control of matters related to oneself, e.g. the processing of personal data and the use of biological samples of human origin. In addition to these autonomy rights the Charter of Fundamental Rights of the European Union also lays down rights of each individual to social security benefits and social services in cases of illness (Article 34) and the rights of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices (Article 35). As described, the charter of the European Union recognizes both the autonomy right and the right to health care and social services in cases of illness as fundamental individual rights, notwithstanding that there may also be societal and public health related interests concerned.

KU Leuven Faculty of Medicine, Belgium

We believe that this recommendation could further articulate stewardship responsibilities of sample collectors and their rights, e.g. maintaining ownership of materials. Moreover, it is critical to elaborate how much control sample collectors would maintain when transfer of the samples to third parties takes place.

Lund University, Sweden

The phrase "age category", which is referred to in three places in the document, is problematic. Chronological age is not a real property. What is important is not what age you are but how healthy you are. What is important is your "biological age". This is true regardless of your chronological age. The phrase is particularly problematic when talking about children or, for example, frail elderly.

There is also another reason for avoiding this phrase or concept. The text is intended to protect individuals, not groups. Group based reasoning rarely protects individuals. We suggest that these passages are reformulated, and that there is a clear focus throughout on individual rights, meaning that concepts like "age category" are avoided.

Patrick GAUDRAY (à titre personnel), Directeur de Recherche au CNRS, Membre du Comité Consultatif National d'Ethique, France, France

- The Council of Europe working document seeks to draw up an ethical framework to ensure respect for the dignity of persons and, in particular, their private life. In a context of applied ethics, it focuses on a series of rules and regulations of a legal nature, resulting in a code of good practice which can only be a somewhat "reductive" component of the ethical approach. While this is legitimate given the nature of the text and the institution from which it comes, it would be helpful for this to be specified in an introduction and for it to be made clear that the document is not an exhaustive ethical reflection, but that it addresses a number of fundamental ethical issues.
- Although referred to several times, the information which must be provided to participants remains an open subject of concern. This information, both on the anticipated outcomes of the research and the feedback which may and must be given to each participant needs to be given in terms that he or she can readily understand. However, contrary to what the text might suggest, there are not two categories of individuals – those able to give consent and those who do not have that capacity – there is a continuum of understanding, the level of which is difficult to ascertain and therefore to assess.
- Accordingly, it seems to me to be dangerous to restrict an individual's participation in a research endeavour to that individual's consent to the project presented to him or her. Would it not be more "ethical" to present his or her participation in the form of a choice. A choice implies that the individual is responding to the information provided, displaying the fact that this information has been understood.

  Consent would appear to dismiss the concept of an alternative, and therefore, to a certain extent, the concept of uncertainty. This, however, is the very essence of the scientific approach. Moreover, uncertainty is no barrier to choice.

  Surely, the information given to participants should include the uncertainty that exists, in particular with regard to the fact that the genetic material present in any biological sample could be identifiable at any time? Is it better to give the impression that there is no such uncertainty or to indicate that this dimension could be taken into account thanks to special vigilance regarding the use of the material taken?

Prof. Alexander Tonevitsky, Head of the Department for Translational Oncology at the Hertsen Moscow Research Oncology Institute

I am very grateful for the opportunity to take part in the consultations regarding the biological materials of human origin! As a Head of the Department for Translational Oncology at the Hertsen Moscow Research Oncology Institute I find this topic well-timed and highly demanded. This important area is needed to be thoroughly regulated and the regulations should be properly updated. To my knowledge similar regulations are currently being developed in Russian Federation and I hope these harmonized laws will provide a good basis for our current and future collaborations with the scientists from EU.

Removal, storage and use of biological materials from persons not able to consent (Articles 12, 14 and 17, paragraph 4).

In all mentioned articles this important topic is properly covered. I totally support the suggested version of the document.

Prof. Jacques SIMPORE, Professeur Titulaire de Génétique et de Biologie Moléculaires, Burkina Faso

First of all I would like to congratulate you and your team on having produced such a high-level, well-drafted document which covers the various aspects and standards of research using biological material of human origin. The standards referred to in the document provide guidelines and afford protection not only for those who freely offer their samples in health services or research centres, but also for their progeny.

It was also a wise move to focus on human tissues, avoiding all the problems and controversies concerning research on human material such as embryonic stem cells, foetal tissues and frozen human embryos.

A thought
With the advances made in genomic science, modern medical imaging and molecular diagnostic techniques, would it not be possible to take into consideration the future carrying out of analyses for diagnostic and/or treatment purposes not available at the time the material was removed and stored?

Research on the origin of HIV by means of stored samples

Retrospective analyses of serums collected for other reasons have made it possible to identify anti-HIV antibodies in samples taken in 1959. Moreover, from tissues prepared for a histological examination in Manchester, 30 years later the paraffin blocks were still stored. The DNA was therefore extracted from this sample and analysed by PCR with the help of gag gene primers. This test confirmed that the patient in question had been HIV-positive.2 According to 1959 indications, the patient had died from cytomegalovirus and Pneumocystis carinii. At that time there were no kits for HIV screening as it was still unknown. These retrospective analyses were carried out for the purpose of scientific and epidemiological knowledge in order to improve world public health.

According to the UNESCO “Explanatory Memorandum on the Preliminary Draft of the International Declaration on Human Genetic Data”, if stored samples are of undeniable

[2] WATSON, Gilman , Witkowski, Zoller, 1994. DNA Ricombinante, De Boeck-Wesmael S.A., Brussels, p. 504.

significance for medical or scientific research or public health purposes, their use to these ends even in the absence of consent of the persons concerned may be permitted. However, this document stipulates that the relevant ethics committees must be consulted and will have to decide on the undeniable value of the stored biological samples for medical or scientific research or public health.3

Based on the foregoing, it would be necessary to clearly define the standards authorising analyses having a diagnostic and/or therapeutic purpose not specified in the sampling protocols. Such analyses for diagnostic and/or therapeutic purposes could be ethically feasible, if and only if the following conditions were met:

4.1 – It was no longer possible to obtain the consent of the patients (whether alive, of unknown whereabouts or dead) who had provided their samples many years previously;

4.2 – There was no intention to conduct genetic profiling on the stored samples;

4.3 – Confidentiality (cf. Article 8) and anonymity in order to "protect the dignity and identity of all human beings and guarantee everyone (…) respect for their integrity, right to respect for private life and other rights and fundamental freedoms" with regard to the applications of biology and medicine (Article 1);

4.4 – There was an anonymity protocol ensuring that it was impossible to trace the stored samples;

4.5 – It contributed to the well-being of the local community and to improving public health at world level.

Prof. Klaus Hoeyer, MA, PhD, Department of Public Health, University of Copenhagen

As a medical ethicist with long-standing experience with research on donor attitudes to informed consent processes I find it deeply troubling that CoE does not attempt to let an update of the guidelines reflect the research conducted during the past decade.
Studies have shown how donors did not understand the information they got (Barr 2006), preferred information about something else (Ducournau 2007), were subjected to coercion, undue influence, or inducement (Brekke & Sirnes 2006), and that the information offered did not affect decisions to participate (Busby 2006, Hoeyer 2003, Felt et al. 2009). Furthermore, informed consent has very unfortunate effects and meanings in cultural contexts where signing documents (by illetarates) is associated with stealing land etc. (Patra & Sleeboom-Faulkner 2012).

It ought to be clear by now that good ethics is about developing supplementary tools, not about strengthening consent demands. The suggested guidelines are a step in the wrong direction which will only invite practitioners to circumvent the rules; not enhance their ethical reflections.

Also, the update does not address the many sources of confusions and it is not taking into account the potential participants' interests in the outcome of studies that can only be conducted on samples for which there cannot be obtained consent. I urge you to begin embracing the literature and let the guidelines reflect the generated insights.

[3] UNESCO, Explanatory Memorandum on the Preliminary Draft of the International Declaration on Human Genetic Data, SHS/EST/03/CONF-203/4, Paris, 6 June 2003, Article 17, pp 12-13.

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

General comments about our challenges :

- Working with children with rare diseases, our Biobank stores DNA/cells for new disease gene identification and possible development of genetic tests. In this context we have difficulty as to the type of consent and we opt for ''broad consent'' since at the outset we can not specify a particular project to make the acquisition of the samples.
- Parents who need to sign the consent are sometimes not educated enough with little comprehension of the biobanking activities. This creates a vulnerable group and it becomes difficult to convey the message that results may not be coming in a short time in the form of diagnosis or appropriate therapy. We need counsellors who are educated in biobanking and its governance since this activity will only be increasing in the future.
- Recontact for altered scope is not always practical since families move with internal migrations with no change of address notification. In addition, unfortunately many patients die at early ages and reaching the patient at the appropriate age for a new consent is not feasible!
- International collaborations especially with EC research consortia will be taxing with the new Data Protection Regulation since flow of data can not be in a bilateral manner until all countries outside EU have a similar code for protection of data. This makes collaborations assymetric ; especially with rare diseases where 'numbers' are scarce we need to share the data in a very optimum fashion.
- As for residual material, getting a consent for storage may be neglected during the operations. This causes a loss of valuable infrastructure especially in cancer research and potential benefit for the patients. The propriety issue from pathology departments is another challenge that sometimes makes access to fresh frozen samples for biobanking purposes difficult.

Sahlgrenska Academy at University of Gothenburg

The Sahlgrenska Academy at University of Gothenburg recognizes the importance of these issues and supports the Committees working document. It is important to protect human rights and personal integrity, and at the same time make it possible for present and future research in the fields of medicin and health care.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

RD Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research, http://rd-connect.eu/
NeurOmics: integrated European project on omics research of rare neuromuscular and neurodegenerative diseases, http://rd-neuromics.eu/
EURenOmics: developing new and better therapies for rare kidney diseases, http://www.eurenomics.eu/

IRDiRC ISC: fostering international collaboration to produce new rare disease diagnostics and therapies, http://www.irdirc.org/
Eurobiobank: European network of DNA, cell and tissue banks for rare disease, http://www.eurobiobank.org/

Background
Our area of interest is rare disease research. The scarcity and therefore elevated value of biological materials for research in rare diseases provides an argument for making use of all available materials, within a relevant ethical framework and subsequently the encouragement of international sharing of biological materials. This is an important consideration when recognising the right of people living with a rare disease to benefit from health care, prevention, and medical treatment.

Introduction
The Recommendation by the Bioethics Committee correctly emphasises the right of autonomy of each (European) citizen and from this the subsequent duties of governments, public authorities, universities and private organisations to protect privacy and restrict access to personal sensitive data. However, the recommendations do not, in our view, fully reflect the significant rights of each citizen to health and prevention of illness, through health research. In particular we would like to emphasise that, with regard both to autonomy rights and rights to health care, broad consent should be the favoured procedure for prospective sampling and for previously collected samples, re-consent, opt out or no re-consent(with approval from an ethical review board) should be the options considered.
It should be recognised having participants specify the of types of research their samples can be used for is not in the best interests of scientific progression. Participants in rare disease research recognise that there is an element of solidarity in their actions and also that they may benefit from unrelated research in the future. This potential crossover of benefit can not be anticipated and it is important not to unduly restrict research to particular disease boundaries.

Alongside this we would encourage improved transparency as per Recommendation 20 as well as better on-going contact between researchers and participants through the use of information and communication technologies.

We respond firstly in order of priority highlighted by the Council's specific request for comments on Articles 13, 12, 14, 17(4), 20, 21, 22, 23 and 24.

Comments on areas other than those highlighted by the Council

We believe that the Recommendation needs to better reflect rights to privacy as well as rights of access to preventive health care, and the right to benefit from medical treatment.

The preamble rightly states the significance of protecting private life. However it should also explicitly address the rights of each citizen to access to prevention and medical treatment. The Charter of Fundamental Rights of the European Union (2010/C 83/02) emphasises the right of each individual to integrity within the fields of medicine and biology, implying free and informed consent according to the procedures laid down by law (article 3). Article 8 in this Charter grants the individual the right to the protection of their personal data, implying that the processing of such data requires the consent of the person concerned or some other legitimate basis laid down by law. These articles are in agreement with the European Convention for the Protection of Human Rights and Fundamental Freedoms, the Social Charters adopted by the Union and by the Council of Europe.

These and other rights in the Charter may be motivated by a fundamental respect of each individual's autonomy and right to have control of matters related to oneself, e.g. the processing of personal data and the use of biological samples of human origin. In addition to

these autonomy rights the Charter of Fundamental Rights of the European Union also lays down rights of each individual to social security benefits and social services in cases of illness (article 34) and the rights of access to preventive health care as well as the right to benefit from medical treatment under the conditions established by national law and practice (article 35). As described, the Charter of the European Union recognises both the autonomy right and the right to health care and social services in cases of illness as fundamental individual rights, notwithstanding that there may also be societal and public health related interests concerned.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

Lif commends the Committee on Bioethics for making the proposals outlined in document DH-BIO/INF (2014)3. As a pharmaceutical industry organisation where members conduct research across many countries in the world, we understand the impact of local, varying and inconsistent policy and legislation on biomedical research that exists from country to country.

The proposals contained in DH-BIO/INF (2014)3 set the scene for harmonisation of national policies and legislative frameworks across European countries that would assist research by providing a single harmonised governance framework and also afford citizens across European countries a consistent level of protection and potential opportunity to participate in and benefit from research using donated human biological materials.

The general recommendation that member states adapt their national laws and practices to ensure implementation is very welcome as, currently, the legislative framework across Europe is patchy and inconsistent in both coverage and specific requirements. Additionally, the recommendation to establish codes of practice will assist individuals and organisations involved in research using human biological materials to maintain both legal compliance and socially responsible research activities.

In drafting this response, we have considered not only the implications of the document relating to the specific interests of Lif's member companies but also the wider interests of the citizens of European countries and biomedical research undertaken across Europe.

Lif wishes to thank the Committee on Bioethics for making the proposals outlined in document DH-BIO (2014)3 available for consultation. We support the intention of this document and believe that its implementation across member states will make a positive contribution to socially responsible and productive biomedical research.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

EFPIA through its direct membership of 35 national associations and 40 leading pharmaceutical companies, represents on the EU scene the more than 1,900 pharmaceutical companies operating in Europe and committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.

Thank you for the opportunity to respond to the consultation regarding the working document on research on biological materials of human origin (DH-BIO/INF (2014)3). We welcome the lead taken by the Council of Europe in addressing an area where there is a strong need for more consistent approaches across countries in the interests of advancing medical research. The sharing of health data is essential to effectively address current and emerging health

threats, whether these are outbreaks of infectious disease or long-term changes in patterns in morbidity. We would encourage the Council while finalizing the document to consider the need for pragmatic and workable rules.

EFPIA would like to support the comments submitted jointly by the International Pharmaceutical Privacy Consortium (IPPC) and the Industry Pharmacogenomics Working Group (I-PWG) and add the following points of emphasis. We also endorse the comments of our member association LIF, particularly regarding issues of scope.

PROFESSIONAL ORGANISATION

European Society of Human Genetics (ESHG)

The working document is very well written and addresses the issues related to biomedical collections and biobanking in a comprehensive way. It will serve as a useful basis for researchers and biobankers, especially in countries where specific legislation on these issues is lacking.

International Society for Biological and Environmental Repositories' (ISBER)

ISBER is an international organization addressing the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens (see www.isber.org for additional information). Although not restricted to human specimens intended for research, the great majority of ISBER members focus on human tissues procured for research purposes, either directly or indirectly (e.g. from clinical specimens procured for non-research purposes). ISBER membership and expertise in the area of human tissues used for research is extensive, longstanding, ongoing, and representative of the best practices in the field. ISBER's Best Practices for the Collection, Storage, Retrieval, and Distribution of Biological Materials for Research, which were published in Biopreservation and Biobanking (BIO), April 2012, reflect the collective experience of its members and have received broad input from other repository professionals. ISBER's membership is global and includes thought leaders in Europe with expertise in bioethics. ISBER has a keen interest in the Working Document on Research on Biological Materials of Human Origin and believes it is in a unique position to contribute.

We wish to thank the Committee on Bioethics of the Council of Europe for the invitation to submit the following comments for further consideration:

Much research is now global, particularly with regard to specimen and data sharing. Therefore, it will be important to consider how the recommendations in the Working Document comport to existing regulations and standards not only within Europe, but also outside Europe and their implications on multi-national research and global specimen and data sharing.

ETHICS COMMITTEES

Comitè de Bioètica de Catalunya, Spain (CBC)

The Standing Commission of the Committee on Bioethics of Catalonia (CBC), at the meeting on 2 July 2014, has analysed the working paper on research on biological materials of human origin.

The initiative is deemed important and appropriate by the CBC, as it leads to an improvement in the storage of samples of human origin, the compatibility of research with the respect for citizens' rights and, ultimately, because it can guide and improve state regulations on the issue.

Comité de Etica (CSIC), Spain

In general, the document is appropriate, guarantees the anonymity of people who provide biological samples; free, prior, and informed consent is required (if not, guardian or legal representative) and it is expected that the samples are deposited in tissue banks.

Norwegian National Committee for Medical and Health Research Ethics (NEM)

In short, NEM finds the working document to be well written, comprehensive and for most in accordance with Norwegian laws and regulations.

However, NEM still sees a need for a few clarifications. In particular, NEM considers it necessary to define even more clearly what the document covers; that the working document article 2 scope, describes biobanks used for medical and health related research only (not sports research or archeology); furthermore NEM suggest clarification of the differences between biological materials of human origin that is covered by the guidelines and not covered research with products derived from human tissue, e.g. cell lines.

Irish Health Research Board (HRB)

The HRB welcomes the update of the document and the consultation process to input into the changes. Overall, the document strikes a good balance between protecting research participants and enabling research whilst giving space to different national approaches where necessary. As a general point of feedback, it would be useful to make clear that this document would apply for collections of biological materials of human origin going forward, but not to historic collections.

Finnish National Committee on Medical Research Ethics (TUKIJA)

National Committee on Medical Research Ethics (TUKIJA) is an independent agency on medical research ethics in Finland. TUKIJA's primary roles are to advise and coordinate regional ethics committees in matters of ethical principle related to medical research, and to issue opinions on the ethics of clinical drug trials unless this task is delegated to a regional ethics committee. TUKIJA's duty is also to evaluate the ethical acceptability of the establishment of the new biobanks in Finland. TUKIJA provides training on medical research issues, and acts as a "second-opinion" organ to applications which have previously received negative opinion from regional ethics committee.

TUKIJA is grateful for the opportunity to comment on working document on research on biological materials of human origin.

Swedish Central Ethical Review Board

The members of the Swedish Central Ethical Review Board support the idea of developing common guidelines for Member States on biobank research and find that the proposed recommendation is well thought out and we broadly agree with its content. However, it is important to distinguish between the collection and storage of specific research projects and, on the other hand, collection and / or storage for future unspecified research. The recommendations should preferably be made even clearer when it comes to this distinction.

Furthermore, we strongly suggest that the recommendation also includes a definition of what is meant by biological material, this can tentatively be made in Article 2.

Comité National d'Ethique de Recherche (CNER), France

Generally speaking, the text is well written and corresponds to the current practices in Luxembourg.

Swedish National Council on Medical Ethics (SMER)

SMER welcomes and appreciates that the Committee on Bioethics (DH-BIO) of the Council of Europe updates its recommendations concerning research on biological materials of human origin and by this emphasizes the importance of the ethical considerations concerning these issues at the European level.

It is of great importance to strive for common guidelines for research including materials from biobanks in Europe. Research is taking place in a highly international context with increased exchange and cooperation between research groups across the European countries and from other parts of the world.

Developments in the field of genome sequencing and information technologies highlight the importance of questions concerning privacy and personal integrity raised by research on biological materials even further. An ethical perspective must always be applied to development and research. Every trade-off in favor of research is not ethically acceptable, and it is not always possible to predict certain outcomes concerning integrity aspects.

In the Swedish debate Smer has repeatedly stressed the importance of integrity and privacy issues concerning large-scale databases/biobanks that contain collections of biological materials without a specific research purpose. For example Smer has proposed that a specific national ethics committee/board should have a monitoring role for this kind of large-scale databases at the national level.[4]

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

Preliminary remark: in Belgium there is a planned legal framework (in the final pre-publication phase) governing the organisation and operation of the "biobanks", these being structures which, for purposes of scientific research with the exception of research which has human medical applications, obtain, process as appropriate, store and make available human body material as well as, should the case arise, the related data concerning this material and the donor.

The suggestions made below are often based on these projected legal texts.

Etablissement français du sang

Part of this recommendation raises issues of **change in the destination** of samples taken for purposes of scientific research.

[4] Please find opinions from the Swedish Council on Medical Ethics at www.smer.se.

In the present context of rapid technological and scientific developments, research goals are often up against the concept of change of destination and the need to re-contact donors of biological material with a view to the implementation of objectives and/or technologies which pose no particular ethical questions as to their legitimacy but which could not be foreseen, even in theory, at the time of removal. This difficulty is all the more significant to the extent that the samples are in long-term storage, as the possibilities of investigation are amplified with time whereas a donor becomes increasingly hard to re-contact.

Would it be possible to envisage in this context that the recommendation clearly authorise the possibility of sample-taking intended for research with the sample to be anonymised at the outset, irreversibly and under the control of a qualified process, thereby allowing the sample to be used, possibly re-used, without re-contacting the donor?

This type of management would be founded on the donor's fairly broad consent, entailing information about the concept of development of knowledge and of scientific research, with an assurance to the donor that the research projects using his/her donation would undergo mandatory examination by internal and/or external ethical bodies *ad hoc*.

Ideally, this sample-taking arrangement could allow the creation of biological banks intended for scientific research whose legitimacy could be based on an overall, non-predetermined cognitive objective. Such evolution of the texts would make for streamlining of the acquisition of scientific knowledge.

Norwegian Institute of Public Health (NIPH)

The Norwegian Institute of Public Health (www.fhi.no) is under the Ministry of Health and Care Services. Its mission is to improve public health and it is a national center of excellence in epidemiology, control of infectious diseases, mental health, environmental medicine, forensic toxicology, and drug abuse. It is also a national competence institution for governmental authorities, healthcare services, the judiciary and prosecuting authorities, politicians, the media and the general public. NIPH has a Department of Biobank and Infrastructure with state of the art large scale automated storage facilities and processes biological samples for use in national and international research. A quality management system based on NS-EN ISO 9001:2008 is in effect to ensure good quality of the biological materials and the administrative processes; quality programs for the different types of biomaterial have been developed and implemented. The quality management system (QMS) pertains to all activities of the Biobank and ensures the quality of the biomaterial. It includes a quality policy, customer focus and contact, resource management, document handling, processes and procedures for product realization and control, internal audits and continuous improvement, which is one of the pillars in the NS-EN ISO 9001: 2008 standard. Thus, the QMS ensures usage of findings and results from all our activities, including our biospecimen quality program, to improve our processes and quality. The Biobank manages biological samples collected through large population based epidemiological cohort studies as well as small-scale research projects. More than 4 million biological samples are currently stored in the premises.

In this context, we are submitting the following comments for further consideration in the preparation of the final document and hope the comments can be useful in the context of this consultation.

OTHERS

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

I suggest using initial capitals for Appendix throughout
When referring to the Additional Protocol, use initial capitals throughout.

Preamble

Biobanks

EUROPEAN, MIDDLE EASTERN AND AFRICAN SOCIETY FOR BIOPRESERVATION AND BIOBANKING (ESBB)

a) With regard to paragraph 2 of the Preamble: a reference for Private Life should be given.
b) With regard to paragraph 3 of the Preamble: we recommend adding the words "access to quality research" at the end of this paragraph.
c) With regard to paragraph 7 of the Preamble: "taking into account the current and planned development of collections*"*, we recommend changing this to: "taking into account the current and planned changes in infrastructure for human biological sample collections".
d) After paragraph 9 of the Preamble: we recommend addition of anew paragraph as follows:
"Taking into account the fact that stored biological materials must also be considered a personal patrimony that may need to be referred to in case of disease progression and/or the need for future health analysis".
e) With regard to paragraph 10of the Preamble, we recommend changing to "feedback on potential health-related findings" which includes both incidental and unsolicited findings.
f) With regard to paragraph 18 of the Preamble, we recommend adding that "..... there should be policy to allow fair access to the collections of human biological materials".
g)Finally, the Preamble should include a statement that all personnel involved in 'research on biological materials of human origin' should be adequately trained.

Biobanking and BioMolecular resources research infrastructure BBMRI-ERIC

The preamble is not very balanced. There are many provisions and repetitions regarding privacy, protection of human etc. but only one provision regarding interests of medical and biomedical science and benefits. One should remember that freedom of research and right to pursue professional activities are also fundamental rights. In addition, this kind of an approach seems to reflect traditional regulation on clinical trials on humans, but biobanks only collect biological specimens and research only use samples in repositories. *Which welfare issues are really at stake?*

Swedish National Council of Biobanks (NBR)

NBR agrees with the preamble and the object (Article 1) concerning the importance of respect for human integrity and of private life.

However, we also believe that it is very important to emphasize the rights of all citizens to live in a society

- with a broad knowledge about prevention of diseases as well as corresponding health recommendations, screening and vaccination programs,
- which can provide diagnostic methods that both enables early detection as well as to ensure that the correct treatment is given,
- which can ensure that each patient can receive adequate treatment for his/her disease, either to mitigate, control or to cure.

This cannot be achieved without medical research. Research based on human biological material (hereafter called samples) is of great importance for development and knowledge in several medical disciplines. Stored samples, together with information about the samples and about the patients, are fundamental for reaching a better understanding of the diseases genetic background, in order to identify predictive markers of risk for the individual patient and to develop more efficient and more personalized treatments with fewer side effects.

Therefore, it is in the interest of every citizen that samples can be made available for medical research. This should be done in a way that respects the privacy interests of individual sample donors.

ACADEMIA

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

In order to touch the relations between patients/health citizens and researchers, we suggest a rewriting of article 1: “Member states and their individual citizens can benefit from research on biological materials of human origin, but member states are required to secure that such research is done under the protection of the dignity and identity of all human beings and guarantee that everyone without discrimination is respected for their dignity, right to respect for private life and other rights and fundamental freedoms with regards to any research governed by this Recommendation.”

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We agree that privacy is a key issue when dealing with human biological materials.
As a result, we consider that the sentence “*Stressing the importance of the right to privacy in the field of biomedical research, as defined in data protection instruments*” perhaps should also include “*and clinical research instruments*” as these also govern privacy in clinical research.

We respectfully request that the Committee on Bioethics consider this addition.

ETHICS COMMITTEE

Swedish National Council on Medical Ethics (SMER)

Definition of biological materials
The recommendation lacks a clear definition of biological materials.
Clarification concerning conditions under which a person should be able to/should be allowed to re-examine consent

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

The Recommendation should provide a more complete and balanced perspective on rights. In addition to supporting the rights to privacy, the rights of access to preventive health care

and the rights to benefit from medical treatment should also be presented. This would be consistent with the Charter of Fundamental Rights of the European Union (2010/C 83/02), which emphasizes a) the right of each individual to integrity within the fields of medicine and biology, implying a free and informed consent (Article 3); b) the right to the protection of personal data concerning an individual (Article 8); c) the rights of each individual to social security benefits and social services in cases of illness (Article 34); and d) the rights of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices (Article 35).

European Union

European Commission (DG JUSTICE)

Please note that our comments are set against the benchmark of the Commission's proposed General Data Protection Regulation (COM(2012)11final): http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012PC0011&from=en
Preamble: reference should be made also to the Convention 108, since "identifiable biological materials" are personal data, so that the principles and rules on the protection of personal data apply.
A horizontal provision should clarify that the safeguards set out in these recommendations should also encompass the protection of other personal data, which are processed in this context; e.g. such data which allow identification;

OTHERS

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

In the penultimate paragraph of the Preamble, I suggest replacing “law” in the penultimate paragraph by “legislation”.

CHAPTER I – Object, scope and definitions

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

General comment on Chapter 1:
It would be necessary to define the terms “biological materials” (or “human biological resources” or “identifiable/non-identifiable human biological samples” as suggested earlier) as well as the term “collection”, used in the recommendations (e.g. Chapter V) within this Chapter or in a separated section of Definitions; Also, for this latter we propose to change the term “collection” by the new commonly used “biobank” term or to explain the difference between these two terms..

Article 1 – Object

Member states should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to respect for private life and other rights and fundamental freedoms with regard to any research governed by this Recommendation.

BIOBANKS

3C-R, réseau français de biobanques

Comment on Article 1

Human materials can be used properly for research purposes only if they are characterised by biological, clinical and medical data. Respect for private life accordingly also extends to the collection, use and storage of sensitive personal data. This concept is covered by Article 2.3 of the recommendation, but could also be incorporated in Article 1. Privacy issues include providing donors with the necessary information, obtaining their consent and the right to have data corrected or deleted.

Proposal for wording Article 1

Member states should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to respect for private life and other rights and fundamental freedoms with regard to any research ***concerning their biological materials*** governed by this Recommendation.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

“Member states should protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity, right to private life and other rights and fundamental freedoms with regard to any research involving their biological samples governed by this recommendation.”

ACADEMIA

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

In order to touch the relations between patients/health citizens and researchers, we suggest a rewriting of article 1: “Member states and their individual citizens can benefit from research on biological materials of human origin, but member states are required to secure that such research is done under the protection of the dignity and identity of all human beings and guarantee that everyone without discrimination is respected for their dignity, right to respect for private life and other rights and fundamental freedoms with regards to any research governed by this Recommendation.”

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

The word ‘identity’ should be defined. What does the concept mean in this context?

Article 2 – Scope

1. This Recommendation applies to
- the obtaining of biological materials of human origin for storage for future research purposes;
- the storage of biological materials of human origin for future research purposes; and
- the use in a research project of biological materials of human origin that are stored or were previously obtained for another purpose, including a previous research project.

2. This Recommendation does not apply to
- embryonic and foetal tissues; and
- the use in a specific research project of biological materials of human origin removed for that purpose. This is within the scope of the Additional Protocol concerning Biomedical Research (CETS No. 195).

3. The collection, storage and use of biological materials of human origin may be accompanied by associated personal data. Where in this Recommendation provisions make reference to biological materials of human origin these extend, where relevant, also to associated personal data.

BIOBANKS

3C-R, réseau français de biobanques

Comment No. 1 on Article 2

This article is hard to read because it has two focuses:
1. The origin of samples (obtained for research or obtained previously for another purpose, embryos or foetuses)
2. The use made of these samples (obtaining, storage and use).

Comment No. 2 on Article 2

The term "research" could be defined so as to eliminate any ambiguity regarding the recommendation's scope: fundamental research, including conservation of historical collections, pre-clinical research, biotechnological research, use for validation of methods and quality controls needed for research protocols.

This definition would make it possible to dispel the ambiguity surrounding the various possible uses of human biological materials other than those that are medical in nature (care, diagnosis, prognosis). Apart from being used for research in the strict sense (fundamental and applied), such materials can be used to validate methods and to conduct quality controls that are absolutely essential to the quality of research activities or medical care.
These last two uses are generally poorly defined, and therefore regulated, by the legislation. For example, in France the control of medical biological analyses or of medical devices is cited as a possible use of human blood (L.1221-4 of the Public Health Code) but not of other types of samples.

Comment No. 3 on Article 2

It should be noted that if the scope of this recommendation excludes research coming under the Additional Protocol concerning Biomedical Research (CETS No. 195), any collection of

human materials involving interventions on human beings is de facto excluded from the recommendation. An exception has been introduced into French law (Article L 1221-8-1 of the Public Health Code) to permit the collection of blood samples for specific use in research not involving clinical trials (biomedical research or interventional research). Furthermore, should the exclusion be maintained this article can be seen to be inconsistent with Articles 11 and 12 that deal with removal of biological materials for storage for future research.

Proposal for wording Article 2

Article 2-1: This recommendation applies to all activities concerning biological materials used in research in the field of human health: obtaining, removal, collecting of blood samples, re-use, preparation, transformation, storage, qualification, validation of methods, preparation, inclusion in a collection, making available.

Article 2-2: For the purpose of this recommendation the term research shall encompass any fundamental research, including conservation of historical collections, preclinical research, biotechnological research, use for validation of methods and quality control of medical care or research activities. This recommendation does not apply to research on embryonic cells or to research projects coming under the Additional Protocol concerning Biomedical Research (CETS No. 195): research involving interventions on human beings or research on foetuses.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 1.
Proposal of specifications:
Does this Recommendation apply to microorganisms of human origin? To what extent?
Proposal: Insert an explicit referral to the obtaining, the storage, the use of microbial materials contained in human biological samples (or human clinical isolates)
Are the blood, urine, hairs included?

Does a specific procurement of human biological sample for future research purposes is in the scope of this Recommendation? In such a case, is this covered by paragraph 2 and thus only by the Additional protocol CETS No.195? Need for clarifications about the articulation between these texts.

From this article, the position of the actual recommendation on biomaterial collected for primary diagnostic use and/or surgical left over is not clear. Left materials after diagnosis and/or surgical and/or clinical trials may be destined to future research only if there is a warranty of quality management of the material from the collection. Under the right circumstances this “residual biological material” is a valuable source of human biological resources for research that would otherwise be destroyed. A direct mention of this material should be included in this section. Also it is proposed to refer to “residual biological material/samples”.
Para. 2.
- the obtaining, storage and use in a specific research project of biological materials of human origin removed for the sole purpose of that project. This is within the scope of the Additional Protocol concerning Biomedical Research (CETS No. 195).

Para. 3.

Proposal of specifications: …these extend, where relevant according to Article 3, also to associated personal data (link with the Council of Europe Convention N°108, http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm)...

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 2: Scope.
I cannot understand the distinction being made in 2.2 regarding the non-applicability of this recommendation to "the use in a specific research project of biological materials of human origin removed for that purpose. This is within the scope of the Additional Protocol concerning Biomedical Research (CETS No. 195)."

How does this substantially differ from the inclusion criteria of "the use in a research project of biological materials of human origin that are stored or were previously obtained for another purpose, including a previous research project."?

In practice there is little to distinguish these two activities that I can imagine and often specimens obtained by researchers for a specific project will subsequently be used by the same team for a related but different purpose later on.

In my opinion it would be more straightforward to state that this recommendation, "Applies to all uses of human biological materials for research purposes regardless of whether they were obtained specifically for that purpose or have been stored for future use"

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

The working document does not state whether this recommendation applies both to collections of biological materials and data that were created *before* and *after* the entry into force of this recommendation.

In order to avoid misconceptions in relation to restrictions, we suggest including the following passage into the working document: "An important consideration for the conduct of research is that this should be made possible in all situations where health personnel are expected to treat patients without their consent. Such situations include attempted suicide and conditions with blurred or loss of consciousness. These examples demonstrate important aspects of the ethical consideration. In the case of suicide, treatment may be in direct opposition to the wishes of the patient and even documented in a letter. Nevertheless, physicians are expected to do whatever necessary to save the life of the patient. Improving lifesaving treatment could involve new treatments to detoxify the patient and such treatments should be allowed to be developed. Such procedures could well involve collection of biological materials. The situation of neurological emergency is one where each second matters. There is no ethical problem with attempting to save the patient, but there is not time at all to secure consent from anyone. Again collection of biological materials could be an important part of developing new treatments." We note that Danish legislation on Ethical Committees incorporates a paragraph outlining the conditions for research projects in acute situations where pre-consent is not possible, §11 in https://www.retsinformation.dk/Forms/R0710.aspx?id=137674

It would be useful if Article 2 defines exactly if it also refers to umbilical cord blood tests, which often is used in connection with neonatal screening projects.

Dr. Amin El-Heliebi, Dr. Karine Sargsyan, Biobank Graz, Medical University Graz

Article 2.2

Placental tissue is although also foetal tissue but it is a residual material (waste) and should not be excluded in these recommendations as it is an attractive source for biomedical research.
--e.g.: embryonic and foetal tissues (excluding placental tissue)

The scope of this recommendation should exclude the use of biological material for the forensic applications.

--the use of biological materials of human origin for forensic analysis

KU Leuven Faculty of Medicine, Belgium

First of all, we found problematic the fact that the scope of the recommendation, based to Article 2 paragraph 2, seems not to apply to the use in a specific research project of biological materials of human origin removed for that purpose. The use of the word 'specific' is confusing. Reading this, we understand that this recommendation could not apply to population-biobanks, which could be considered a specific research project.

Prof. Kelly Tilleman, PhD, Universitair Ziekenhuis Gent, Belgium

As a general remark I would say that if one collects material for future scientific research, you would have to store the material for some time (short or longer).
So, I would suggest trying to omit redundant paragraphs throughout the text. Some paragraphs are repeated many times: removal – collection – storage – general principles: these actually apply for removal and storage: why not keep only this and state that this principles apply for both removal of tissues and cells and storage?

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

Within this article the scope usefully includes the end-to-end processes relevant to human biological materials, starting with the removal of the biological materials from the body through to its end-use in research. In governance terms we consider that all of these processes, when the intended end-use is future research, constitute research. We, therefore, feel that a definition of research that includes all processes extending from the identification and recruitment of donors of biological materials and the obtaining of the biological materials through to end-use would be valuable to ensure that all parts of the activity chain are appropriately governed.

We also consider that it might be useful to more clearly define the term "human biological materials" as there is wide scope for interpretation of this term.

We respectfully request that the Committee on Bioethics consider 1) including a broad-based definition of research to effect a clearer statement on the scope of this Recommendation and 2) including a definition of human biological materials.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

We respectfully request that the DH-BIO consider biological samples that are no longer identifiable (anonymized or anonymous) to be out of scope of this recommendation. In circumstances where the biological samples have been anonymized or collected anonymously it may be impractical to ensure traceability of consent including the permissions granted by the persons concerned and the rights of a person to direct the future use and access to the sample.
If not deemed out of scope, then we recommend that the DH-BIO clarify how a researcher could reasonably maintain a link between the anonymised or anonymous sample and the original permissions within the informed consent while ensuring the privacy protections offered by anonymisation.

ETHICS COMMITTEE

Swedish National Council on Medical Ethics (SMER)

Definition of biological materials
The recommendation lacks a clear definition of biological materials.

Swedish National Council on Medical Ethics (SMER)

Age categories
The phrase "age category" is used in three places in the document. Age-based categories are particularly problematic when talking about children or the elderly, but there is also another reason: the text is intended to protect individuals, not groups. Group-based reasoning rarely protects individuals. We propose to focus on protecting individuals, and to formulate the text so that it becomes clear that this is the intention.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (1) of this article indicates that the recommendation applies to “the obtaining of biological materials from human origins for future research purposes”. The scope is too limited and should be modified to encompass the full range of situations for which biological specimens may become available including residual samples from clinical settings.

Issues of sample disposal and de-identification should also be covered.

Paragraph (3) refers to the collection of “associated personal data”, and should specify that the provisions related to associated data comply with national and European data protection laws.

EUROPEAN UNION

European Medicines Agency (EMA)

Article 2.2
Please consider that there is an increasing research work related to amniotic stem cells as well as foetal DNA recovered from mother's peripheral blood: criteria for exclusion of such bio-specimens are not intuitive.

OTHERS

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

Insert comma after “origin” in para. 3 of Article 2.

Article 3 – Identifiability of biological materials

Biological materials referred to in Article 2 may be identifiable or non-identifiable:

i. *Identifiable biological materials* are those biological materials which, alone or in combination with data, allow the identification of the persons from whom the materials have been removed, either directly or through the use of a code.
In the latter case, hereafter referred to as “coded materials”, the user of the biological materials may have direct access to the code or, alternatively the code may be under the control of a third party.

ii. *Non-identifiable biological materials*, hereafter referred to as “anonymised materials”, are those biological materials which, alone or in combination with data, do not allow, with reasonable efforts, the identification of the persons from whom the materials have been removed.

BIOBANKS

3C-R, réseau français de biobanques

Comment No. 1 on Article 3 i

This article deals specifically with the possibility of identifying a person by means of biological materials, alone or in combination with data. In this context, it could be understood that when biological materials contain DNA they can be considered identifiable if they can be linked to an existing genetic profile.

Comment No. 2 on Article 3 i

The law is far stricter regarding the use of identifiable biological materials. In the case of researchers using coded materials, where the code is under the control of a third party (which applies to biobanks or Biological Resource Centres), it could be considered that they are working with biological materials which they themselves cannot identify, and that responsibility for access to the person is borne by the supplier of the biological materials. This distribution of responsibilities would make it possible to fulfil a twofold requirement which may at first seem contradictory: retaining a means of tracing samples if they need to be destroyed for various reasons (for example if the person from whom they were removed withdraws consent, or is a minor and withholds consent on coming of age, or it is impossible to obtain consent, and so on) while ensuring that samples are anonymised at the time of their use.

Proposal for wording Article 3 i

Identifiable biological materials are those biological materials which, ~~alone or~~ in combination with data, allow the identification of the persons from whom the materials have been removed ***or collected***, either directly or through the use of a code ***referring to a correspondence table***. In the latter case, hereafter referred to as "coded materials", the user of the biological materials may have direct access to the code. ~~***or, alternatively the***~~

~~***code may be***~~ ***If*** the code is under the control of a third party ***the user shall be considered to be working with non-identifiable biological materials.***

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Comment on "Anonymised"
The given definition of "anonymised materials" is questionable and subject to an ongoing debate in the scientific community, as the (genetic) information within the material itself in principle allows an identification of the person from whom the materials have been removed. Subject to anonymisation can only be the meta data coming along with the material. The material as such contains the full genome.

As sequencing has become quite feasible and affordable, the concept of anonymising biological material is challenged to an extent that it should not be used without a clear statement of the risk.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Definition and level of identification of biological materials to be collected and or stored for research (either prospective or retrospective) are basic element of the handling of human biological samples for both therapeutic and research aims.

There is not presently a harmonised "vocabulary" on the identifiability of human biological materials for research involving biobanks. Each geographical region adopts different terms and categories in relation to the identification of donors of biological specimens and associated data. Based on the existence of different concepts and related meanings, we recommend that this document should state clearly that each region (including, for example, Europe, Americas, Asia, etc.) utilizes different terminology on the identifiability of samples given to a biobank for research aims. This could be achieved by adding a table summarising different terms and meaning according to different countries. Towards the same aim, we recommend a reference to a paper by Bernice Elger and Artur Caplan on biobanks and anonymization (12) in which the terminology on the identifiability of samples and data used in research in different international regulatory contexts is reviewed.

From a practical point of view,we recommend clarification of the fact that biobank personnel are responsible for utilizing appropriate measures of reversible anonymization processes of samples and data. Biobanksmust have dedicated personnel not involved in the research. Samples and data given out for research shall be distributed without any reference to the donor.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 3: The problem with the definition here is that it lacks contextual reference. Identifiability depends on the person using the material A human biological sample with some limited clinical information may not be identifiable to a user but the supplier of that material may retain a code from which they can readily identify the person. The reality is that 'anonymised' samples do not actually exist outside of a specific context. So it is possible a human biological sample may be 'non-identifiable' to the user under your definition but still be 'identifiable' to the supplier.

KU Leuven Faculty of Medicine, Belgium

Article 3.ii
When it comes to Article 3 ii, we think that it may be more consistent to repeat the term "biological materials" and not interchange it with "materials", if data or other materials are to be excluded.

Prof. Cassiman, University of Leuven, Belgium

Article 3.ii
Anonymisation of samples is not considered anymore as being possible. There are many ways around it….'encoding, encrypting' or other words are probably better and more realistic.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

We note that this article outlines the differences between identifiable and de-identified materials but then switches to using the term anonymised. This is confusing and we recommend using identifiable/de-identified only and avoiding the use of anonymous. This will bring the document in line with practice in the USA as per the HIPAA Rule[5] which is significant, as the standardisation of terms is key for expediting the international sharing of materials and data.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

The definitions of identifiability used in this document seem confusing. Further, the definitions of "identifiable" vary greatly in the field. For example, the definitions used in this document appear to be different from the definition of "identifiable" under the US human subjects regulations ("Common Rule"). The Common Rule uses a "readily ascertainable" standard (readily ascertainable to the investigator). Research using coded specimens in some circumstances is not considered human subject research if certain conditions have been fulfilled, and therefore, in those circumstances may not require IRB review or informed consent. This is an important distinction between the requirements of this document and what is permissible under US regulations. Definitions of these terms may vary among countries in Europe as well. The European Medicines Agency (EMA) has issued an International Conference on Harmonization Document, ICH E-15, in which the terms related to identifiability are defined (see http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf).

[5] (http://www.hhs.gov/ocr/privacy/hipaa/understanding/summary/privacysummary.pdf)

It is our understanding that these definitions have been accepted by the Food and Drug Administration in the United States as well as the EMA. They should be considered for inclusion in the Working Document as this may help reduce confusion, promote harmonization and increase consistency in use of these terms globally.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basis tenant of this article.
However, we request some clarification of when biological materials can be considered "*non-identifiable*"

1) We consider that the phrase "*with reasonable efforts*" is too open to interpretation to be useful.
2) We also consider that "coded materials", where "*the code may be under the control of a third party*" who is acting as a safe-haven guardian of identity should be considered as non-identifiable for practical purposes as it would take more than reasonable efforts to break the privacy protection provided by the third party.
3) Indeed, we suggest that to avoid misinterpretation the article be amended to recognise that there are in fact 3 categories:
    a. Identifiable biological materials
    b. Coded biological materials
    c. Fully anonymous biological materials.

We consider that the ethical and legal issues, as well as matters of practicality, merit recognition of these 3 categories as distinct and that any future laws or recommendations developed from this Working Document will be strengthened by considering each category for their own specific implications.

We respectfully request that the Committee on Bioethics consider these points.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

We would encourage the Council to consider aligning the document with existing data definitions and to use terminology which reflects the measures that have been taken to limit identifiability such as those contained in the ICH HARMONISED TRIPARTITE GUIDELINE E15[1.]. The measures taken to protect data subjects are important in themselves, but also because they have relevance for the consideration of the issues raised in other parts of the document.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

We support the intent of this article yet recognize that there is opportunity for further clarification of categories by which biological samples may be identified in order to better align with existing frameworks including the ICH Harmonised Tripartite Guideline E15[1] which defines four general categories of coding: identified, coded, anonymised and anonymous. We believe such differentiation would support the justification of identifiability (Article 7) as well as support better understanding of the feasibility of additional tenants proposed by DH-BIO, for example related to re-contact of donors of identifiable biological material to seek additional consent (Article 17) or to provide relevant results.

If existing frameworks are not adopted, we ask that the definition of "identifiable biological materials" be clarified to make it clear that a biological sample is not considered identifiable unless other data capable of identifying the persons from whom such materials have been removed are linked to the sample. Re-identification of a sample of biological materials without access to either an identified reference sample or data set requires disproportionate effort. Furthermore, we propose that the definition of "non-identifiable biological materials" include samples where the link has been irreversibly broken, such as coded materials provided through controlled transfer to a researcher who has no influence over or access to the code. In such a case, it would take more than reasonable efforts to break the privacy protection provided by the third party.

Regeneron Pharmaceuticals, USA

Article 3.ii
Suggested Revision: We propose replacing the term "anonymised" with "de-identified", or "coded" wherever noted within this document. If it is determined that our proposal is not agreeable, we request that the term, "with reasonable efforts" be further clarified or defined to allow researchers to connect a subject's identifying information with his/her sample and data.

ETHICS COMMITTEES

Irish Health Research Board (HRB)

The definitions of identifiable and non-identifiable are somewhat loose, and there may be different interpretations in different countries. National legislation or regulation may be needed to specify exactly what is meant.

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 3.ii: TUKIJA is not certain whether "do not allow with reasonable efforts the identification of the persons" means the same as "anonymised". In TUKIJA's opinion it rather means hard-identifiable or difficult to identify than non-identifiable or anonymised. TUKIJA further encourages contemplating whether the concept of anonymisation is still relevant in modern scientific world where the means to identify practically any sample exist. Still, TUKIJA notes that some kind of protection is warranted even though anonymisation is no longer possible and, thus, TUKIJA finds the distinction of the article itself relevant.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

The practicable application of this article is difficult with respect to biospecimens because there is not good consensus regarding what is 'identifiable' and 'non-identifiable' and biospecimens typically hold the potential to provide identifiable information once they are analyzed.

Article 3 addresses individual identifiability but should also address identifiability at the level of the family and community.

European Union

European Commission (DG JUSTICE)

Article 3.ii: "with reasonable efforts" should be clarified: "with means reasonably likely to be used" (see recital 23 of the proposed Regulation);

CHAPTER II – General provisions

ACADEMIA

***Prof.** Jacques SIMPORE, Professeur Titulaire de Génétique et de Biologie Moléculaires*

In Articles 3, 11, 12, 13, 14 and 17 it should be made clear that the acquisition, storage and use of biological material of human origin to be conserved for subsequent research or which had been obtained previously for another purpose, including an earlier research project, must not be used for genetic fingerprinting tests (genetic profiling) on those from whom they had been obtained. For example, no file based on the genetic fingerprint obtained from these stored samples may be compiled and entered into a national DNA database.

Article 4 – Risks and benefits

1. The risks for the persons from whom biological materials have been removed and, where appropriate, for their family, related to research activities, in particular the risks to private life, should be minimised, taking into account the nature of the research activity. Furthermore, those risks should not be disproportionate to the potential benefit of the research activities.

2. Possible risks for the individuals in the same group as the person from whom biological materials have been removed should also be taken into consideration in this context.

BIOBANKS

3C-R, réseau français de biobanques

Comment No. 1 on Article 4

Since this article addresses the risks and benefits inherent in the use of human samples for research it might be appropriate to define a risk and a benefit in the sphere of use of biological materials.

Comment No. 2 on Article 4

Reference is made to the families of persons from whom biological materials have been removed. Given that the rules on medical secrecy are generally laid down in national law, including with regard to informing family members, this article could indicate that information must be provided solely in accordance with national law.

Proposed wording of Article 4. 1

The risks arising from the use of biological materials in research concern both risks relating to the collection or removal of materials and those linked to the use of research results. The risks for the persons from whom biological materials have been removed and, where appropriate, for their family, related to research activities, in particular the risks to private life, should be minimised, taking into account the nature of the research

activity. ***If information concerning such risks affects medical secrecy it must be disclosed only in accordance with national law.***

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 1.
Proposal for textual specifications
Specify the notion of "family" and/or refer to national laws.

Proposal of textual modification
The risks for the persons from whom biological materials have been removed and, where appropriate, for their family or their relatives, related to research activities, in particular the risks to private life, should be minimised, taking into account the nature of the research activity.

Para. 2.
Proposal of modification
Possible risks or benefits for the individuals in the same group as the person from whom biological materials have been removed should also be taken into consideration in this context.

Proposal of textual specifications
Specify who are the "individuals in the same group". It would be appropriate to give some examples, in order to avoid misunderstanding and facilitate the application of this paragraph.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Article 4.2: the term "group" should be defined
We recommend addition of a third paragraph as follows:
"Where possible at least one aliquot of biomaterial should be retained for the future personal use of the donor".

Regarding the risks and benefits that should be explained the general patient information to be published by ECPC (13) provides a useful reference.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 4: the reference to risk here is not particularly helpful. It would be better to simply state
" Donors of human biological materials are entitled to the same protection against risk as for any other research activity. Researchers and ethics committees are responsible for ensuring that there is an appropriate balance between the risk of harm to donors, their family or members of any group they are associated with, and any benefits that may arise from the research activity. "

KU Leuven Faculty of Medicine, Belgium

Article 4
Regarding Article 4, we believe that the notion of minimizing the risks to private life should be further specified. We also think that it may be important to clarify what is meant by "the individuals in the same group as the person from whom the biological material has been removed", as mentioned in the second paragraph of the same Article.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO)[6]

Include Benefits:

Article 4.3
Persons from whom biological materials have been removed could benefit of obtainning the information derived from their samples, once the studies has been published.

***Prof.** Jacques SIMPORE, Professeur Titulaire de Génétique et de Biologie Moléculaires*

What is meant in the French text of Article 4.1 by *"Les risques pour les personnes chez lesquelles les matériels ont été prélevés et, le cas échéant, pour leur famille, liés à des activités de recherche, en particulier les risques pour la vie privée, devraient être réduits au **minimum** eu égard aux caractéristiques de l'activité de recherche"*? My question is the following: should the risks to private life be "réduits *au maximum"* rather than "*au minimum"* ?[7]

ETHICS COMMITTEES

Irish Health Research Board (HRB)

The HRB welcomes the approach of proportionality between risk to the donor and potential benefit of the research activities.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Article 4 (1) focuses primarily on risks to persons and their families. However, benefits should also be emphasized and include benefits to the individual and benefits that extend more broadly to the society and public health. These considerations should also be reflected in the text describing the proportionality of the risks.

Article 5 – Non-discrimination

[6] Private/public partnership

[7] Translator's note: Here the author is questioning what is to be understood by risks being "reduced to the minimum" rather than "reduced to the maximum". The English text of this Article does not have the same ambiguity, stating that such risks "should be minimised".

1. Appropriate measures should be taken, in the full range of research activities, to avoid discrimination against, or stigmatisation of, a person, family or group.

2. Refusal to give consent or authorisation to the removal, storage or research use of biological materials or the withdrawal or alteration of the scope of the consent or authorisation given should not lead to any form of discrimination against the person from whom biological materials have been removed, in particular regarding the right to medical care.

BIOBANKS

3C-R, réseau français de biobanques

Comment on Article 5.2

The addition of point 2 to Article 5 makes it possible to clarify the scope of non-discrimination with precision.

Proposed wording of Article 5.2

Refusal to give consent or authorisation to the ***collection***, removal, ***re-use***, storage or research use of biological materials or the withdrawal or alteration of the scope of the consent or authorisation given should not lead to any form of discrimination against the person from whom biological materials have been removed, in particular regarding the right to medical care.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 2.
Proposal of textual clarification:
"Refusal to give consent or authorisation…" What does the term "authorisation" mean in the context of this text, what is the difference with the consent notion as used along this Recommendation? Does it refer to consent given on behalf of a person by somebody else (a competent representative or authority, when so provided by law)? Such key terms should be clearly and consensually defined in order to enhance harmonisation while keeping the possibility to refer to national laws for specific detailed definitions). Clarification is needed: authorisation vs informed consent vs opting-out or presumed consent.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

We recommend addition of a third paragraph as follows:
"A person should be allowed the right to opt to be included in a research project, even if the actual risk of being identified cannot be avoided".

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (2) of this article reads "*Refusal to give consent or authorisation to the removal, storage or research use of biological materials or the withdrawal or alteration of the scope of the consent or authorisation given should not lead to any form of discrimination against the person from whom biological materials have been removed, in particular regarding the right to medical care*." This is difficult to follow; what does 'alteration of the scope of the consent' refer to? Alteration by whom? The text need to be reviewed and edited for clarity.

Article 6 – Prohibition of financial gain

Biological materials should not, as such, give rise to financial gain.

BIOBANKS

3C-R, réseau français de biobanques

Comment on Article 6

To avoid any difficulty of interpretation, Article 6 could be clarified so as to explain the commercial activities that can be carried out thanks to value added through research or through the management of biological materials.

Proposed wording of Article 6

In accordance with the principle of non-ownership of the human body, biological materials should not, as such, give rise to financial gain ***or to ownership relations. This principle in no way precludes deriving financial benefit from research results that lead to a marketable product or service, or charging a fee for making biological resources available for a non-profit activity (as in the case of biobanks and Biological Resource Centres).***

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Proposals of adds
Biological materials should not, as such, give rise to financial gain ***or patrimonial provisions.***

Proposed add: ***…"without prejudice to intellectual property rights or legitimate rewarding provided by law".***
E.g. fees for maintaining the quality of the biological resources.

Proposed add: ***"Production costs if the material has been transformed, characterized, purified, produced can nonetheless be charged".***

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

We recommend clarification of the term "no direct financial gains".

Academic biobanks (ie. non-commercial entities) are not supposed to become for-profit businesses. Academic biobank samples may not be sold at a profit, as dealing with human samples is prohibited in Europe. It does cost money to collect and store samples, and therefore medical researchers who use the samples may be asked by the biobank to pay the costs involved in collection, preservation, storage, quality control, retrieval and transportation (called 'cost-recovery' or 'added value' to the sample by creating a derivative or processing in some way). This does not mean that the sample itself has been sold by the biobank, but is rather a method forsharing the costs incurred in sample collection and management.

Comité de Etica (CSIC), Spain

This is a very important provision. Otherwise, there's a risk that medical professionals might use or obtain benefit from patient material.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 6 is ill defined as written. Research may give rise to discovery of new diagnostics and treatments that are able to realize a commercial benefit to those that make them. This clause appears to rule that possibility out. If you mean to limit trade in human tissue itself then it is best to state this. Perhaps "Human biological material should not give rise to financial gain (profit) for those who collect, store and distribute them. " I refer you to a paper produced by the NHMRC of Australia on this topic. (ref).

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

Inventions and results from research projects are communicated or sold to private companies in order to develop them to new products/services. In order to avoid misunderstandings regarding the relationships between researchers and private companies, we suggest to elaborate Article 6.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

We suggest that the explanatory memorandum that accompanies this document include a discussion that accepts cost recovery models for use of specimens and/or specimen derivatives.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basic tenant of this article.

However, we consider that in its current wording ("*Biological materials should not, as such, give rise to financial gain.*") it may give rise to unintended interpretations. Perhaps further

explanation can be included, as was provided in the Explanatory Memorandum to the previous Rec(2006)4.

It would be useful to emphasise that:

- It is legitimate for research using human biological materials to be for commercial purposes, such as the discovery and development of new methods of preventing, diagnosing or treating disease;
- Fees can be levied for fair recovery of costs (without profit) of acquisition, handling, storage or supply of human biological materials;
- Fees can be levied for services using the application of specialist skills and know-how that add genuine value to the research user of human biological materials. It is legitimate to profit from the application of skill and the provision of services, but not from the supply of samples themselves.
- It can be legitimate to provide donors of human biological materials with fair compensation for reasonable expenses and for time, trouble, discomfort and risk as is a commonly accepted practice in relation, for example, to participation in clinical studies.

All of the above indirect methods of financial gain are commonly conducted, accepted and are vital for the sustainability of research using human biological materials. To unintentionally imply that these are not acceptable will have detrimental effects on legitimate research.

Additionally, it might also be beneficial to positively state that the human body and its parts should not be commoditised. Examples of commoditisation would be a) setting higher fees for commonly sought biological materials, to reflect demand; b) setting higher fees for biological materials from rare diseases, even if the costs associated are no more than for commonly occurring disease materials.

We respectfully request that the Committee on Bioethics consider these points to effect a clearer statement on prohibition of financial gain.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

The statement “Biological materials should not, as such, give rise to financial gain” is open to misinterpretation. We assume that it was not the intention to proscribe commercial research using human materials or to preclude those who are responsible for processing those materials from earning fair return from their efforts. It should also be noted that it can also be legitimate to recompense individuals for their participation in research activities which involve the donation of samples. It would be helpful to expand this article to make the intent clear.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

We suggest elaboration of this article to make its meaning explicit. For example, there are companies that collect biological materials under IRB/EC-approved protocols for the purpose of making them available through sale for research purposes. The article should clarify that the prohibition on financial gain does not extend to these activities which promote the efficient advancement of medical research and treatment and which do not have a negative or coercive effect on persons concerned. In addition, the article insufficiently distinguishes the question of financial gain derived from the knowledge obtained through the use of biological materials. To address this second scenario, we suggest further clarification to

reflect that the use of biological materials by commercial entities would not be prohibited in circumstances where there may be commercial gain derived from the findings of research on biological materials, given the critical role this may play in the advancement of medicine. Furthermore, we recommend that DH-BIO distinguish other commonly accepted financial gain in the context of biological research, including where expenses are charged for minimal recovery of costs or payment for services, or where donors are provided fair compensation for time and effort.

Regeneron Pharmaceuticals, USA

Suggested revision: "Biological materials should not, as such, give rise to financial gain to those individuals from whom biological samples are obtained. This does not prohibit compensation of study subjects for participation in research, in accordance with local laws and regulations." Furthermore, it should be clearly stated that the donors of specimens will not receive direct financial benefit from any discoveries made from analysis of their specimens.
Rationale: We recognize that this clause is already captured in the current recommendations. However, given the opportunity to comment, we believe that the clarification noted above should be appropriately captured to note that financial gain is prohibited only for those individuals or persons from whom biological samples are obtained, while still allowing for general compensation of subjects participating in research, in accordance with local regulations and laws, whenever applicable.

EUROPEAN UNION

European Medicines Agency (EMA)

Article 6
Please consider that in modern medicine, R&D of medicinal products is based on the use of biological materials. It is therefore important that the constraints of financial gain are compatible with the legitimate sourcing materials for medicinal products including Advanced Therapy Medicinal Product (ATMP). Development of ATMPs should be facilitated.

Article 7 – Justification of identifiability

1. Biological materials should be anonymised as far as appropriate to the research activities concerned.

2. Any use of biological materials in an identifiable form should be justified in advance by the researcher.

BIOBANKS

3C-R, réseau français de biobanques

Comment on Article 7

The complete anonymisation of biological materials makes it entirely impossible to guarantee individuals' rights with regard to the withdrawal or modification of consent or the provision of information of importance for their medical follow-up. Doctors monitoring individuals and BRCs or biobanks can ensure the traceability of biological resources by

means of a code permitting the identification of patients with a view to safeguarding their rights, while making biological materials available to their users in an anonymous way.

Proposed wording of Article 7.1

Biological materials ***to be used in research*** should be ***either*** anonymised as far as appropriate to the research activities concerned ***or coded under the responsibility of a doctor monitoring the person concerned or a BRC (or biobank) duly authorised to that effect.***

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Proposal to insert a new paragraph about the principle (e.g. new para. 1):
E.g. "Use of directly identified human biological resources should be an exception. Human biological resources should be pseudonymised as far as appropriate to the research activities concerned".

Related comments on "anonymisation":
Perhaps it should be clarified, that the collection does not need to be anonymised - i.e. a biobank can (probably should) be able to identify the material/resource (through a code etc.) but for individual research purposes the material would be coded/pseudonymised again?

The concept of anonymising human biological material/resources as a means to enable research without explicit consent is not in conformity with standards in data security (e.g. in Germany). "Anonymisation" of biological material/resource does not only restrain research, (no possibility of adding and updating of supplementary information) but also restrains the donor in its right to object to any further research on a given probe. Thus it is preferred to destroy donated biological materials/resources upon consent withdrawal. However, ***if for certain research purposes human biological materials/resources maintained and anonymised are appropriate, it is mandatory to inform the donor on the risk that withdrawal of consent for biomedical use of the donated material/resource and/or its destruction is no more possible.***

In contrast, anonymisation of the meta data (not the materials/samples as such - see above) is feasible but is not generally recommended, since it always retails the right of withdrawal. In addition, feeding back any incidental findings is no more feasible. ***Therefore pseudonymisation is generally preferred.***

Proposal of add about the characterisation of identifiability:
Where the researcher or another person handling the materials/human biological resources does not have a need to identify the persons from whom the materials have been removed, and where such identification is disabled by sufficient technical and other means, the materials/human biological resources may be considered as non-identifiable human biological materials/human biological resources for the purposes of handling by such a party.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

With regards to follow up and the return of results, the meaning and consequences of sample anonymization should be explained to patients.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 7 does not articulate the ethical principle here and so appears to require something that is not always necessary. It also seems to add little that isn't achieved by **Article 8**. The critical issue is to keep confidential any private information. Anonymisation is not always the best way to achieve this, nor necessary. It also misses the contextual subtlety I outlined above in that there is a chain of custody for any biological materials with differing amounts of personal information for different users. I would suggest deleting article 7 entirely and rephrasing **Article 8** to read
"Personal information associated with biological materials should be managed in such a manner that a persons confidentiality is maintained at all times. Those involved in obtaining, storing or using human biological materials should provide details to and obtain approval from any regulatory bodies on how they will achieve this"

KU Leuven Faculty of Medicine, Belgium

Article 7.1
Moreover, it seems like Article 7 paragraph one, according to which "biological materials should be anonymised as far as appropriate to the research activities concerned", may contradict Article 21 on individual feedback. We are of the opinion that if the latter Article is to be taken seriously, standard coding should be put in place in order to make possible for individuals to be contacted in case of incidental findings. Furthermore, we believe that in the second paragraph of the same article, it is necessary to further elaborate the conditions under which the use of biological materials in an identifiable form is justified.

Prof. Cassiman, University of Leuven, Belgium

Article 3.ii, **Article 7.1**, Article 13.3, Article 14.5, Article 16.1, Article 17.3
Anonymisation of samples is not considered anymore as being possible. There are many ways around it…'encoding, encrypting' or other words are probably better and more realistic.

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

Article 7.1
In a research/hospital based biobank biological material and related personal data is treated as a single entity, anonymization may not be a reality until an access to the material or the data is requested by a researcher. Since material is stored for long periods of time with not yet a targeted specific project, irreversible anonymization at the onset of the acquisition maybe detrimental to the consequent results and return of any benefit to the donors.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basic tenant of this article.

We consider it important to clarify to whom "*any use of biological materials in an identifiable form should be justified in advance*"?

We wonder if the intention of Article 7, part 2 is fulfilled by "**Article 18** - ***Independent Review***"? Should the justification for use of identifiable biological materials be made to, for example, an independent ethics committee? If so, we consider that Article 18 as it is written currently would only apply if research is defined as starting with recruitment and donation of biological materials as we suggest in our comments to Article 2, otherwise there could be an unintentional gap in the coverage of independent review that excludes the processes of donor identification, recruitment, removal of biological materials from the body and subsequent storage prior to use in a research project. This could create an unwarranted gap in governance and oversight.

We respectfully request that the Committee on Bioethics consider these points.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

EFPIA supports the intent of this article. However, we think it is important to clarify its relationship to the conditions for securing consent for re-use of data which are considered later in the document.

Regeneron Pharmaceuticals, USA

Article 7.1
Rationale: This document should more clearly differentiate between "non-identifiable" and "anonymised". While we recognize these terms are sometimes used interchangeably, they are not necessarily synonymous. Therefore, we suggest utilizing the definitions outlined in ICH E15 or make reference to it.

If a sample is truly anonymised, it cannot be traced back to the subject. It should also be recognised that, technically, genetic data can be traced back, although it may be difficult to do so. If a sample is truly anonymised it would render research/analysis futile because it offers no correlation to the clinical data. It should also be noted that if samples are truly anonymised, it would be impossible to inform a subject of any new health information that is identified in the future. If samples are not anonymised, they can be made non-identifiable by utilizing double coding. In addition, access to the coding could be restricted such that even the site monitors do not have access to the double coding.

In order to respect subject confidentiality and privacy while attempting to advance knowledge and potential treatments from biomedical research, we propose de-identifying data instead of truly anonymising their information by following the principles outlined in ICH E15. In situations where more stringent de-identification processes may be advisable, we recommend double-coding which will maintain subject privacy while still allowing for a correlation to clinical data.

EHICS COMMITTEES

Comitè de Bioètica de Catalunya, Spain (CBC)

There is concern that, as it is interpreted from the current wording, it may result in a poorly reflective and excessive anonymisation of the biological materials stored, leading in many cases to a decrease in the utility for research purposes.

Irish Health Research Board (HRB)

Longitudinal data and samples from an individual are of particular relevance to health research. The HRB appreciates that this is not ruled out in the suggested wording, and would like to see it emphasised stronger.

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

According to the draft recommendation, anonymisation is the rule; use of biological material which is identifiable (whether directly or by a code) must be justified beforehand by the researcher. In the proposed Belgian law, a living donor (or his/her representative) can choose between traceability (always encoded) or non-traceability. In the case of residual human body material or human body material removed from a deceased person, the option of traceability or non-traceability rests with the person furnishing the biobank with the material;

Etablissement français du sang

Is Article 7, which can be construed as presenting anonymisation as the principle and non-anonymisation as the exception, compatible with Article 11.3?

Norwegian Institute of Public Health (NIPH)

The content of this article seems inconsistent with the article title "Justification of identifiability' because paragraph (1) refers to biological materials being anonymised.

EUROPEAN UNION

European Medicines Agency (EMA)

Article 7
Please be aware that anonymisation entails the complete removal of any identifier from a certain dataset. In order to ensure that traceability of biological materials (e.g. in medicinal products), a system of pseudonymisation is recommended (see opinion of EDPS on Pharmacovigilance Regulation or tissues and cells Directive)
Article 7.1
Please note that in the EU tissues and cells have to have traceability systems including coding between donor and recipient.
Article 7.2
Please add: and the rationale explained in context for the coding methodology undertaken.

Article 8 – Confidentiality

1. Any information of a personal nature collected at the time of removal, storage or use of biological materials, or obtained through research should be considered as confidential and treated according to the rules relating to the protection of private life.

2. Appropriate security measures should be in place to ensure confidentiality at the time of removal, storage, use and, where appropriate, transfer of biological materials.

BIOBANKS

3C-R, réseau français de biobanques

Proposed wording of Article 8

Any information of a personal nature collected at the time of removal, storage or use of biomedical materials or obtained through research should be considered as confidential and treated according to the rules relating to the protection of private life. ***Processing of personal data shall be managed in accordance with national law.***

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

With regards to to the increase in collection and sharing of different kind of personal data, in particular for genomics or genetic research, it is recommended that for reasons of clarity the document should give examples of “information of personal nature”.

ACADEMIA

KU Leuven Faculty of Medicine, Belgium

Article 8
We believe that Article 8 on confidentiality should not be restricted to information collected at the time of removal but also include information collected at other points. Moreover, it may be desirable for the above mentioned information of personal nature to be protected by both the rules relating to the protection of private life and those relating to data protection.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basic tenant of this article, but additionally suggest that the phrase “where appropriate” is redundant in part 2 and could be deleted.

We respectfully request that the Committee on Bioethics consider this suggestion.

ETHICS COMMITTEES

Irish Health Research Board (HRB)

This article should refer to both protection of private life and to national data protection legislation.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

The title of this article is insufficient as the content of this article pertains to both confidentiality and protection of personal information. Maintaining confidentiality is the duty of professionals while protection of personal information relates to security measures put in place at each stage of data and sample storage and handling. The heading should be changed to reflect that this article is about 'Protection'.

Paragraph (1) states that 'Biological materials should be anonymised as far as appropriate..'; this text should be reassessed for several reasons. Biological materials are often identifiable by their very nature, and given the potential future need for being able to identify the materials (i.e. recontact, follow-up studies) it is a sounder practice to put protection measures into effect rather than to emphasize anonymisation. The content should be revised to reflect this.

Paragraph (1) refers to the "rules relating to the protection of private life". This should be expanded to encompass data protection laws and should read "rules relating to the protection of private life, biological materials and personal data".

Paragraph (2) should be rephrased to reflect that 'appropriate security measures are in place to ensure protection at the time of removal…'

Article 9 – Public information

Member States should take appropriate measures to facilitate access for the public to general information on the nature and objective of research collections and on the conditions relating to the obtaining, storage and use of biological materials for research purposes, including matters relating to consent or authorisation.

BIOBANKS

3C-R, réseau français de biobanques

Comment No. 1 on Article 9

This article is intended to permit states, biobanks, collection managers and researchers to take the measures necessary to provide general information to the public on the use of biological materials and the overall results obtained. As mentioned under Article 19.2 in the comments concerning feedback, this article could be sufficient for the entire recommendation.

Comment No. 2 on Article 9

Article 21 "Individual feedback" could be moved here as Article 9.2 (regarding the proposed modification of the wording on individual feedback, see the comments on Article 21).

Proposed wording of Article 9

Article 9 – ~~Public~~ Information *and feedback*

1. ***Public information***: Member States should take appropriate measures to facilitate access for the public to general information on the nature and objective of research collections and on the conditions relating to the obtaining, storage and use of biological materials for research purposes, including matters relating to consent or authorisation.

2. ~~Article 21 –~~Individual feedback:
i. Clear policies should be developed on feedback concerning findings that are significant for the health of the persons arising from the use of their biological materials.
ii. Feedback should take place within a framework of health care or ***genetic*** counselling ***in accordance with the conditions of national law.***
iii. The wishes of individuals not to be informed should be observed.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

We recommend that public information shall never refer to the donor of the human biological materials, unless otherwise agreed. Where allowed, information referring to to the donor shall be kept in secure databases.

With regard to the paragraph:"Member States should take appropriate measures to facilitate public access to general information on the nature and objectives of research collections and on the conditions relating to the obtaining, storage and use of biological materials for research purposes, including matters relating to consent or authorization" **a sentence could be added as follows:**
"Each biobank should make its communication policy publicly available**".**

ACADEMIA

Dr Imogen Evans, UK

Line 2: the word 'conditions' is used elsewhere to mean "illness or disorder". For clarity, it might be better in this article to say "safeguards relating to..." or "protections that apply to".

KU Leuven Faculty of Medicine, Belgium

We consider that it may be more appropriate for Article 9 on public information to be placed on Chapter III on information and consent, rather than on Chapter II regarding general provisions.

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

This article is very important since in many countries there is not much public awareness of biobanking activities and their benefits for health care. Biobanks are sometimes considered as private collections of researchers and a major question remains as who do the samples belong??!

Article 10 – Wider protection

None of the provisions of this Recommendation should be interpreted as limiting or otherwise affecting the possibility for a member state to grant a wider measure of protection than is stipulated in this Recommendation.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support this article if we can be assured that this will not simply lead to further disparity, inconsistency and inequality of research using human biological materials across European states.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

The value of this document lies in the role it may play in improving alignment of approaches to this issue. While not disputing that the article is correct, as a contextual perspective on the recommendations, EFPIA suggests it might be more relevant as part of the preamble.

CHAPTER III – Information and consent

BIOBANKS

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

General comment:
Information and consent procedures needs elaboration:
There is accordingly a need of balancing autonomy rights and rights to health care, prevention and medical treatment, and this needs to be better described in the guidelines. ***The present formulation of Chapter III, Article 11 does not reflect the rights of access to preventive health care and the right to benefit from medical treatment to be acquired with the help of biomedical research.***

ACADEMIA

Karolinska Institutet, Sweden

Taking samples from persons not able to consent
In addition to integrity and privacy concerns one should also acknowledge patient interests related to safety with regard to diagnosis, treatment and care, interests that need research in order to be fulfilled. Demented patients are not able to provide an informed consent and their integrity in the sense of protection of autonomy cannot be respected, however, samples still need to be taken in order to protect their safety interests with regard to diagnosis and treatment.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

While we appreciate the wording in this article is the same as in the current (2006) Recommendation, the details of the Recommendation are now different. We would like to see a change in emphasis in this article which encourages equal standards in the pursuit of achievement of greater unity and which reminds MS that enacting stricter standards and/or legislation can hamper the sharing of biological samples for research – a consideration which has added importance for rare diseases and could lead to discrimination regarding access to health care, prevention, and medical treatment for people living with a rare disease.

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

Chapter III (Information and consent) could be better structured, drawing a distinction between identifiable and unidentifiable biological material;

Article 11 – Removal of biological materials for storage for future research

Information

1. Prior to requesting consent to remove biological materials for storage for future research, the person concerned should be provided with comprehensible information:

i. that is specific with regard to the intervention carried out to remove the materials; and

ii. that is as precise as possible with regard to:
- any research use foreseen;
- the conditions applicable to the storage of the materials; and
- other relevant conditions governing the use of the materials.

2. The persons concerned should also be informed of the rights and safeguards prescribed by law for their protection.

3. The persons concerned should be offered the possibility to exercise choices with regard to the type of research use of their biological materials.

Consent
4. Biological materials may not be removed for storage for future research without the free, express and documented consent of the person concerned:
- that is specific with regard to the intervention carried out to remove the materials; and
- that is as precise as possible with regard to the research use covered, in the light of the information provided in paragraph 1, ii., and includes possible choices made in accordance with paragraph 3.

BIOBANKS

3C-R, réseau français de biobanques

Comment No. 1 on Article 11.1

If Article 11 solely concerns the use of samples taken specifically in connection with a research project (and not the use of materials removed during medical care and reclassified at a subsequent stage), this should be specified to prevent confusion.

Comment No. 2 on Article 11.1

Although in certain cases the removal or collection of biological materials is carried out specifically for a given research project, many projects use existing biological materials which were initially removed either with a view to constituting a collection or during medical care and were reclassified at a subsequent stage. Article 13 covers these cases. As Article 13 refers to Article 11 with regard to the conditions of information and consent, it is important to word Article 11.1 so that it covers all these instances. At the time of the initial removal or collection of biological materials it is sometimes impossible to give the person concerned specific information on "any research use foreseen". Retrospective use typically occurs when collections are managed by BRCs, whose role is to manage biological resources in such a way as to optimise their use and to make them available for promoting research. Nevertheless, although the precise use to be made of samples may not be known in

advance, information may very well concern the conditions of collection or removal, the conditions and place of storage (which enables the person concerned to exercise their right of withdrawal if the samples are not anonymised) and the conditions of use.

Proposed wording of Article 11.1

1. Prior to requesting consent to remove, ***collect or reclassify*** biological materials for storage for future research, the person concerned should be provided with comprehensible information:

i. that is specific with regard to the ~~intervention carried out to remove~~ ***conditions of collection or removal of*** the materials; and

ii. that is as precise as possible with regard to:

- ~~any~~ ***the*** research use foreseen **or at least the type of research, or possibly information on the possible use of the materials in other areas linked to improvements in human health**;
- the conditions applicable to the storage of the biological materials; and
- ***all*** other relevant conditions governing the use of the ***biological*** materials.

Comment No. 2 on Article 11.3

The persons concerned "should be offered the possibility to exercise choices with regard to the type of research use of their biological materials". The difficulty lies in the interpretation given to the word "type", since it could entail an obligation for researchers and biobanks to be very specific when describing research (see the comment on Article 11.1) and to manage the fine details of consent and therefore of potential uses. This paragraph may considerably restrict the possibilities of obtaining broad consent for use in research activities.

Proposed wording of Article 11.3

The persons concerned should be offered the possibility to exercise choices with regard to the type of research ~~use of their~~ ***for which they do not wish*** their biological materials ***to be used***.

Comment No. 3 on Article 11

Multiple forms of consent may be provided for by law (express consent, but also free and informed consent or non-opposition) and the concept of "free, express and documented consent" seems inappropriate. Moreover, express consent for subsequent use cannot be required in the case of persons with whom one has lost contact or who are deceased. Exceptions to the requirement to inform the person and obtain their consent should be permitted subject to an official body's oversight (such as a research ethics committee (as with the Comité de Protection des Personnes in France)), the aim being to avoid the "loss" of valuable collections that could no longer be utilised due to a lack of consent, whereas their use could result in important therapeutic advances for society without endangering anyone.

Proposed wording of Article 11.4

Biological materials may not be removed for storage for future research ~~without~~ unless the ~~free, express and documented consent~~ ***free and informed will*** of the person concerned ***has been expressed in accordance with national law***.

General comment:
It has to be notified that this article 11 does not apply to "residual biological material" as defined e.g. in the Belgian law.
Proposal: either modification of the title replaced by "Removal of biological materials exclusively for storage for future research" and additional article on "residual biological material" (i.e. presumed consent) or extension of article. (cf. art 13)

Inconsistency
Having regard to the elected scope of the recommendation, i.e. that the recommendation applies only to the obtaining and storage of biological materials of human origin for storage for future research purposes and the use of biospecimens previously obtained for another purpose (Art.2) the requirements in Art 11 that information and consent should be specific about the intervention carried out to remove the materials is, at best, misleading since it doesn't apply to already collected materials.

General comment/Question:
Does the practice of a broad consent is respecting this provision?

Related proposal for modifications (to the above comment/question) :
The recommendation that information and consent should be as precise as possible with regard to the research use is also potentially misleading since the sampling referred to is for future research with only general purposes described. It is today also common knowledge within biobank based research that samples collected for general medical purposes, e.g. for research on cardiovascular diseases, often later tusks out to deliver great benefit for patients with other types of diseases, e.g. identification of early factors behind Rheumatoid Arthritis 10-15 years before onset through a cardiovascular biobank. Research like this is of tremendous importance for early detection and treatment of Rheumatoid Arthiritis (ref. Eriksson C, et al, Arthritis Res Ther. 2011 Feb 22;13(1):R30.E-pub). On this background there should be no offering of selection for types of research. Neither patients nor researchers know at the time of sampling for what good purpose the samples may be used.
We suggest therefore that the appropriate term to be used is "broad consent for future research purposes" and this should be made explicit in Article 11. (BBMRI.SE / BBMRI.BE)

Discrepancies on this specific above proposal for modification

It is preferable not to quote broad consent as the model that should be used by any countries notably because ethical debates are still ongoing and because other mechanisms are currently being developed (e.g. multilayer consent, or dynamic consent processes, or information and non-opposition mechanisms). These mechanisms could present the same advantages than the so-called broad consent without adopting a broad approach by default. Furthermore, "broad consent" is not a recognised legal term and is not fully accepted by all jurisdictions. Thus, to date, it would be better to keep an objective/flexible wording, as proposed by the Council, as it allows many different and ethically sounded practices to develop, and does not orient legislators for adopting a particular and yet still debated method. (BIOBANQUES, FR)

Proposals for specifications:
It should also be made explicit that each future research project should be approved by an ethical review board.

Since the recommendation also involves previously collected samples, information and consent procedures should be specified for them as well, the two options generally used

being opt-out or use without renewed consent, in both cases associated with approval by an ethical review board.

Proposals for specifications of the information to be provided:
The person concerned should always be informed about:
- The way of how feed-back of incidental findings is managed.
- The risk that he/she could be obliged to disclose any genetic risk-information he is aware of to e.g. insurances.

Sequencing and genetic analyses require information and consent of the person. The information must address the risk of potential re-identification in the future, which will increase with technical progress.

Para.1
Proposals for specifications:
It is not clear what is meant by "an intervention to be carried out to remove the materials". If this refers to the method of sampling, e.g. drawing blood or taking biopsies, the recommendation is redundant. Every individual is already by law protected against someone drawing blood or performing biopsies without his knowing and free consent. If "intervention" here means to say something more about the purpose of removing the samples and the need to be specific this is not possible for sampling done for future research purposes and would be counter productive for the fulfilment of rights of access to preventive health care and the right to benefit from medical treatment.

Proposals for minor textual modifications:
1. Prior to requesting consent to remove human biological materials ("samples" or "resources" preferred, depending on the intended breadth given to these provisions) for storage for future research, the person concerned should be provided with comprehensible information:
   i. that is specific with regard to the intervention carried out to remove the biological materials; and
   ii. that is as precise as possible with regard to:
      - any research use foreseen;
      - the conditions applicable to the storage of the biological materials; and
      - any other relevant conditions governing the use of the materials.

Para. 2.
Proposed add: The persons concerned should also be informed of the rights and safeguards prescribed by law for their protection "as well as the means offered to effectively exercise their rights".

Para. 3.
Good ! **Proposed adds:** "The person concerned should be informed about the consequences that such offered choices could induce. Where relevant, the person concerned should also be informed about the potential costs related to the exercise of these choices". (BIOBANQUES, FR)

Proposal of specifications
There is an indefinite number of potential choices and in reality not all of them can be implemented. It may be that if a person wants to limit the use of material to a certain type of research, the biobank cannot accept the material for storage. The possibility to choose (limit consent) may and should be given, but only if it is understood that limitation may in reality be equal to not giving a consent at all, and the actually available choices may be to participate or not. There should be no obligation for a biobank or a researcher to accept material they

cannot reasonably use or when they cannot e.g. for practical or financial reasons reliably manage different types of consents. (BBMRI.FI)

Discrepancies on the above comments on para.3.

Not so good for prospective clinical studies because at any moment verification is necessary about whether the storage and use of materials complies with the choice expressed, with the consequence that clinical studies will be delayed, postponed or impossible.
Modifications proposal para 3: - by analogy to the Belgian law - the persons (…) materials, as long as the use of the biological material in a research project has not been decided upon.

Bad! For retrospective residual and studies based on residual material. In this context, at the moment of storage it is impossible to offer to the donor the possibility to precisely be informed of the aim of the future research. Nevertheless, general research information can be given by different ways (website, leaflets…). Moreover, all the studies are submitted for approval to the Ethical committees which guarantee the patient's rights.
Proposal of adds: - by analogy to the Belgian law 2008 Art. 20. § 1 3rd paragraph – When it is impossible to ask authorisation for a "secondary" use or when it is exceptionally inappropriate, the biological material can be used based on an approval of an ethical committee. (BBMRI.BE).

Proposal for deletion
This is not useful. This Paragraph should be deleted. By doing this, we would be encouraging people to make choices they would probably never have asked for. It would only make information tracking more difficult and increase the likelihood of errors. A minefield of complexity, cost, potential for error and risk of harm to persons concerned.
It is not clear what problem this paragraph is trying to solve. Some focus groups or studies may indicate that people would like to know how their samples are being used. For example on page 35 of the BBMRI ELSI WG "Biobanks and the Public", it is written: "On the issue of consent almost 7 in ten Europeans opt for specific permission sought for every new piece of research." It is not clear what "opt" means here, but even if this represents an unbiased, undirected and spontaneous preference, it is still not certain that it is in the best interests of research or of the persons concerned themselves to go down this road.
A few persons might currently be lost by not offering this choice, but there is no evidence that this is a real problem nor that this paragraph would solve it if it existed. (IBBL – Integrated Biobank of Luxembourg)

Para. 4.
Ask for specifications:
What is the meaning of "express"? Does that mean written? Does that mean informed? Does that mean actively opted-in (like explicit consent)? This term is subject to very different interpretations.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Information
Members of the European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB) Working Group had a variety of different opinions on article 11, as reported below.

The ESBB working group members recognise the need to make a distinction between requirements of information and consent to store human biological materials(1) for specific future research and *(2)* for unforeseen and unspecified research.
With regard to the first scenario, the ESBB working group members agree that information and consent should be as precise and comprehensible as possible.
With regard to the second scenario, relating to the use of residual biological materials(including tissues), we recommend that an "opt-out "model of consent should be permitted.

With regard to Article 11.3, a clarification of the kinds of choices that could be exercised by donors is recommended, in order to help explain the level of proposed autonomy .
On this aspect, there were differences of opinion within our group:.
One opinion was that the aforementioned choices cannot be made in most research projects.

A second opinion was that informed consent and the related choices should be designed according to the disease or the organ. This seems particularly appropriate for cancer research.

A third opinion was that paragraph 3 of this article is not useful. The main underlying reason is that, by recognizing this level of autonomy, people would be encouraged to make choices they would probably never have asked for. Moreover, the consequences of this disposition for partnerships are not clear: if one biobank does not offer such a choice possibility to its donors, will other partners who do, refuse to collaborate, or to catalogue or distribute the samples of that biobank? And how will IT platforms be programmed to take these choices into account when for sure every biobank will have a different approach to offering choice? A few donors might be lost by not offering this choice, but there is no evidence that this is a real problem nor that this paragraph would solve it if it existed. In conclusion, this Paragraph should be deleted.

Consent
We recommend the opt-out approach to consent. The alternative is very inefficient and. makes observational research on residual material or under secondary use too complicated and expensive to carry out.

Swedish National Council of Biobanks (NBR)

It is essential that the individual receives adequate and understandable information about the purpose of removing the sample. It is not clear, however, what the purpose or gain is of giving "comprehensive information that is specific with regard to the intervention carried out to remove the material". It is, however, important that the information withholds contact information as to where the patients/donors should turn if they want to withdraw their consent.

ACADEMIA

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

- Chapter III, article 11, paragraph 2: It must be specifically emphasized that:
  - any research project must be approved by a research ethics committee,

- a research project with the potential to produce results of consequence for the donor requires re-consenting, *unless* the donor has specifically declined being re-contacted for that purpose.

- Large biobanks/population biobanks should be obliged to inform the donors about the specific research activities being conducted using material from the biobank. The information could be posted on biobank webpages and in newsletters.
- Data protection: in terms of recognition of a broad consent to future research it is highly important to sustain public trust in health research. Focus on:
  - development and implementation of appropriate research infrastructures to ensure protection of personal data not only during collection and handling/storage in biobanks but also during research usage.
  - concrete instructions to researchers on how to handle/store/disclose personal data to ensure compliance with national and international legislation.
  - control of institutions and research projects by national bodies to ensure compliance with data protection rules.

Article 11.1,3 (Information and Consent)
Since all future types of research use cannot be foreseen, specification of the choices should be carefully considered in order not to invoke inexpedient restrictions on future research use, perhaps made on an uneducated basis. The research ethics committees have an essential role in evaluating any concrete research project.

Dr. Amin El-Heliebi, Dr. Karine Sargsyan, Biobank Graz, Medical University Graz

Article 11.3

To offer a patient the possibility of decision of “exactly in what type of research” the material can be used, would dramatically limit the usage of biological materials. E.g. The same breast cancer tissue foreseen for receptor – biomarker research would be not possible to use in auto-immune research. So if it is predetermined to a certain research type, it would be locked-in, and may make the research in general and biobanking in special almost impossible.
--Paragraph 3 should be removed.

Karolinska Institutet, Sweden

Information and consent procedures needs elaboration
There is accordingly a need of balancing autonomy rights and rights to health care, revention and medical treatment and this must be better described in the guidelines. The present formulation of Ch. III, Article 11 does not reflect the rights of access to preventive health care and the right to benefit from medical treatment to be acquired with the help of medical research. Having regard to the elected scope of the recommendation, i.e. that the recommendation applies only to the obtaining and storage of biological materials of human origin for storage for future research purposes and the use of bio-specimens previously obtained for another purpose (Art.2) the requirements in Art 11 that information and consent should be specific about the intervention carried out to remove the materials is at best misleading since it doesn’t apply to already collected materials. It is furthermore not clear what is meant by an intervention to be carried out to remove the materials. If this refers to the method of sampling, e.g. drawing blood or taking biopsies, the recommendation is redundant. Every individual is already by law protected against someone drawing blood or performing biopsies without his knowing and free consent. If intervention here means to say something more about the purpose of samples and the need to be specific this is not possible for sampling done for future research purposes and would be counter-productive for

the fulfilment of rights of access to preventive health care and the right to benefit from medical treatment.

The recommendation that information and consent should be as precise as possible with regard to the research use is also potentially misleading since the sampling referred to is done for future research with only general purposes described. It is today also common knowledge within bio-bank based research that samples collected for general medical purposes, e.g. for research on cardiovascular diseases, often later turn out to deliver great benefit for patients with other types of diseases, e.g. identification of early factors behind Rheumatoid Arthritis 10-15 years before onset through a cardiovascular bio-bank. Research like this is of tremendous importance for early detection and treatment of Rheumatoid Arthritis (ref. Eriksson C, et al, Arthritis Res Ther. 2011 Feb 22; 13(1):R30.E-pub). With this background there should be no offering of selection for types of research. Neither patients nor researchers know at the time of sampling for what good purpose the samples may be used.

We suggest therefore that the appropriate term to be used is broad consent for future research purposes and this should be made explicit in Article 11. It should also be made explicit that each future research project should be approved by an ethical review board.

Since the recommendation also involves previously collected samples, information and consent procedures should be specified for them as well, the two options usually used being opt-out or use without renewed consent, in both cases associated with approval by an ethical review board.

KU Leuven Faculty of Medicine, Belgium

Article 11
An element that we find rather problematic in several parts of the document is the definition of consent. More specifically, in Articles 11, 12, 13 and 16 it may be desirable to specify whether the consent needed in each case should be explicit or implicit and, if needed, make clear that a tiered model of consent may be used applied, providing different standards in different situations.

In terms of information to be provided to research participants, as provided by the Article 11 inclusion of information about potential commercialization of biobanks is particularly important. Growing public-private partnerships along with considerable concerns of research participants with regard to commercial partnerships of public-funded biobanks suggested by empirical evidence, highlights the importance of communicating such information to research participants in advance. Thereby individuals could make an informed decision in the light of potential future commercial involvement in collection, storage and use of biological materials.

Article 11.3
In paragraph 3 of the same Article, it may be important to specify what is meant by “exercise choices”, by indicatively listing some of the potential choices that the person concerned may have.

Article 11.4
Paragraph 4 of the same Article highlights the above mentioned problems related to Article 2 paragraph 2, since according to this paragraph the consent of the person concerned should be “as precise as possible with regard to the research use covered”, while Article 2 seems to limit the scope of this recommendation to biological material removed for research that is yet to be specified.

Lund University, Sweden

Article 11 is vague and leaves too much room for interpretation - the requirements can be interpreted very broadly, which is not good.

Patrick GAUDRAY (à titre personnel), Directeur de Recherche au CNRS, Membre du Comité Consultatif National d'Ethique, France, France

With reference to the French text, there is a striking imbalance between the use of the present tense when the verb is "**pouvoir**" ("may") and of the conditional tense when the verb is "**devoir**" ("should"). This gives an optional sense to what should be injunctions, for example in Article 11 (Chapter III) with regard to the provision of information, the possibility of exercising choices and the ban on removal without consent. This optional sense does not correspond to what is intended.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO)

Article 11.3
I do not agree with this point.

Most of the patients will agree to donate samples for scientific research (biomedicine)

Research must be only based on the approval of the ethics committees and not on the patients wishes.

If the person do not agree on these conditions it would be better not to take the sample.

Consent

Article 11.4
This can involve too much paperwork and stop fluidity of research.

The consent should clarify that the samples should only be used for research approved by the corresponding ethics committees.

Prof. Francesco d'Agostino, Honorary President of the Italian National Committee for Bioethics

Information
Article 11.1
The type of consent should be pointed out with regard to future research, whether it be directly or indirectly connected with the research activity; further details should be provided in relation to the possibility for the biological sample of being dislocated to a different place and where. If it is transferred to other countries to what different regulation the latter must adhere to should be specified.

Article 11.3
A person shall be given the opportunity to exercise free choice: namely, either a positive choice as to what kind of research they deem preferable, or a negative one, in the sense of eliciting whatever type of research they would refuse (conscientious objection)

***Prof.** Jacques SIMPORE, Professeur Titulaire de Génétique et de Biologie Moléculaires*

Article 11.1.ii states that at the time of the removal, patients should told of "*any research use foreseen*" on his or her material.

Furthermore, **Article 11.3** also states: *"The persons concerned should be offered the possibility to exercise choices with regard to the type of research use of their biological materials."*

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

There is a need to balance autonomy rights and rights to health care, prevention, and medical treatment and this needs to be better described in the Recommendation. The present formulation of this article does not reflect the rights of access to *preventive* health care and the right to benefit from medical treatment via medical research. The scope of the Recommendation is stated in article 2 as obtaining, storage and use of biological materials of human origin for future research and the use of biomaterials previously obtained for another purpose In this context, the requirement in article 11, that information and consent should be specific about the intervention carried out to remove the materials, is misleading as it does not apply to materials already collected. Furthermore, it is not clear what is meant by an "intervention carried out to remove the materials". If this refers to the method of sampling, e.g. drawing blood or taking biopsies then the Recommendation is redundant. Every individual is already protected by law against someone drawing blood or performing biopsies without their knowledge and consent. If "intervention" here has some implication for the purpose of the samples taken and the need to be specific, this would exclude taking broad consent which allows using the samples for future research purposes. We see this section of article 11 as counterproductive for the fulfilment of rights of access to preventive health care and the right to benefit from medical treatment.

The recommendation that information and consent should be as precise as possible with regard to the research use is also potentially misleading since the sampling referred to is for future research with only general purposes described. It is today common knowledge within biobank based research that samples collected for general medical purposes often later deliver great benefit for patients with other types of diseases. For example the identification of factors causing Rheumatoid Arthritis were discovered through a cardiovascular biobank, showing that this secondary research can be of tremendous importance for unrelated conditions. Given this, we do not think participants should be allowed to select types of research that their biosample may be used for. Neither patients nor researchers know at the time of sampling what good purpose the samples may be used for.

This general use of samples should be made clear in the information to participants and the consent form. The consent should also include a statement as to whether a participant is willing to be re-contacted should the need arise. In addition we encourage secondary researchers to publicly disseminate aggregate results and research progress. We suggest therefore that the appropriate term to be used is broad consent for future research purposes and this should be made explicit in article 11. It should also be made explicit that each future research project would have to be approved by an ethical review board.

As the Recommendation also involves previously collected samples, information and consent procedures should also be specified for these cases, including re-consent, opt-out or use without renewed consent, with the latter two being subject to approval by an ethical review board.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

It would be helpful to clarify what is meant by future research. Does this mean research that is not included in the initial protocol and informed consent?

Clarification is also needed regarding the level of specificity required for consent and what types of consent are permissible (broad or tiered). Is item #3 referring to use of a tiered consent model? If so, this particular model presents operational challenges in tracking choices, as well as potentially making it difficult to decide whether future use is permissible. While this model was at one time the "gold standard" for obtaining consent for future use of specimens, there has been a movement away from this model for precisely that reason. A broad consent model may be preferable in this regard and, in fact, studies show that this model is acceptable to many participant populations. We would like to suggest that the Working Document recognize that different consent models exist for future use of specimens and that the choice of the best consent model is context specific. In their report, Privacy and Progress in Whole Genome Sequencing (Oct. 2012; http://bioethics.gov/node/764), the US Presidential Commission for the Study of Bioethical Issues concluded "*[a]s long as consent processes are equivalently effective in informing individuals about what they are consenting to, and as long as they do not unduly shape or undermine individuals' ability to make genuinely voluntary choices, there is no philosophical or ethical imperative to use one kind of consent process over another."* The Commission also discusses opt-out as a permissible model. We agree with the Commission on these points and strongly suggest that the Working Document allow flexibility in determining the most appropriate consent model based upon the research context, study population, etc.

We understand that the proposed EU Data Protection Regulation, at least in its current form, would require an explicit and specific consent for use of personal data and that it may not permit the use of these other consent models for use of data that may accompany specimens. However, we note that the requirement for a specific, explicit consent would pose significant barriers to biomedical research requiring the use of human biological samples. Furthermore, it is at odds with the proposed EMA regulations requiring the sharing of individual level data from clinical trials. Thus we hope that the EU will consider modifying this requirement. We strongly advocate for considerable flexibility in the types of consent models appropriate in the current document from the Council of Europe, including broad consent.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support this article in general, with some suggestions for clarification.

The article contains the text "*the person concerned should be provided with comprehensible information:*
i. ……..; and

ii. that is as precise as possible with regard to:
- any research use foreseen;
- the conditions applicable to the storage of the materials; and
- other relevant conditions governing the use of the materials."

The key phrase here is "*as precise as possible*", as it must be emphasised that the model of *precise and specific consent* is both unnecessary and unrealistic, and it is increasingly being superseded by the *generic consent* model. It is never possible to predict all future uses of a stored human biological material, especially with advances in knowledge and scientific techniques. Therefore, it is impractical to provide such information in precise detail to support consent. In addition, such information should be "*comprehensible*", which is not the case when it contains precise and detailed scientific information. Therefore, the model of generic and reasonably enduring consent is becoming the preferred method of providing proportionate and comprehensible information to participants. It is still possible to provide reasonable information under this model, but it cannot be precise.

We respectfully request that the Committee on Bioethics clarify that good examples of the generic consent model can be considered "*as precise as possible*"?

With regard to the requirement that "*The persons concerned should be offered the possibility to exercise choices with regard to the type of research use of their biological materials*", we would like to emphasise that this is not always practicable as the provision of choices and the subsequent tracking of those choices can be difficult as many samples flow between organisations in pursuit of a research project.

The consequences are that: 1) research may not be conducted on some samples as it cannot be confirmed that the research use aligns with the choices made by the participant; or 2) that research that is outside of the individual participant's choice is done because the flow of information relating to that choice has be inaccurate or incomplete. As a result, we believe that it is legitimate, and safeguards all involved, to use a consent model with only two choices – to participate in full or not.

We respectfully request that the Committee on Bioethics consider that this article say "*It is preferable where reasonable and practicable, that persons concerned should be offered the possibility to exercise choices …..*"

European Federation of Pharmaceutical Industries and Associations (EFPIA)

Articles 11-17 taken together propose how consent issues should be addressed. Consistent with the IPPC and I-PWG, EFPIA considers that in order to enable the re-use of materials for legitimate research purposes, a more flexible approach will be needed. This will of course raise questions concerning accountability to the original subjects which will need to be addressed. The main points that EFPIA would highlight in the document are as follows:

It will be difficult in practice to provide subjects with precise descriptions of the future uses to which their data will be put, as proposed in article 11. Although the working document's language contains a caveat, it may be better to introduce the concept of broad consent into the document explicitly and work towards an approach to consent that is as informative as possible within that framework.

The Working Document addresses re-consent in a number of articles. EFPIA has doubts about the general feasibility of re-consent at the individual level and we note that the Declaration of Helsinki recognizes the need for recourse to ethics committees as an

alternative where re-consent is not feasible. We would support greater weight being given to the role of ethics committees beyond being a last resort where re-contact has been attempted and has not succeeded.

The retrospective exercise of choice regarding the uses made of personal data will be very difficult to achieve in practice. As the documents notes, international research and exchange of data between entities is becoming more common. There are also very concrete concerns about making certain research infeasible or undermining the value of whole collections if such choices are exercised. EFPIA suggests that such choices should be limited to data which exist in identifiable form.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

Article 11 explains that, prior to requesting consent, the donor should be presented with comprehensible information that is that is "as precise as possible" with regard to future research use, conditions applicable to storage and relevant conditions governing the use of the material. The requirement for this detail to be as "precise as possible" is of concern. We support permitting general or generic consent for future research on biological materials. It is often impossible at the time of the initial consent and collection to understand the range of analyses that researchers may wish to perform on such biological materials in the future. Nevertheless, we believe it possible to offer a comprehensible and acceptable level of detail to persons concerned utilizing a generic consent. In addition, this standard is consistent with the recommendation given by the UK authority (HTA), which seeks to obtain generic consent in effort to maximise the utility of the sample for research:

> *UK HTA Code of Practice #1 – Consent:*
> *40. Generic consent typically only applies to research. If conducting research on samples of tissue, it is good practice to request generic consent because this avoids the need to obtain further consent in the future.* [2]

Further, we recommend that within this article the DH-BIO consider scenarios in which approval by an authorised body (e.g. Ethics Committee) may waive the requirement for consent of the persons concerned and be permissible within the law.

With regard to the requirement that "*The persons concerned should be offered the possibility to exercise choices with regard to the type of research use of their biological materials*", we would like to emphasise that this is logistically difficult to implement and may increase the risk that research conducted is not aligned with the expectations of persons concerned. As long as providing biological materials is a voluntary activity and the scope of use of the materials is defined, it should not be required to give persons additional choices. Individuals may always choose not to give biological materials if they are opposed to the stated research uses. Subsequent provision of choices could divide the research cohort, potentially introducing an element of bias in future analyses because the samples utilized are no longer representative of the cohort. This may be of particular concern in future research use of clinical trial specimens to address hypothesis related to safety or efficacy of a drug or class of drugs that arise later in development or post-approval.

Regeneron Pharmaceuticals, USA

Suggested revision to 11.3: We propose broader language that is sensitive to the interest of subject participation in future biomedical research by offering the following consent options to subjects with regard to the type of research: 1- use in research for any disease that can affect the human condition (including functioning as control sample); 2- use in

research limited to the disease under study or related diseases; and 3- do not use sample for any research.

Suggested revision to 11.4: We propose that consent forms for future research include language that specify that samples will only be held for a specified number of years (i.e., 15 years, 20 years) and research would be appropriately limited to one of the three (3) broad options proposed in the previous paragraph. Moreover, any changes to this scope would be adjudicated by an independent committee such as an IRB, EEC, or Independent Data Monitoring Committee (IDMC) for appropriateness.

Rationale: This proposition could be especially burdensome because it offers a myriad of options that could vary widely according to following:

- Individual subject preference: Given the choice, each subject may have specific and unique requests, they themselves may not fully understand, with which researchers would be required to comply.
- Institutional Review Boards (IRBs) and Ethics Committees (ECs): They often dictate the types of use of samples, what they can be used for or the duration for which samples can be retained.
- Nature of research: There are instances where future research is unforeseen or it is impossible to list all of the various types of research that can or may be conducted because each advancement could lead to another.
- Health Authority (HA) or Regulatory Agency (RA): researchers can and do receive ad hoc request from HA and/or RAs for additional unplanned analyses

Examples of variability in options include but are not limited to differences in the number of years samples can be stored, or differences in the types of research that can or cannot be conducted, thereby delaying a researcher's ability to test and analyze samples in the hopes of advancing knowledge for the benefit of subjects and patients alike.

All of these options and layers of consideration that result in added complexity and time to discovering advances in biomedical research may limit contributions or the potential development of new knowledge or treatments that could save or improve a patient's life, which is one of the tenets noted in the preamble. Furthermore, this may not benefit subjects since their agreement to allow their samples to be analysed for unknown and unstated future research is often altruistic and knowledge of each individual possible research may not alter or impact a subject's initial intent. When subjects consent to future biomedical research of their samples, they are aware that scientist and clinicians are themselves investigating these samples to obtain more knowledge about a specific disease, condition, pathway etc. As currently worded, this principle adds a layer of specificity that does not appear to be productive. The three options provided as "Suggested Revision" could also improve consistency between the recommendations requested by IRBs.

We further acknowledge that in order to protect the interests and privacy of subjects, samples cannot be used indefinitely.

ETHICS COMMITTEE

Comité National d'Ethique de Recherche (CNER), France

As a research ethics committee, the CNER finds Chapter III to be particularly relevant, as it deals with the information which must be provided to research participants, before obtaining their consent and before their biological materials are collected. The recommendations of Art. 11 are in line with the format of informed consent (with variable scope) used in Luxembourg in studies or projects where biological materials are collected and may be used

for other, future projects, and in which the participant separately marks his consent to these future uses.

However, still in Art 11, the text could be made more precise in paragraph 3, concerning the kinds of choices which are referred to. Also, in paragraph 4, the word “prior” could be added in the first sentence before “(...) free, express and documented consent of the person concerned”.

Comité de Etica (CSIC), Spain

The inclusion of this provision can complicate and delay the conduct of research

EuroSIDA Steering Committee

Article 11.ii
Please see comments to article 17-1:
Observational research on large cohort datasets collected from routine care of participants and supplemented with collection of biological specimens for future research by nature generally address not yet identified research questions (at the time of participant consent) since the projects run over many years and the field of research develops during the conduct of the cohort studies; this makes defining the scope of the research challenging and often result in participant consents with a very broad formulated and general scope.

Irish Health Research Board (HRB)

Article 11.3, 11.4
The HRB suggests deleting the proposed Article 11.3, as the layered consent suggested has proven difficult to implement and will prevent research due to practical difficulties. Also, the layered approach means that the numbers of participants giving wider consent will reduce with each layer, whereas the experience in Ireland has been that once people are clear about the procedure involved and wish to contribute to a specific project, there is very little concern about that sample / information then being used in another research project subject to appropriate safeguards being put in place for each individual project wishing to access the sample, such as research ethics approval.

Consequently, the HRB also suggests deleting the reference to Article 11.3 in Article 11.4

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

The wording of Paragraph (1) is confusing. The phrase ‘Prior to requesting consent to remove biological materials for storage for future research’ is ambiguous. Does the word ‘remove’ refer to obtaining the samples from the body of the donor or from obtaining the samples that are already stored? If the former than this should be phrased as ‘Prior to obtaining the biological sample from the donor..’; if the latter than it should be reworded to reflect this.

Paragraph (1) is also confusing with regards to the phrase’ “intervention carried out to remove the materials”. What does ‘intervention’ refer to? If it the method of obtaining the sample from the donor this should be explicit, the word “intervention” has a different connotation in biological research than is being used here.

Paragraph (1) indicates that the person is provided with comprehensible information that is as precise as pssible with regard to any research use foreseen, it should also stipulate that the biospecimen and data may be used for unforeseen research purposes subject to ethics board oversight.

Paragraph (3) indicates that the person should be offered the 'possibility to exercise choices with regard to the type of research use of their biological materials'. This should be modified because it is not always feasible to offer such choices and the person should not be misled, further it can become too burdensome to the person and to the administration of the biospecimen and data usage when the tree of choices becomes complex. We suggest this phrase is modified to reflect that such choices will be offered when feasible.

Paragraph (4) is confusing for the same reasons outlined for Paragraph (1). It states that '*Biological materials may not be removed for storage for future research without the free, express and documented consent of the person concerned'.* What does 'removed' refer to? Is this removed from the person or removed from the storage facility? If from the person it should read 'obtained from the donor'.

Much of the information in Paragraph (4) is redundant with Paragraph (1). These should be combined and edited for clarity as described above.

Article 11 should include a new paragraph covering broad consent that indicates that biological Materials may be collected for use in future research projects which are not known at the time of the collection. Further, it should indicate that the use of these materials for projects unforeseen at the time of collection would be subject to the approval of an ethics committee or other competent body.

State data protection inspectorate of the Republic of Lithuania

In paragraph 1 of Article 11 of Working document it is proposed to add words "in writting" after the words "comprehensible information".

The proposal is to define that the person concerned should be informed about his/her right to withdraw consent or authorisation to remove biological materials for storage for future research, also about the intended transfer of biological materials to third countries. It is proposed to define the person's concerned right to know about the use of biological material and purposes of use.

European Union

European Commission (DG JUSTICE)

Article 11(4) – consent: in the chapeau sentence should read: "freely-given, specific, informed, express..." (Art. 4(8) of the proposed Regulation). Furthermore a horizontal clause should be added: "Consent as referred to in these recommendations should not provide a legitimate ground for the processing of identifiable biological materials or other personal data, where the removal for storage for future research is prohibited by law." (see Article 9(2)(a) of the proposed Regulation); in accordance with such clause, the references to consent should only apply where there is no such prohibition by law;

European Medicines Agency (EMA)

Article 11. 4

Please consider that there may be instances where the precise use of the material will be difficult to be foreseen in advance (e.g. manufacture of ATMP)

OTHERS

Prof. Henriette Roscam Abbing, Netherlands

Art. 11, removal for future research (also against the background of art. 13.1 and 16): 11. 3: gives the impression to be a once for all choice regarding type of research only. Does the person not also have a choice about the use of identifiable or un-identifiable use? (Idem art. 11.4). See also under 13.3. below.

I advise to make it clear also that choices include the possibility of refusal (as is also indicated in art. 13.1.)

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

No full stops after ii in Articles 11, 13, and 14.

Article 12 – Removal of biological materials from persons not able to consent for storage for future research

1. Biological materials may only be removed for storage for future research from a person who, according to law, is considered not able to consent with the written authorisation from the representative or an authority, person or body provided for by law. The representative, the authority, the person or the body concerned should beforehand be given the information required by Article 11, paragraph 1, i and ii and paragraphs 2 and 3.

2. Persons not able to consent should be informed in a manner compatible with their understanding. An adult not able to consent should as far as possible take part in the authorisation procedure. The opinion of a minor should be taken in consideration as an increasingly determining factor in proportion to age and degree of maturity. Any objection by the person not able to consent should be respected.

3. Biological materials from persons not able to consent may only be removed for storage for future research having the potential to produce [real and direct benefit to their health or, in the absence thereof,] benefit to persons in the same age category or afflicted with the same disease or disorder or having the same condition. The removal should entail only minimal risk and minimal burden for the person on whom it is carried out.

4. Where a person not able to consent, from whom biological materials have been removed for storage for future research attains the capacity to consent, the consent of that person for continued storage and research use of his or her biological materials should be sought.

BIOBANKS

3C-R, réseau français de biobanques

Proposed wording of Article 12.1

Biological materials may only be removed for storage for future research, ***including genetic research***, from a person who, according to law, is considered not able to consent with the written authorisation from the representative or an authority, person or body provided for by law.

[Suggestion de phrase alternative pour corriger les problèmes de syntaxe en anglais :

When the person concerned is considered by law to be unable to consent, biological materials may be removed from that person for storage for future research, including genetic research, only with the written authorisation of the person's representative or of an authority, person or body provided for by law.]

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 2.
Last sentence: is this covering the exercise of a right to withdraw from a person not able to give consent but who expressed its will towards a withdrawal?
Para. 4.
Proposal of add:
Where it is impossible or inadequate to recontact the person or where this involves disproportionate efforts an approval from a competent Ethics Committee should be sought in order to continue the activities under the appropriate standards of protection.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

With regard to persons not able to consent, easy access to medical research programs using their biological materials should be carefully considered and - where all the requirements are satisfied - authorised in case their disease cannot be studied in other groups. The forms used for the objection against the use of human biological materials for medical research need to be ready and clear for the guardian or legal responsible person to fill out the form.

With regard to Article 12.2, we recommend separation of dispositions concerning minors and dispositions relating to adults who are not able to consent.

With regard to children under the age of 18, we recommend that minors of a certain age, for example 16 years, are recognized to give their consent autonomously.

With regard to Article 12.3, we recommend clarification on who should be allowed to evaluate the risk of the removal and decide whether it is minimal risk? Should the risks to the person's relatives and descendants be evaluated, especially for DNA/gene test? Shouldit be recommended for rare diseases? The same consideration applies to **Article 14.3**.

With regard to adults who are not competent to give consent, we recommend giving specific examples of conditions that may lead to incapacity to give consent, making a distinction between temporary and permanent conditions of incapacity. A support process should be recognised and available for next–of-kin or guardians, where an individual is not able to provide consent

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 12: Whilst I agree with the general principle to seek consent from a person if they were unable to consent at the time the material was taken, this will only apply to circumstances where biological material is left over when taken for a therapeutic procedure. To take material from a person without their consent for any other reason is a common law assault/battery and should be forbidden. If one then applies this article specifically to that circumstance, material left over from performing a medical procedure carried out in the best interests of the person, then the key issue is not the use of the biological material but the personal information that goes with it. The article here does not appear to allow for an ethics committee to waive the need for consent on the basis of an evaluation of public good versus private need for privacy. This is at odds with current practice across the world and it would not necessarily be helpful to rule this out in the manner that would occur from this present article.

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

Article 12 needs a clarification. If parents have given a written consent in order to take a sample and use it for future research, and the children have accepted it, the child should be asked again when he/she is of legal age.

Further, in case the patient is dead, it is unclear if the stored materials can be a part of new research in the same area of disease that the patient suffered from. Furthermore, in case of dead children: shall we contact the parents and obtain their written consent?

Finally, Article 12 apparently deals with extra material removed for the purpose of storage for future research [as opposed to Article 14 which is residual material]. Examples are extra blood samples drawn during a concrete research project or during clinical diagnostics/treatment for the purpose of storage for future research.

Article 12.3
Since the nature of the future research project is not known at the time of removal for storage for future research, the part of the paragraph describing the potential research is misplaced and rather belongs to *Chapter IV Use of biological material.*

Article 12.4
How is that to be realized? In practice, consent for continued storage and research use may not be sought at the time when the person attains the capacity to consent but is for practical reasons probably only sought at the *time* when an actual concrete research project applies for using the material. In other words, the material may well be *stored* but not *used* without seeking re-consent from the person who has gained the ability to consent.

If the person attains the capacity to consent during the time of *conduction* of a research project, then the person should consent to the continued use (not covered by this Recommendation?) and storage of the material, which was collected during the project.

Dr. Amin El-Heliebi, Dr. Karine Sargsyan, Biobank Graz, Medical University Graz

Article 12.2
The term “authorization procedure” is vague. Better would be “process of consenting”.

- An adult not able to consent should as far as possible be involved in the process of consenting.

Article 12.3
Defining specific categories (age, specific disease, etc.) for which the biological material can be used would dramatically limit the usage of biological materials and make biobanking in this case impossible. The research scope cannot be foreseen in most cases. If from the research in young man would benefit the science of geriatrics and elderlies, it is still a big benefit.

- Biological materials from persons not able to consent may only be removed with minimal risk and minimal burden for the person on whom it is carried out.

KU Leuven Faculty of Medicine, Belgium

Article 12
An element that we find rather problematic in several parts of the document is the definition of consent. More specifically, in Articles 11, 12, 13 and 16 it may be desirable to specify whether the consent needed in each case should be explicit or implicit and, if needed, make clear that a tiered model of consent may be used applied, providing different standards in different situations.

When it comes to the removal of biological materials from persons not able to consent for storage for future research, as described in the Article 12, we believe that putting the phrase "real and direct benefit to their health or, in the absence thereof" in square brackets makes the meaning of this paragraph unclear and it does not adequately stress that such removal may be conducted primarily for the benefit of the person concerned. For the above mentioned reasons it would be desirable to remove the square brackets from this sentence, as well as from the same sentence in Article 14 paragraph 3 and Article 17 paragraph 4.

Article 12.3
The same sentence reads that biological material from persons not able to consent may only be removed, if not to produce real and direct benefit to the person concerned, in order to produce "benefits to persons in the same category or afflicted with the same disease or disorder or having the same condition". We consider that the notion of benefits in this case should be further clarified. This is because if benefits are to be interpreted in a strict sense that would only include real and direct benefit to these groups, this would be problematic for biobanks for general purposes, for example in the case of neonatal biobanks, which aim to produce benefits that would be shared with broader parts of the population.

Lund University, Sweden

Article 12.1 states: "Biological materials may only be removed for storage for future research from a person who, according to law, is considered not able to consent with the written authorisation from the representative or an authority, person or body provided for by law. The representative, the authority, the person or the body concerned should beforehand be given the information required by Article 11, paragraph 1, i and ii and paragraphs 2 and 3."

It should be stated here that these representatives must take the individual's interests into consideration, and base their decisions on this convention as well as interests of the individual they are representing. In its current wording it is possible that they base their decisions on completely different grounds.

We question why **12.2 and 14.2** are so different from each other? Perhaps they cannot be completely identical, but it would be preferable if 14.2 reiterates (as much as possible) what is stated in 12.2.

Article 12.4 states: "Where a person not able to consent, from whom biological materials have been removed for storage for future research attains the capacity to consent, the consent of that person for continued storage and research use of his or her biological materials should be sought."

Please note that the formulation "should be sought" can be problematic – particularly in regards to children. Is it practically possible to get informed consent from all persons (children) from whom biological materials have been removed once they have the capacity to consent? We suggest that this is explained.

Prof. Alexander Tonevitsky, Head of the Department for Translational Oncology at the Hertsen Moscow Research Oncology Institute

Removal, storage and use of biological materials from persons not able to consent (Articles 12, 14 and 17, paragraph 4).

In all mentioned articles this important topic is properly covered. I totally support the suggested version of the document.

Prof. Francesco d'Agostino, Honorary President of the Italian National Committee for Bioethics

It would be possible to make clear that, in case of minors, given their specific vulnerability, a 'broad' consent is not to be granted by parents, but only a 'restricted' or 'partially restricted' one, since they retain control over the use that is made of the biological sample of their child, until the degree of maturity will be reached by the minor, along with his/her ability of adequately expressing an autonomous will.

It is incumbent upon the biobank to contact the parents, in order to explicitly invoke their duty to inform their child regarding the donation and to maintain contact with the biobank to enable the latter to succeed in the consent. All information provided to minors should be gradually and appropriately conveyed, so that children are not traumatized (i.e. by the knowledge of being affected by cancer, if the sample is stored in a department of pediatric oncology).

An article mentioning rare pathologies should be explicitly provided for, emphasizing the role of donation as particularly important, therefore, awareness shall be raised in society in this respect. It is important in order to increase the provision of samples in the informative interview that the physicians present the parents/legal representative with the particular significance of this gesture of solidarity, which is essential for the advancement of research for the benefit of other sick children.

It is important that the issue related to the right to "know" and the right "not to know" of parents and the legal representative be clearly dealt with in the text. Biobanks disclose the data obtained from research, only at the express request of the person concerned, in order to respect the right to know and not to know. It must be considered that incidental findings may emerge, in the context of results, also related to late-onset incurable diseases, causing significant psychological distress.

With regard to minors, when parents grant consent, they shall be informed that in the event of significant results in diagnostic, therapeutic, preventive terms or for reproductive health, the information 'must' be given to the parents, as part of their responsibility. In this case, there is the duty to know on behalf of the parents, even if this entails a psychological burden.

In this case, the interest of the minor with regard to health shall prevail. Under these circumstances, an appropriate psychological counselling service should be recommended for the parents and the child.


Pediatric_Biobanks.pdf


Abstract_Pediatric_Biobanks.pdf

***Prof.** Jacques SIMPORE, Professeur Titulaire de Génétique et de Biologie Moléculaires*

Article 12.2: "The opinion of a minor should be taken in consideration as an increasingly determining factor in proportion to age and degree of maturity. Any objection by the person not able to consent should be respected." The terms of this question need to be properly clarified. In the case of children or persons with serious mental retardation who do not understand what is happening and who, out of fear of the removal of a sample, state in advance that they do not want their blood to be stored, should one listen to them?

Prof. Kelly Tilleman, PhD, Universitair Ziekenhuis Gent

Article 12.1:
In case of a minor (a child), this representative is the parent or legal guardian. In principle: both parents should agree and only if one parent is deprived of its parental authority, then 1 parent consenting is sufficient. Also, if one parent is deceased: I guess it is clear that the surviving parent shall exercise parental authority.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

See comments to article 14.
Delete paragraph 4.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

Paragraph 4 – is this paragraph intended to refer to both adults and children? We think the terminology is fine for adults but should be different where materials from minors are concerned. Given that parental consent is already in place for materials taken from minors we believe that when re-contacting the child at the age of majority where this is feasible), the following information should be provided:

i. a statement about the nature of the collection;

ii. the reason for re-consent (eg: this is the organisation's policy or a new project is proposed)
iii. a reminder of the possibility of withdrawal
iv. a clear mechanism for withdrawal.

We believe this approach will prove less burdensome to participant and collection holder alike.

We would also like paragraph 4 (and all other paragraphs in the Recommendation where the same wording appears) to include provision for the use of materials where an attempt at re-contact has been unsuccessful. Taking into account our earlier comments on the scarcity and elevated value of biological materials for rare diseases we would again like to stress the need to make use of all available materials within a relevant ethical framework.

For adults the time scale between moving in and out of capacity tends to be limited and so re-contact is generally unproblematic. The case is different for children where there could be a long period of time (potentially 16 years) between parental consent being given and the child reaching the age of majority. The child may have died, and this is more likely in the case of a child with a rare disease than in the general population. While we recognise that keeping details up-to-date and re-contacting an individual is always preferable, this will not always be possible.

If the collection holder has lost contact with the family/child it could transpire that

i. re-contacting a family where the child has died without the collection holder being aware is burdensome and upsetting for family members and/or
ii. the collection holder does not have sufficient resources to track down contact details for all those concerned, given the possibility that the family could have moved to another location (more than once), moved to another country and/or that parents may have divorced, died or remarried.

We think this paragraph (and all others with the same wording) should therefore include the possibility of using samples where re-contact has not been successful, as long as the research is subject to local ethical review.

PROFESSIONAL ORGANISATION

European Society of Human Genetics (ESHG)

In general, the ESHG agrees with article 12. However, the ESHG finds the following wording in 12.4. problematic: "*Where a person not able to consent, from whom biological materials have been removed for storage for future research attains the capacity to consent, the consent of that person for continued storage and research use of his or her biological materials should be sought.*" Asking for new consent might lead to serious bias in the collection. The ESHG suggests a wording demanding that when children reach adulthood, they should be informed and have the possibility to withdraw their consent (meaning that they do not have to actively consent).

International Society for Biological and Environmental Repositories' (ISBER)

Article 12.4 refers to situations in which original consent for stored materials were obtained by proxy (e.g., parent for child). The Article recommends that a secondary or amended consent is required for continued storage or research once the person has regained capacity to consent. It is unclear whether the original consent form would state an expiration date for proxy consent (e.g., when the child becomes a certain age) and if/when a secondary consent would be needed for future storage/research. We recommend that guidelines for informed consent of children should be specified to include what determines the need for re-consent (e.g., age) in the future for storage of materials and research.

Furthermore, the US regulations permit a waiver of consent when the child reaches the age of majority if an IRB finds that the criteria for a waiver have been met. However, the Working Document does not mention allowance for a waiver. For example, what if it is difficult to locate the individuals from the study population to obtain a new/secondary consent? Would their specimens no longer be able to be used? Specimens are now routinely being stored for 15 – 20 years on most clinical trials. Thus, it may be very difficult to locate individuals after this length of time. Failure to include these individuals in the research project because secondary consent could not be obtained could bias the study findings and lead to inaccurate conclusions. This could actually harm those populations intended to benefit from the study. We strongly suggest that provisions for a waiver of consent by an IRB/ethics committee be included in this article.

The conditions stipulated in Article 12, paragraph 3 seem too prescriptive and may limit certain kinds of research. Would this prohibit those who are not able to consent from giving blood as normal controls in a project?

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basic tenant of this article, but additionally suggest that with respect to the text in Part 1, all parts of Article 11 apply and the subsequent phrases are redundant and could be deleted.

We also suggest that a statement be added that the age or situation whereby a person attains the capacity to consent is "*as defined as per applicable national laws of member states*". The same provision would apply to Article 14.

We respectfully request that the Committee on Bioethics consider these suggestions.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

Articles 12 and 14: Where capacity to consent is attained (e.g. a minor reaching age of majority) the consent of that person for continued storage and use of biological materials should be sought.

Regeneron Pharmaceuticals, USA

Articles 12.4, 14.4
Suggested Revision: We propose an approach of shared responsibility which would dictate that should a person later attain the capacity to consent, they reserve the legal right and ability to contact the researcher or Sponsor (in the case of clinical studies), by way of their physician, to request a change in their initial consent.

Rationale: This principle could raise a number of logistical questions: What would such an initiative entail? Does this apply to subjects who were consented as children and are now legal adults? How would one demonstrate due diligence? What types and level of documentation must be maintained? At what frequency and under which specific circumstances should consent be continually sought?

This suggested revision empowers subjects to be active in their own participation in medical research and still affords them the right to confirm or revoke consent. This can be

accomplished by adding a statement or wording to the consent form informing subjects of their rights.

ETHICS COMMITTEE

Comitè de Bioètica de Catalunya, Spain (CBC)

Article 12.4
Point 4 of this article should make it much clearer that reference is made only to persons not having the capacity to consent in that moment, not to persons not having the legal capacity to do so, and who are requested their consent from their representative.

Irish health research board (HRB)

Articles 12, 14, 17.4
In the HRB's view, these Articles capture the balance between protection of research participants and enabling research well. The HRB has no further comments on the proposed text.

Comité de Etica (CSIC), Spain

Article 12.1.
If a person is not able to consent with the written authorization, unless he or she is legally incompetent, his/her will should always be taken into account and prior, verifiable and informed consent of his or her legal representative should be always required.

Article 12.4.
The guardian or the legal representative should be present.

Consent from minors should be seriously considered. When they reach adulthood they should be able to deny at any time the use of their biological material obtained from them in the past.

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 12.4: The proposal is to require a new consent of the person after the possible change in the capacity to give a consent, e.g. in case of minors. However the obligation to obtain a written informed consent may not be appropriate in all situations. In our opinion, individual participant can be respected also by providing him/her relevant information on the research project and by giving him/her a possibility to opt-out from the research project.

Swedish Central Ethical Review Board

Articles 12.4 and 14.4 address the situation when someone is only temporarily unable to consent, and provide that in such cases consent should be sought later. It should be required that consent be sought as soon as possible when the person who the biological material is collected from is able to take a stand.

Swedish National Council on Medical Ethics (SMER)

In article 12 it is important to clarify/state that when consent is given by a written authorization from the representative or an authority, person or body provided for by law, for a person not

able to consent, the representative must in their decision have in mind the best interests of the person not able to consent, as a starting point for the decision.

Article 12.4 and article 14.4 states that "Where a person who has not been able to consent, from whom biological materials have been removed for storage for future research attains the capacity to consent, the consent of that person for continued storage and research use of his or hers biological material should be sought." This sentence could preferably be clarified and state that the consent of that person should be sought as soon as possible.
The content of article 12.2 and 14.2 differs to some extent, and can be understood differently. Preferably article 14.2 should be reformulated to better match the writings in article 12.4.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (2) The text reading "*The opinion of a minor should be taken in consideration as an increasingly determining factor in proportion to age and degree of maturity. Any objection by the person not able to consent should be respected where possible*." should be supplemented with balancing information about assent. If there is no capacity to assent, there is no capacity to object, but the best interest test prevails.

Paragraph (3) The following sentence is problematic and does not reflect the science of contemporary biomedicine because it restricts the context to persons of the same age or same affliction: "*Biological materials from persons not able to consent may only be removed for storage for future research having the potential to produce.. benefit to persons in the same age category or afflicted with the same disease or disorder or having the same condition*". In light of significant knowledge linking factors in early life to later life health outcomes and taking into consideration that current diagnostic boundaries are becoming obsolete in light of genetic pleiotropy and shared biological pathways underlying different diseases this sentence should not restrict the benefits to any groups based on age or same disease affliction.

Paragraph (4) refers to seeking consent from persons who previously were not competent to provide consent. To minimize potential harm information should be provided regarding how to recontact persons to attain such consent. Further, the form of consent (i.e. written) should be described.

In addition, the information in Paragraph (4) should indicate whether each country establishes their own criteria to determine when people attain the capacity to provide consent.

State data protection inspectorate of the Republic of Lithuania

In paragraph 1 of Article 12 of Working document it is proposed to add words "against signature" after the words "beforehand be given" and words "understandable to them" after the words "the information".

This Article foresees the provisions concerning the receiving of consent from persons not be able to consent to remove biological materials for storage for future research. However there are no provisions concerning the receiving of consent from person who is able to consent, but due to physical handicaps, desease or other reasons is unable to sign the consent.

European Union

European Commission (DG JUSTICE)

Articles 12(3), 14(3) and 17(4) (removal and storage of biological materials from persons unable to consent and their usage in research projects): we suggest to consider framing the conditions for persons unable to consent by: "when it is necessary to protect the vital interests of that person or of any other person" (cf. Article 9(2)(c) of the proposed Regulation);

European Medicines Agency (EMA)

Article 12.2
Would this cover situations such as umbilical cord tissue?
Informed consent concept of legal representative of the child should be discussed further.

OTHERS

Prof. Henriette Roscam Abbing, Netherlands

Art. 12.3: This is a debatable issue at least in the case of incompetent adults, especially because it concerns removal for future yet unknown research – where the benefits for the person concerned are at the least doubtful. This would be different if there are previously expressed wishes to donate material for research (= advance decision making for re-use of biological material).

Article 13 – Storage for future research of residual biological materials

1. Biological materials removed for purposes other than for storage for future research should only be stored for future research with the consent of the person concerned, provided for by law. This person should beforehand be given appropriate information, as referred to in Article 11, paragraph 1, ii. and paragraphs 2 and 3, including on the right to refuse.

2. Whenever possible, information as referred to in paragraph 1 should be given and consent requested before biological materials are removed.

3. Biological materials removed for purposes other than for storage for future research and already anonymised, may be stored for future research subject to authorisation provided for by law.
Anonymisation should be verified by an appropriate review procedure.

BIOBANKS

3C-R, réseau français de biobanques

Proposed wording of Article 13

Biological materials removed ***or collected*** for ***the*** purposes ~~other than~~ of storage for future research, ***including genetic research***, should only be stored for future research with the consent of the person concerned, ***as*** provided for by law.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

General Comments/Questions:
What about the possibility to obtain a permission/authorisation/approval from a competent Ethics Committee to requalify the samples for research uses? Is this covered by this article? Referral to national law for planning other legitimate grounds should be used.

We stress that is it absolutely necessary to be able to store also identifiable old samples in an appropriate manner under a governance for future research without a consent.
It seems possible under Article 17.2 to use samples for research without consent under certain procedure. Why not apply the same for storage? And if it has not been possible to store the samples due to lack of consent, how could one use them for research? Does this mean such samples that have not been stored, but exist e.g. in pathological archives? Is it then de facto a by-pass? Now this seems, that a person has to consent a) for storage under 13.1. **and** then b) separately for research under 17.1. This is not sensible or practical or does not even safeguard participants' interest. We suggest the Finnish model: broad consent for storage *and* use for future research within certain field of activities under a certain governance model; possibility to follow for which research samples and data have been used and right to withdraw. Research protocol specific consent is elementary in clinical trials, but *does not fit here*. (BBMRI.FI)

> *Discrepancies on this last proposal:*
>
> We agree about the main point stressed above. However, we oppose to the explicit quote of "broad consent" as the recommended model to use as it is, again, not officially recognised by all National Laws in Europe and there might be efficient and ethically less controversial alternatives in a near future. Thus, provided that appropriate governance policies are effective (referral to Chapter V could be done), that all the public authority/ethics committee authorisations have been obtained and that independent oversight is ensured, the storage for future research purposes should be valid, whatever the form of consent that has been used (broad or specific; opt-in/opt-out consent). (BIOBANQUES, FR)

Para.1.
Proposal for textual harmonisation:
"1. Residual identifiable biological samples…"

Proposal for textual specifications
What is consent under this text? Opt-out or non-opposition systems, are they considered as consent? In paragraph 1 consent seems not to require anymore to be "express". A definition of "consent" and "authorisation" would be very useful.

We would prefer wording in the recommendation which explicitly says that the "opt-out" system (i.e. that, subject to information being readily available to persons concerned, consent for use of residual materials for future research will be assumed unless the persons take the initiative to opt out) is one legitimate way in which these recommendations could be implemented in member states.
Old collections can be very large and it is unrealistic that all persons could be contacted directly. It is often not feasible to recontact the persons and may sometimes even be unethical (source of stress,…). Opt-out consent should be valid as well as opt-in. A public announcement mechanism with a possibility to object, and with Ethics Committee approval +

official governmental authorisation (e.g. like in Finland), should be an option to avoid wasting important and valuable collections, which would be unethical.

Proposed Modifications: "[…] should only be stored for future research with the presumed or explicit "consent of the person concerned. This modification is necessary to allow studies on residual biological material as provided under several National laws (E.g. Belgian, French laws).

Para. 3.

3. Biological materials removed for purposes other than for storage for future research and already anonymised, may be stored for future research subject to authorisation provided for by law and notably in the respect of information and consent requirements.

Anonymisation should be verified by any existing competent authority according to an appropriate review procedure.

Dutch National Tissue bank Portal BBMRI-NL

Article 13.1, 13.2

This article implies that the patient should be informed about the fact that their left over tumor tissue blocks are stored for primary diagnostic re-use purposes and must give consent to the storage for a possible secondary use (research or educational purposes) in the future.

In the Netherlands we consider it to be part of good clinical practice that these FFPE blocks are stored and used in the benefit of the patient. Consenting to have a certain treatment or operation includes having your tissue stored for yourself, relatives, research or education if needed.

Of course adequate information about this primary and secondary use is of utmost importance, but this should not interfere with the patient-doctor relationship whose task it is to spend time informing the patient about their diagnosis and future perspectives. Research has shown that patients are in favor of having their left over tissue used for research purposes after having had adequate information and a possibility to opt-out.[8] In the Netherlands we have a Code of Conduct stating that for this specific secondary re-use an opt-out system is appropriate.[9] I believe this to be the case. It would be a time consuming burden and a huge administrative process to obtain consent for every storage and possible secondary use of these tissue samples.

Comment on this part of article 13:

Because FFPE tissue blocks are stored primarily for diagnostic re-use for the patient himself or his relatives, it would be irresponsible to store them anonymized. It is necessary to be able to go back to the tissue block when a patient or their doctor requests it for a diagnostic revision.

In order to know which tissue block belongs to which patient, access to the Pathology department IT health system is necessary. Researchers do not have access to these systems but of course the biobank manager does need access to be able to register if a FFPE block has been sent out or for instance to register an opt-out for secondary use of that patient. Good clinical practice requires that the tissue blocks are stored identifiable and *not* anonymised.

8 In: Geesink, I. & Steegers, C. (2009) Nader gebruik nader onderzocht. Zeggenschap over lichaamsmateriaal. Den Haag: Rathenau Instituut ,TA 09-01

9 Stichting FMWV FEDERA. Human Tissue and medical Research: Code of Conduct for responsible use (2011) Rotterdam, The Netherlands.

To conclude:

1. It is not in accordance with good clinical practice to require consent. An opt-out system is more appropriate.

Requesting consent for every storage and possible use of these diagnostically obtained tissue blocks will not only lead to practical difficulties (time consuming and an administrative burden) but will also not benefit the patient – doctor relationship.

Instead of focusing on consent, I believe it to be more important to focus on adequately informing patients about primary and secondary use of their tissue, and giving them the possibility to opt-out. This information could be provided by hospital management in general, for instance when a patient enters the hospital and is registered centrally. Or by giving a patient access to their electronic medical records with the possibility of registering their opt-out there.

2. **Anonymized storage interferes with standard medical care (primary re-use).**

Not storing these tissue blocks would not be in line with good clinical care.

It is necessary for biobank managers to be able to go back to the tissue block and know the identity of the patient when a patient or his doctor requests it for primary re-use. Also when researchers request tissue blocks, it is necessary for biobank managers to be able to check if there is an opt-out from patients and to register that these blocks are sent out. I believe focusing on *anonymized release* is a much more important issue.

I hope I have made my comments clear on article 13 and that this might be of some use for your re-examination of the Recommendation (2006) 4 of the Committee of Ministers of the Council of Europe, on research on biological materials of human origin.

I want to stress that being able to do research with left over tissue, like these FFPE blocks, is of utmost importance. Not only for the patients whose tissues are being used at this very moment, but also for future patients. We should not create barriers that could harm important research to be performed. We should create an infrastructure in which both patient's rights and patient's benefits go hand in hand with facilitating research (please see Appendix for a visual representation of the process).

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

This sounds like compromise wording between one camp that wanted full written consent for the use of residual materials and another that wanted freedom to use biological materials with little administrative difficulty. If this wording is used it does in effect leave it up to national legislations, that keeps the door open for local differences, which in general is good news. It is recommended to include wording in the recommendation which explicitly says that the "opt-out" system (i.e. that, subject to information being readily available to donors, consent for use of residual materials for future research will be assumed unless donors take the initiative to opt out) is one legitimate way in which these recommendations could be implemented in member states.

With regard to paragraph 1 of article 13:

"Biological materials removed for purposes other than for storage for future research should only be stored for future research with the consent" the sentence: "or absence of objection" should be added after the term "consent".

With regard to paragraph 3 of article 13:

"Biological materials removed for purposes other than for storage for future research and already anonymised, may be stored for future research subject to authorisation provided for by law".

This moment need to be postponed until the human biological materials are given out for research purposes, because the samples remain in the archive for a certain time set by law.

With regard to the sentence:
"Anonymization should be verified by an appropriate review procedure**"** a clarification of what is meant for "appropriate review procedure" is recommended.

With regard to article 13, a new paragraph could be added as follows:
4. Diagnostic biomaterials that are retained in the setting of a doctor-patient relationship and that are not collected and stored under standardized procedures and/or kept under the final institutional responsibility, cannot be used for research purposes, but only for further use in patient care**.**

Article 13 could be modified by combining paragraph 1 and 3 and removing paragraph 2, hence by taking as a principle that storage of residual human biomaterials for future research may occur subject to authorisation (e.g. by an Ethics Committee). In this case, the modified article 13 would read as follows:
1.Biological materials initially removed for purposes other than for storage for future research, may be stored for future research with the consent of the person concerned or subject to authorization of an Ethics Committee or other competent body, provided for by law.
2. Whenever possible, the person concerned should beforehand be given appropriate information, as referred to in Article 11, paragraph 1, ii. and paragraphs 2 and 3, including on the right to refuse.

Swedish National Council of Biobanks (NBR)

The largest biobanks exists within health care and the samples are collected and sored for medical purposes. Those samples can be made available for medical research after an ethical vetting. Each specific research project must be approved by an ethical review board.
Furthermore, access to stored samples should always require a decision from the person responsible for the biobank, who shall ensure that sufficient material remains for the patient's care and treatment (and also control with consent the patients has given). The direct benefit of the individual sample donor shall always have the highest priority. This means that if there is lack of sample material to use for the donor own health care, diagnosis or treatment, either one of those purposes should have a higher priority than research. This should also apply to biological material that has been stored for the purpose of future research.

It is important that information is given and that patients and sample donors are aware of which purposes other than the explicit one for which the samples are taken (such as health care), that are permitted for their samples (such as quality assurance, education and research). Information about health care biobanks and how a patient can withdraw an earlier given consent or restrict the use of their sample should also be easy to find (for examples on web-sites). An infrastructure should exist which makes it possible for a patient to withdraw an earlier given consent or restrict the use of their sample (for example so that the sample can only be used for their own health care).

When samples removed and stored for another purpose than research are to be used for research, and the patients or donors prior consent to the specific sample does not oppose that the sample is used for research, the ethical review board that approves the new purpose

should also decide which the requirements are concerning what information and consent regulations that shall apply.

That is, we do not agree with Article 13, paragraph 1. General requirements of this kind are impossible to apply to every specific research project and will hinder several important research projects with the aim to reach a better health care. However, if the country that the donor resides in cannot provide an infrastructure that enables the donor to find information and withdraw an earlier given consent or restrict the use of the sample, the suggestion in Article 13 and paragraph 1 may be taken into consideration.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

As written this would effectively render all pathology archival material off limits from research. Given the fact that a great deal of our current medical practice has been based upon understanding of disease founded in pathology this would appear to be unfortunate. Anonymisation is not the only issue to permit usage. Waiver of consent should continue to be an option in this circumstance. However, I would agree that as a rule it would be helpful to push pathology services/healthcare practices toward a requirement to obtain consent from all patients given the invaluable contribution such material makes to medicine.

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

Article 13 is a limitation of the Danish rules, a tightening we want to avoid. In Denmark, we have a long tradition for generation of biobanks, for example the major collections/samples at “Statens Serum Institut” and the regional, pathological institutes. According to Article 13, as we read it, one gets the impression that these collections/samples only can be used for research when we have collected written consents from the subjects.

Article 13.1
While Article 11 apparently covers material removed for storage for the *purpose* of future research (*extra material collected in a previous research project* and *extra material collected for future use during diagnosis/treatment)*, article 13 covers *residual* material initially removed within a clinical context or for a specific research project. Paragraph 2 then harbours an intrinsic contradiction: if the information as stipulated in Article 11 is given before removal, then the [extra] material is removed for the *purpose* of storage for future research and is then covered by Article 11.

In some clinical biobanks (e.g. tissue banks at pathology departments), *surplus* material may have been removed within a clinical context for the purpose of diagnosis/treatment without providing the information to donor as stipulated in ii. Today, according to the Danish legislation, the Research Ethics Committee may decline from the obligation to obtain consent for usage of such materials. A *requirement* for the information as stipulated here could impede research using surplus material from clinical biobanks. In our opinion, the emphasis should rather be on confidence in the Research Ethics Committee’s as safeguarding the donors/patients and ethical aspects of research, and on the possibility for opting-out.

Dr Astrid Stuckelberger, Institute of Global Health, Faculty of Medicine, University of Geneva

I think it should always be reminded that the purpose of the study using biological materials should always be explicit and transparent in writing and in the information given. This lacks in the 3 points somewhere and could be overseen.

Also the duration of storage must be clearly given, hence the authorisation of the person must be given clearly in the timing, e.g. for one use or for multiple usage, and should be clearly stated that information on its use for what purpose should be disclosed. (the risk being that biological material is used for military or non ethical purposes)

Dr Imogen Evans, UK

Para1, line 2 - the phrase "provided by law" is not needed
Para 3. The chronology is unclear re removal and anonymisation. Probably better to say "Biological materials previously removed for purposes other than for storage for future research and already anonymised..."

EuroSIDA Steering Committee

Article 13.1
We find it important to highlight the potential down side of restrictions as formulated here. The field of research that forms the basis for development of algorithms to support and fine tune personalised medicine often use data from routine hospital care for data mining to identify potential trends, factors or markers that might contribute to excess risk or bad outcomes. Such searches for potential markers focus on a huge number of potential factors that are considered in the algorithm, tested, validated and kept or neglected – a process that need excessive computer power because factors included in initial analysis are all available results obtained. Such big data research will not be possible under regulations that require specific consent at the time of specimen/data collection.

Article 13.2
Further, data mining of routine results might lead to identification of specific markers of potential predictive impact that are only available from a restricted number of cases, but where specimens are stored from routine care and potentially available for analysis of the potential factor(s). The nature of this research exercise requires high through-put: as the number of factors identified will be high and most of the analysed markers after testing and validation will not be considered in the final algorithm predicting treatment outcome – such research will be negatively impacted if each factor analysed requires specific patient consent – especially since renewed testing for potential biomarkers from specimens in routine care bio-banks will be conducted much later than the treatment episode generating the specimen.

KU Leuven Faculty of Medicine, Belgium

An element that we find rather problematic in several parts of the document is the definition of consent. More specifically, in Articles 11, 12, 13 and 16 it may be desirable to specify whether the consent needed in each case should be explicit or implicit and, if needed, make clear that a tiered model of consent may be used applied, providing different standards in different situations.

Prof. Alexander Tonevitsky, Head of the Department for Translational Oncology at the Hertsen Moscow Research Oncology Institute

Article 13.3
The suggested points are clear-cut and do not need any further clarifications with the exception of the “appropriate review procedure” for the anonymisation of the samples from

the point 3. I would recommend to add a reference to the document describing this kind of procedures.

Prof. Jacques SIMPORE, Professeur Titulaire de Génétique et de Biologie Moléculaires, Burkina Faso

"Storage for future research of residual biological materials"; paragraph 1 of this Article states: "Biological materials removed for purposes other than for storage for future research should only be stored for future research with the consent of the person concerned, provided for by law. This person should beforehand be given appropriate information, as referred to in Article 11, paragraph 1, ii. and paragraphs 2 and 3, including on the right to refuse."

Prof. Kelly Tilleman, PhD, Universitair Ziekenhuis Gent

Article 13.3
It is not completely clear to me what this paragraph means. So if you would store material that is anonymised (e.g. anonymous sperm donor?) and thus initially not for research, then it would be okay to use it for research? What exactly does the sentence: 'may be stored for future research to authorisation provided for by law' – means. Could the council elaborate on that?

All material that is stored anonymous is actually coded. There is always traceability back to the person originally donating the material – also for residual material. Otherwise it is impossible to carry out good scientific research. I could see this happening in centres, that they might use anonymous residual material for procedure training of new staff members. However, even then, we ask for research consent. Maybe, the council could give an example here, so that it is clear in which situation this might occur, as I might be missing something here to actually give the right feedback.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

Comment
See European Parliament legislative resolution of 12 March 2014 on the 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) http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2014-0212+0+DOC+XML+V0//EN
4 (2a) "pseudonymous data' means personal data that cannot be attributed to a specific data subject without the use of additional information, as long as such additional information is **kept separately and subject to technical and organisational measures to ensure non-attribution"**
9. 1: **"The processing of personal data,** revealing race or ethnic origin, political opinions, religion or philosophical beliefs, sexual orientation or gender identity, trade-union membership and activities , and the processing of genetic or biometric data or **data concerning health** or sex life, administrative sanctions, judgments, criminal or suspected offences, convictions or related security measures **shall be prohibited.**
2. Paragraph 1 shall not apply if one of the following applies : (a) **the data subject has given consent** to the processing of those personal data for one or more specified purposes , subject to the conditions laid down in Articles 7 and 8, except where Union law or Member State law provide that the prohibition referred to in paragraph 1 may not be lifted by the data subject, **or (…)(i) processing is necessary for historical, statistical or scientific**

research purposes subject to the conditions and safeguards referred to in Article 83; or (…)"

83: "1.In accordance with the rules set out in this Regulation, personal data may be processed for historical, statistical or scientific research purposes only if:
(a) these purposes cannot be otherwise fulfilled by processing data which does not permit or not any longer permit the identification of the data subject;
(b) data enabling the attribution of information to an identified or identifiable data subject is kept separately from the other information under the highest technical standards, and all necessary measures are taken to prevent unwarranted re-identification of the data subjects".

Proposal
Article 13.3
Biological materials removed for purposes other than for storage for future research and already anonymised **or pseudonymised**, may be stored for future research subject to authorisation provided for by law.

Anonymisation **or psedonymisation** should be verified by an appropriate review procedure.

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

Title may include : removal of biological materials from minors and other persons not able to consent ..... This may help to attract more attention to minors at the outset.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

Given our context, this article will be helpful for rare disease research in that it outlines how some existing clinical collections may be utilised. We are aware of the fact that in some member states the law is stricter than this Recommendation and therefore prevents such utilisation.

PROFESSIONAL ORGANISATION

European Society of Human Genetics (ESHG)

The ESHG agrees with the wording "may be stored for future research subject to authorization".

International Society for Biological and Environmental Repositories' (ISBER)

The statement in paragraph 1 appears to preclude the storage of residual diagnostic specimens without consent. While Article 17, paragraph 2 i.i. appears to allow for a waiver, it should be explicitly addressed in this Article as well. This will be critical to allow important retrospective research to proceed, particularly research involving specimens collected during the course of routine care (e.g., pathology archives) which was not initially anticipated at the

time the specimens were collected and for which consent would be difficult or impossible to obtain at the time the research will be conducted. There are valuable archived collections which could not be established prospectively today because of changes in standard of care (e.g., untreated node-negative breast cancer collections) and for which consent for research use was not obtained at the time the specimens were collected. In these cases, it is difficult or impossible to re-contact individuals to obtain a new consent. Therefore, it will be important to allow for waivers of consent by an ethics review committee or other competent authority with regard to storage. We suggest that Article 13, paragraph 1 be modified along the following lines, "Biological materials initially removed for purposes other than for storage for future research, may be stored for future research with the consent of the person concerned or upon authorization by an Ethics Committee or other competent body, provided for by law." We also recommend that this article be revised to include specific language that allows storage of residual identifiable material for future use. It would be helpful either in the main body of the document or in the accompanying explanatory memorandum to more clearly define what is meant by residual biological materials and provide some examples (e.g. specimens collected during the course of routine care such as specimens in pathology archives, left over blood samples at clinical laboratories, etc.). In addition, the language regarding storage of residual anonymized materials needs to be clarified to understand which authorization provided by law is required.

Organization of Danish Medical Societies[10]

Our focus is on Article 13 – Storage for future research of residual biological materials which states that biological materials removed for purposes other than storage for future research should only be stored for future research with the consent of the person concerned.

The Danish National Committee on Health Research Ethics is responsible for ensuring that from a research ethical point of view, health research projects are carried out in a responsible manner, and that the rights, safety and wellbeing of trial subjects participating in such biomedical research projects are protected, while at the same time possibilities are being created for the development of new, valuable knowledge.

Under the current Committee Act it is possible for Danish scientist to be granted access to biological materials removed for diagnostic purposes provided that the persons involved have not notified the Danish Tissue Application Register (Vævsanvendelsesregisteret) that they do not wish to have their biological materials used for purposes other than their own medical diagnostic procedures and treatment.

The access can be granted if either it is impossible to obtain informed consent from all participants or if the research results obtained on participants are without clinical consequences.

This system ensures that citizens in Denmark can opt out of participating in medical research projects that involve their own biological materials that were originally stored for diagnostic and treatment purposes. This is regulated in Law no. 312 (May 5, 2004) which also states that Danish scientists who wish to use such biological materials are required to search "Vævsanvendelsesregistret" in order to ascertain whether the persons involved have chosen to notify "Vævsanvendelsesregisteret" as mentioned above.

[10] The Organization of Danish Medical Societies represents 118 Danish medical societies.

The Organization of Danish Medical Societies finds that Danish law already provides the necessary sufficient, easily accessible and unbureaucratic protection of potential research participants in this regard.

A passing of Article 13 into Danish law, on the other hand, will by necessity become an unnecessary obstacle for the development of new valuable knowledge benefitting Danish patients as well as international patient groups that may anticipate improvements in their medical treatments as a consequence of research results obtained in Danish research projects (and international projects that involved Danish scientists and biobanks).

An additional consequence will be that already existing biological materials stored in the relevant biobanks are rendered useless because they cannot be used for notable research projects, and this presents a considerable ethical problem.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We suggest that the Committee on Bioethics consider the possibility of a model of consent in addition to, as an alternative to, individual participant consent. An example would be where a competent research ethics committee or equivalent is able to give group consent in lieu of individual donor consent, in circumstances such as where it is impracticable to re-contact individuals to seek consent especially many years after biological materials were removed, or where efforts to re-contact may cause concern or distress. This is already acceptable under the Declaration of Helsinki, paragraph 32 which states:

"32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee."

It should not be a prerequisite that materials are always anonymised before they can be used without individual consent.

We respectfully request that the Committee on Bioethics consider these points.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

We concur that consent for storage and future research use of samples should be sought prospectively where practical. In circumstances where prospective consent has not been obtained and where it is not feasible or practical to seek additional consent, we recommend that DH-BIO provide for approval by an authorised body (e.g. Ethics Committee), thereby waiving the requirement for consent of the persons concerned as permissible within the law. This approach is described with approval in Declaration of Helsinki:

> [3] *32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.*

Regeneron Pharmaceuticals, USA

Article 13.3
Rationale: This document should more clearly differentiate between "non-identifiable" and "anonymised". While we recognize these terms are sometimes used interchangeably, they are not necessarily synonymous. Therefore, we suggest utilizing the definitions outlined in ICH E15 or make reference to it.

If a sample is truly anonymised, it cannot be traced back to the subject. It should also be recognised that, technically, genetic data can be traced back, although it may be difficult to do so. If a sample is truly anonymised it would render research/analysis futile because it offers no correlation to the clinical data. It should also be noted that if samples are truly anonymised, it would be impossible to inform a subject of any new health information that is identified in the future. If samples are not anonymised, they can be made non-identifiable by utilizing double coding. In addition, access to the coding could be restricted such that even the site monitors do not have access to the double coding.

In order to respect subject confidentiality and privacy while attempting to advance knowledge and potential treatments from biomedical research, we propose de-identifying data instead of truly anonymising their information by following the principles outlined in ICH E15. In situations where more stringent de-identification processes may be advisable, we recommend double-coding which will maintain subject privacy while still allowing for a correlation to clinical data.

Articles 13.3, 14.5, 17.3
Suggested revision: We propose that examples be provided. More specifically: "… Anonymisation should be verified by an appropriate review procedure, such as use of an IRB or EEC, IDMC review, or internal process with a specific and appropriate QC procedure."
Rationale: The term "appropriate review procedure' is not clearly defined and leaves a lot of room for interpretation.

ETHICS COMMITEES

Comité de Etica (CSIC), Spain

Article 13.3
Anonymisation must be strictly preserved at all times (for any present or future research) if the person requests it.

Irish Health Research Board (HRB)

The full remit of this Article was not clear, e.g. if an application of this Clause to historical martials was intended. Every research project using materials of human origin requires research ethics approval, but it was not clear what if any additional safeguards the Clause suggested and in what kind of scenarios it might apply.

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 13.3
TUKIJA is uneasy about the usage of anonymised biological materials for research. Besides the above mentioned restrictions about the term anonymised, TUKIJA feels that the possibility to use the so called anonymised materials for research does not adequately respect the wishes of the persons they were collected from. Hence, TUKIJA wants to raise

the question whether data protection is enough to respect a person's autonomy or should it also require respect for the person's value choices. The right to live according to one's own values is very important feature of being a person, and it should not be offsided by mere data protection.

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

In Belgium, consent to the use of residual biological material for purposes of scientific research is deemed to have been given inasmuch as the donor has not objected to it (= "opting out"). The intended use, together with the possibility for the donor to refuse, are disclosed in writing to the donor beforehand;

Under Belgian legislation, consent for future research must be sought not before removal but prior to the research. At all events, any form of secondary use (= any other use than the one to which the donor has consented in connection with the removal), and the purposes of that use, must have the prior approval of an ethics committee;

Norwegian Institute of Public Health (NIPH)

Content in article 13 could be integrated with content in Article 11 to produce a more streamlined and cohesive document.

State data protection inspectorate of the Republic of Lithuania

In paragraph 1 of Article 13 of Working document it is proposed to add words "against signature" after the words "beforehand be given" and words "understandable to him" after the words "appriopate information".

OTHERS

Prof. Henriette Roscam Abbing, Netherlands

Art. 13: para. 1 requires information to be given beforehand –
Art, 13, para 2 likewise requires information (and also consent) to be given before removal of materials – whenever possible. I presume whenever possible refers to an emergency situation? It looks as if there is some overlap between para. 1 and 2.

Art. 13, para 3 contains an exception in case of data being anonymised. It would be preferable to leave the patient in control of his/her data (autonomy-right). Data should not be anonymised without the patient being informed about this possibility (and about the possibility of refusal). This the more so because with technological innovation anonymity is hardly guaranteed any more.

Article 14 – Storage for future research of residual biological materials from persons not able to consent

1. Biological materials removed for purposes other than for storage fur future research from persons not able to consent should only be stored for future research with the authorisation

from their representative or an authority, person or body provided for by law. The representative, the authority, the person or the body concerned should beforehand be given appropriate information, as referred to in Article 11, paragraph 1, ii. and paragraphs 2 and 3, including on the right to refuse.

2. Whenever possible, information as referred to in paragraph 1 should be given and authorisation requested before biological materials are removed.

3. Biological materials removed for purposes other than for storage for future research from persons not able to consent may only be stored for future research having the potential to produce [real and direct benefit to their health or, in the absence thereof,] benefit to persons in the same age category or afflicted with the same disease or disorder or having the same condition.

4. Where a person not able to consent, from whom biological materials have been removed for purposes other than for storage for future research, attains the capacity to consent, the consent of that person for continued storage and research use of his or her biological materials should be sought.

5. Biological materials removed for purposes other than for storage for future research and already anonymised, may be stored for future research subject to authorisation provided for by law.
Anonymisation should be verified by an appropriate review procedure.

BIOBANKS

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Proposal of add:
Again, what about the possibility to obtain a permission/authorisation/approval from a competent Ethics Committee to requalify the samples for research uses? Is this covered by this article?
This possibility should explicitly be recognised and mentioned in this article and throughout the recommendation; additional referral to national law for planning other legitimate grounds should also be used.

Para.3.
When growing up children may benefit from sampling made when they were young
It is recommended that sampling from persons not able to consent must benefit persons in the same age. However, a growing body of data shows that health events early in life may affect adolescent and adult health. Other empirical studies support the hypothesis that epigenetic changes caused by environmental conditions early in human life can have effects throughout life. Because it is likely that genetic epidemiology will uncover more of these gene-environment interactions, it is essential that scientists with multiple backgrounds and expertise have access to samples and data that are representative of the different phases of life and that sampling can be done for children even when the benefits may come later.

Comment about "anonymisation"
Anonymised samples are often of limited value: why store samples that one cannot connect with any information or follow-up? Instead, it could be non-identifiable for the researcher, but a biorepository has to have a code key safely stored, for instance.
Anonymisation does not allow for withdrawal of consent. If anonymisation is regarded as a panacea, what is then the purpose of this recommendation? Data protection is another thing

and already strictly regulated. Use of anonymised data does not respect individual wishes and values. This is an ignored issue in policy papers which seem to reduce respect for self determination only to identifiable samples and data.

Para. 4.
Proposal of add
Idem than for Art. 12.4: **"**Where it is impossible or inadequate to recontact the person or where it is involving disproportionate efforts an approval or a waiver from a competent Ethics Committee should be sought in order to continue the activities under the appropriate standards of protection".

Para. 5.
Proposal for textual specifications
Biological materials removed for purposes other than for storage for future research and already anonymised, may be stored for future research subject to authorisation provided for by law and notably in the respect of information and consent requirements.
Anonymisation should be verified by any existing competent authority according to an appropriate review procedure.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Article 14.2
"2. Whenever possible, information as referred to in paragraph 1 should be given and authorisation requested before biological materials are removed" it may be noted that they need to be removed anyway, if concerning residual materials. They will then become part of the archive atthat time or before objection can be given in an "opt-out" system. Secondary uses could be allowed after a period of one year and in the case of FFPE material the original lesion should be conserved in the FFPE block after material is taken for research purposes. A support process should be recognised and available for next –of- kin/guardians where an individual is not able to provide consent.

Article 14.5, what does appropriate review procedure mean in practical terms?

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO)

Article 14.3
I do not agree with this point.....

Biological samples should be used for all biomedicine research, not only for the same conditions.....

Swedish National Council of Biobanks (NBR)

Article 14.1,2. See our comment under point 3. We believe that the same conditions should apply.

Article 13 and 14.3, and 17.4
We do not agree with the recommended restriction of the use of samples. Samples taken for one purpose or disease may be very important as control material for other diseases or if the donor later in life develops another type of disease. We believe that there is a risk of discrimination if one, on a general basis, excludes certain groups of people from possible important research. An ethical review board should approve the new purpose and the research project.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 14: covers much of the same issues as Article 12 but has a peculiar requirement under section 3. That there should be some requirement to benefit the person directly. I would suggest removing this requirement as it conflates research with therapeutic practice.

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

Article 14 apparently concerns *residual* material collected for purposes other than for future research, for example residual material from a research project or from a clinical biobank.

Article 14.2
Same contradiction as in 13-2: if information has been given beforehand, then it is covered by Article 12.

Dr. Amin El-Heliebi, Dr. Karine Sargsyan, Biobank Graz, Medical University Graz

Article 14.1
A typo after word “storage” a “fur” should be removed

Article 14.3
Similar to comment in Article 12.3:

Defining specific categories (age, specific disease, etc.) for which the biological material can be used would dramatically limit the usage of biological materials. The research scope cannot be foreseen in most cases.

- New: Biological materials removed for purposes other than for storage for future research from persons not able to consent may only be removed with minimal risk and minimal burden for the person on whom it is carried out.

Dr Imogen Evans, UK

Para 1, line 1 should read "storage for future research"
Line 2, delete "the" before authority
Line 3, delete "the" before person and before body
Para 2 should read" Whenever possible, the information referred to in..."
Para 3: the clause enclosed in square brackets referring to "real and direct benefit" etc is wholly unrealistic and therefore unachievable. This clause should be omitted.

Karolinska Institutet, Sweden

When growing up children may benefit from sampling made when they were young
It is recommended in article 14 that sampling from persons not able to consent must benefit persons in the same age. However, a growing body of data shows that health events early in life may affect adolescent and adult health. Other empirical studies support the hypothesis

that epigenetic changes caused by environmental conditions early in human life can have effects throughout life. Because it is likely that genetic epidemiology will uncover more of these gene-environment interactions, it is essential that scientists with multiple backgrounds and expertise have access to samples and data that are representative of the different phases of life and that sampling can be done for children even when the benefits may come later.

KU Leuven Faculty of Medicine, Belgium

Article 14 on storage for future research of residual biological materials from persons not able to consent does not provide, in its current form, that the persons not able to consent should be informed about the storage in a manner compatible to their understanding. We believe that adding a relevant paragraph to the Article would safeguard broader protection of the persons concerned and it would be consistent with paragraph 2 of the Article 12.

Article 14.3
When it comes to the removal of biological materials from persons not able to consent for storage for future research, as described in the Article 12, we believe that putting the phrase "real and direct benefit to their health or, in the absence thereof" in square brackets makes the meaning of this paragraph unclear and it does not adequately stress that such removal may be conducted primarily for the benefit of the person concerned. For the above mentioned reasons it would be desirable to remove the square brackets from this sentence, as well as from the same sentence in Article 14 paragraph 3 and Article 17 paragraph 4.

Lund University, Sweden

We question why 12.2 and 14.2 are so different from each other? Perhaps they cannot be completely identical, but it would be preferable if 14.2 reiterates (as much as possible) what is stated in 12.2.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO), Spain – Private/Public Partnership

Article 14.3
I do not agree with this point.....

Biological samples should de used for all biomedicine research, not only for the same conditions.....

Prof. Kelly Tilleman, PhD, Universitair Ziekenhuis Gent

Article 14.4
This paragraph would mean that if material was stored for future research obtained from a child, consented by both parents, that when this child turns 18 – the centers would need to seek contact with this individual to find out if he or she is still consenting.
I think this could be difficult in practice. A person can always retract its consent and therefore instead of seeking the consent upon retaining consent, it would be advisable to include a section in the consent form that the patient him or herself should/ can retract its consent. This is clearly stated in art. 16. Therefore, I would suggest to omit this section from the art. 14.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

Comment
Article 14.4
The Directive on data protection, the Proposal for a General Data Protection Regulation and the national legislations (as far as I know) consider that the consent given by the representative person remains valid even after the person not able to consent attains the capacity to consent.

Other issue to consider is that it would be almost impossible to know that a person has attained the capacity to consent in cases when the incapacity is not related to the age of the person but to his / her capabilities.

Article 14.5
See comments to article 13.

Proposal:
Delete paragraph 4

5. Biological materials removed for purposes other than for storage for future research and already anonymised **or pseudonymised**, may be stored for future research subject to authorisation provided for by law. Anonymisation **or pseudonymisation** should be verified by an appropriate review procedure.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

We do not think this article accounts for the fact that children, as they get older, may benefit from sampling made when they were young. A growing body of data shows that health events early in life may affect adolescent and adult health. Other empirical studies support the hypothesis that epigenetic changes caused by environmental conditions early in human life can have effects throughout life. It is likely that genetic epidemiology will uncover more of these gene-environment interactions making it essential for scientists with multiple backgrounds and expertise to have access to samples and data that are representative of the different phases of life and that sampling can be done for children even when the benefits may come later.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We suggest that the Committee on Bioethics consider the possibility of a model of consent in addition to, as an alternative to, individual participant consent. An example would be where a competent research ethics committee or equivalent is able to give group consent in lieu of individual donor consent, in circumstances such as where it is impracticable to re-contact individuals to seek consent especially many years after biological materials were removed, or where efforts to re-contact may cause concern or distress. This is already acceptable under the Declaration of Helsinki, paragraph 32 which states:

"32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee."

It should not be a prerequisite that materials are always anonymised before they can be used without individual consent.

We respectfully request that the Committee on Bioethics consider these points.

Regeneron Pharmaceuticals, USA

Articles 12.4, 14.4
Suggested Revision: We propose an approach of shared responsibility which would dictate that should a person later attain the capacity to consent, they reserve the legal right and ability to contact the researcher or Sponsor (in the case of clinical studies), by way of their physician, to request a change in their initial consent.

Rationale: This principle could raise a number of logistical questions: What would such an initiative entail? Does this apply to subjects who were consented as children and are now legal adults? How would one demonstrate due diligence? What types and level of documentation must be maintained? At what frequency and under which specific circumstances should consent be continually sought?

This suggested revision empowers subjects to be active in their own participation in medical research and still affords them the right to confirm or revoke consent. This can be accomplished by adding a statement or wording to the consent form informing subjects of their rights.

Article 14.5
Rationale: This document should more clearly differentiate between "non-identifiable" and "anonymised". While we recognize these terms are sometimes used interchangeably, they are not necessarily synonymous. Therefore, we suggest utilizing the definitions outlined in ICH E15 or make reference to it.

If a sample is truly anonymised, it cannot be traced back to the subject. It should also be recognised that, technically, genetic data can be traced back, although it may be difficult to do so. If a sample is truly anonymised it would render research/analysis futile because it offers no correlation to the clinical data. It should also be noted that if samples are truly anonymised, it would be impossible to inform a subject of any new health information that is identified in the future. If samples are not anonymised, they can be made non-identifiable by utilizing double coding. In addition, access to the coding could be restricted such that even the site monitors do not have access to the double coding.

In order to respect subject confidentiality and privacy while attempting to advance knowledge and potential treatments from biomedical research, we propose de-identifying data instead of truly anonymising their information by following the principles outlined in ICH E15. In situations where more stringent de-identification processes may be advisable, we recommend double-coding which will maintain subject privacy while still allowing for a correlation to clinical data.

Articles 13.3, 14.5, 17.3
Suggested revision: We propose that examples be provided. More specifically: "… Anonymisation should be verified by an appropriate review procedure, such as use of an IRB or EEC, IDMC review, or internal process with a specific and appropriate QC procedure."

Rationale: The term "appropriate review procedure' is not clearly defined and leaves a lot of room for interpretation.

ETHICS COMMITTEE

Irish health research board (HRB)

Articles 12, 14, 17.4
In the HRB's view, these Articles capture the balance between protection of research participants and enabling research well. The HRB has no further comments on the proposed text.

Comité de Etica (CSIC), Spain

Article 14.1
These individuals should have the right to decide on the use of their biological material, unless he or she is legally incompetent.

Swedish National Council on Medical Ethics (SMER)

Article 12.4 and article 14.4 states that "Where a person who has not been able to consent, from whom biological materials have been removed for storage for future research attains the capacity to consent, the consent of that person for continued storage and research use of his or hers biological material should be sought." This sentence could preferably be clarified and state that the consent of that person should be sought as soon as possible.

The content of article 12.2 and 14.2 differs to some extent, and can be understood differently. Preferably article 14.2 should be reformulated to better match the writings in article 12.4.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Content in article 14 could be integrated with content in Article 12 to produce a more streamlined and cohesive document.

State data protection inspectorate of the Republic of Lithuania

In **Article 14.1** of Working document it is proposed to add words "against signature" after the words "beforehand be given" and words "understandable to them" after the words "appriopriate information".

European Union

European Commission (DG JUSTICE)

Articles 12(3), 14(3) and 17(4) (removal and storage of biological materials from persons unable to consent and their usage in research projects): we suggest to consider framing the

conditions for persons unable to consent by: "when it is necessary to protect the vital interests of that person or of any other person" (cf. Article 9(2)(c) of the proposed Regulation);

OTHERS

Prof. Henriette Roscam Abbing, Netherlands

Art. 14: here also previously expressed wishes can be relevant.

Art. 14, para. 5: anonymisation: remark similar to the one under art. 13.3: Also regarding anonymisation previously expressed wishes and/or substitute decision-making should come into play.

Article 15 – Biological materials removed after death

1. Biological materials should only be removed from the body of a deceased person for storage for future research with the consent or authorisation, provided for by law. This consent or authorisation should have been preceded by appropriate information, including on the right to refuse.

2. Biological materials should not be removed for storage for future research if the deceased person is known to have objected to it.

BIOBANKS

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para.1.

Proposal for textual changes

1. Identifiable biological materials should only be removed from the body of a deceased person for storage for future research with the consent or authorisation, provided for by law. This consent or authorisation should have been preceded by appropriate information, including on the right to refuse.

Para.2.

Proposal for textual changes

2. Biological materials/resources (see comments above) should not be removed for storage for future research if the deceased person is known to have objected to it. The will of the person might be sought by consulting the closest having been able to be aware of the patient's own standpoint.

However,

- Biological material can be obtained during a post-mortem examination - as a diagnostic procedure performed by a pathologist in a hospital. This material becomes "residual material" and could be used for research purposes. The execution of a post-mortem examination is not (always) subjected to informed consent; (e.g. in Belgium, this is subject to presumed consent).
- Similarly, biological material can be obtained when harvesting organs for transplantation. This article is in contradiction with the Belgian legal context.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

With regard to paragraph 2 of article 15, "Biological materials should not be removed for storage for future research if the deceased person is known to have objected to it". This should be applied as a general principle to persons who are not able to give consent (see articles 12 and 14), but who were formerly able to give consent and were known to object at that time.

ACADEMIA

Dr Imogen Evans, UK

Para 1: the second sentence seems too restrictive. In the case of material removed at autopsy, it is unrealistic to suppose that appropriate information should precede the consent/authorisation process unless that information was to be given before the person died! It would be preferable to omit the second sentence.

KU Leuven Faculty of Medicine, Belgium, Belgium

Article 15 on biological materials removed after death, additional clarifications may be needed regarding the persons considered to be entitled to give consent or authorization for the removal of biological material from the body of a deceased person for storage for future research.

INDUSTRY

Regeneron Pharmaceuticals, USA

Article 15.2
Suggested Revision: We propose that if this principle is retained as a recommendation within this document, a statement be added to the consent process that the Legally Authorised Representative (LAR) for the deceased person is the only authorized person that can provide evidence of the objection, if not explicitly captured in the consent form by the person from which human samples were obtained. Alternatively, the physician of the deceased can provide such evidence if it was communicated directly from the deceased individual and documented in medical records.

Rationale: Examples should be provided to clarify how to demonstrate the deceased person's objections. The current clause in this working document raises multiple questions including: How would a person's wishes be qualified? Can it be stated by any family member? What if there are conflicting statements from different relatives? What types of documentation would need to be provided by the person's physician to the researcher or Sponsor company? To improve clarity, suggested revisions have been noted above.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

Comment
The relation between paragraphs 1 and 2 is not clear. Who can refuse in paragraph 1?

Proposal
1. Biological materials should only be removed from the body of a deceased person for storage for future research with the consent or authorisation, provided for by law. ~~This consent or authorisation should have been preceded by appropriate information, including on the right to refuse.~~
2. Biological materials should not be removed for storage for future research if the deceased person is known to have objected to it.
3. When family members of the deceased person could be identified in the future research, the sample will be anonimysed unless they give their own consent.

Comité de Etica (CSIC), Spain

Article 15.1
If a person is not able to consent with the written authorisation only the legal representative informed consent should be taken into account.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (1) refers to consent requirements for the removal of biological materials from the body of a deceased person. However, it does not specify clearly who is consenting and when. Is this consent obtained from the deceased prior to their death or obtained from an authorized person after death? It is recommended that provisions be provided to address both situations (consent prior to death by the deceased, and potential to consent after death by authorized persons when this does not counter the wishes of the deceased and the deceased did not have the capacity to provide consent.). This latter provision is particularly important, for example for cases where the deceased did not have the capacity to provide consent, as in cases of crib death or Alzheimer's disease.

State data protection inspectorate of the Republic of Lithuania

In paragraph 1 of Article 15 of Working document it is proposed to add words "if person did not expressed consent for biomedical research or withdraw it" after words "provided for by law".

In paragraph 1 of Article 15 of Working document it is proposed to add words "understandable to him" after the words "the right to refuse".

OTHERS

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

No comma in line 2 of Article 15 (1).

Article 16 – Right to change the scope of, or to withdraw, consent or authorisation

1. When a person has provided consent to storage of identifiable biological materials for future research, the person should retain the right to withdraw or alter the scope of that consent.

When identifiable biological materials are stored for research purposes only, the person who has withdrawn consent should have the right to have, in the manner foreseen by national law, the materials either destroyed or anonymised. The person who is considering withdrawing consent should be made aware of any limitations on withdrawal of his or her biological material.

2. The representative, authority, person or body provided for by law having given authorisation for storage for future research of biological materials removed from a person not able to consent, should have the rights referred to in paragraph 1.
Where the person from whom biological materials have been removed attains the capacity to give consent, that person should have the rights referred to in paragraph 1.

BIOBANKS

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 1.
Proposal for textual specification:
When a person has provided consent to storage of identifiable biological materials for future research, the person should retain the right to withdraw or alter the scope of that consent at any time.
When identifiable biological materials are stored for research purposes only, the person who has withdrawn consent should have the right to decide (in the manner foreseen by national law), whether the bio-materials shall either be destroyed or anonymised.
(It should be made clear, however, that anonymisation is not a possibility to continue research with such materials because in the end the person has previously withdrawn consent).

Proposal for textual clarification :
Make two new paragraphs for the two last sentences as they are referring to different steps with respect to the right to withdraw.

Proposal adds: the persons (…) materials, as long as the use of the biological material in a research project has not been decided upon.

Comment about "anonymisation" :
Withdrawal of consent should NEVER allow for further use of bio-materials/resources simply by "anonymisation" (against the will of the person concerned!). The anonymisation (-procedure) of meta data must be subject to the person's information/consent.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

With regard to paragraph 1 of article 16, which states that" the person who is considering withdrawing consent should be made aware of any limitations on withdrawal of his or her biological material".

This section needs to specify what limitations there may be to data generated from use of the samples up to the point of withdrawal.
It should also be considered that it is practically difficult to monitor the informed consent process over time, though IT are promising for tracking resources from this perspective.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO)

This point is problematic.

I think that the withdraw should be based in some solid bases and not be a right for all cases.

The withdrawal of samples in the middle of a project can lead to a lot of problems. If that withdrawal is due to some "social tendency" the effect can be dramatic.

ACADEMIA

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

A national opt-out system should be established.

Dr Imogen Evans, UK

There is inconsistency in the use of the word “identifiable" between the paragraphs. "Identifiable" should appear in para 2, line 2 before "biological", and again in line 4 before "biological"
The line spacing is also odd. Was it intended that the sentence beginning "Where the person from whom..." should be part of paragraph 2 , in which case it should be run on to the preceding sentence; or was it the case that this should in fact be the start of paragraph 3?

KU Leuven Faculty of Medicine, Belgium, Belgium

An element that we find rather problematic in several parts of the document is the definition of consent. More specifically, in Articles 11, 12, 13 and 16 it may be desirable to specify whether the consent needed in each case should be explicit or implicit and, if needed, make clear that a tiered model of consent may be used applied, providing different standards in different situations.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO), Spain – Private/Public Partnership

This point is problematic.

I think that the withdraw should be based in some solid bases and not be a right for all cases.

The withdrawal of samples in the middle of a project can lead to a lot of problems. If that withdrawal is due to some "social tendency" the effect can be dramatic.

Prof. Cassiman, University of Leuven, Belgium

Article 3.ii, Article 7.1, Article 13.3, Article 14.5, Article 16.1, Article 17.3
Anonymisation of samples is not considered anymore as being possible. There are many ways around it….'encoding, encrypting' or other words are probably better and more realistic.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support this article without further comment, in relation to the right to withdraw consent, which we agree is an absolutely key basic right.

However, for the same reasons of practicality and risk that are expressed in our comments to Article 11, in relation to *categorical consent* (the provision of choices), we have reservations about this provision being realistic and practicable.

If choices have been given at the time of consent, participants should have the right to alter their choices, but this provision presents real difficulties for those managing biobanks and users of human biological materials who may be trying to conduct research on hundreds or thousands of samples, each with different permutations of categorical consent.

We respectfully request that the Committee on Bioethics reconsider their proposals relating to Articles 11 and 16, in particular the provisions that "*persons concerned should be offered the possibility to exercise choices …..*"

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

We agree with the right to withdraw consent or authorization for storage and use of biological materials and maintain that this right exists only as long as the biological materials remain identifiable. However, we recommend against providing the person concerned with the right to change the scope of authorization as such changes are difficult to manage. The logistical issues are similar to those presented above in the comments on Article 11 relating to choice on the use of biological materials. Namely, individuals may protect their right to choice and autonomy by withdrawing their consent outright. Additional choice as to the scope of authorization will compromise the value of the collection on the whole as the samples later utilized may not be representative of the original cohort (see comments in response to Article 11 for more detail).

We suggest clarifying that the right to withdraw consent or authorization for storage and use of biological materials is feasible only when samples remain identifiable in Article 16.2.

Regeneron Pharmaceuticals, USA

Article 16.1
Suggested Revision: We propose that language be added to this guidance with broad applicability on a process that addresses sample destruction and associated documentation.
Rationale: It must be noted that the working document does not provide any guidance regarding a process for the destruction of samples. From experience, IRBs or EECs often request certificate(s) of destruction. We believe that having more specific language, as suggested above, will harmonise the sample destruction process and minimise the differences in the requests from IRBs and EECs.

Articles 11.3, 11.4, 16.1

Suggested revision to 11.3: We propose broader language that is sensitive to the interest of subject participation in future biomedical research by offering the following consent options to subjects with regard to the type of research: 1- use in research for any disease that can affect the human condition (including functioning as control sample); 2- use in research limited to the disease under study or related diseases; and 3- do not use sample for any research.

Suggested revision to 11.4: We propose that consent forms for future research include language that specify that samples will only be held for a specified number of years (i.e., 15 years, 20 years) and research would be appropriately limited to one of the three (3) broad options proposed in the previous paragraph. Moreover, any changes to this scope would be adjudicated by an independent committee such as an IRB, EEC, or Independent Data Monitoring Committee (IDMC) for appropriateness.

Rationale: This proposition could be especially burdensome because it offers a myriad of options that could vary widely according to following:

- Individual subject preference: Given the choice, each subject may have specific and unique requests, they themselves may not fully understand, with which researchers would be required to comply.
- Institutional Review Boards (IRBs) and Ethics Committees (ECs): They often dictate the types of use of samples, what they can be used for or the duration for which samples can be retained.
- Nature of research: There are instances where future research is unforeseen or it is impossible to list all of the various types of research that can or may be conducted because each advancement could lead to another.
- Health Authority (HA) or Regulatory Agency (RA): researchers can and do receive ad hoc request from HA and/or RAs for additional unplanned analyses

Examples of variability in options include but are not limited to differences in the number of years samples can be stored, or differences in the types of research that can or cannot be conducted, thereby delaying a researcher's ability to test and analyze samples in the hopes of advancing knowledge for the benefit of subjects and patients alike.

All of these options and layers of consideration that result in added complexity and time to discovering advances in biomedical research may limit contributions or the potential development of new knowledge or treatments that could save or improve a patient's life, which is one of the tenets noted in the preamble. Furthermore, this may not benefit subjects since their agreement to allow their samples to be analysed for unknown and unstated future research is often altruistic and knowledge of each individual possible research may not alter or impact a subject's initial intent. When subjects consent to future biomedical research of their samples, they are aware that scientist and clinicians are themselves investigating these samples to obtain more knowledge about a specific disease, condition, pathway etc. As currently worded, this principle adds a layer of specificity that does not appear to be productive. The three options provided as "Suggested Revision" could also improve consistency between the recommendations requested by IRBs.

We further acknowledge that in order to protect the interests and privacy of subjects, samples cannot be used indefinitely.

ETHICS COMMITTEES

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 16 section 1: Based on TUKIJAs experience in issuing opinions on the research on biological materials, it seems not always feasible to storage biological materials in case one wishes to alter the scope of the consent. Therefore TUKIJA proposes to add "when feasible" or "when appropriate" in the first sentence, between the words "or" and "alter".

Swedish National Council on Medical Ethics (SMER)

Article 16 says that a person should retain the right to withdraw or alter the scope of consent, and have the right to have the materials either destroyed or anonymized. It is unclear if it is the person herself who can decide if the materials should be destroyed or anonymized. Further, the limitations concerning anonymization of biological materials should be mentioned, as long as it contains detailed genetic information, it is not possible to guarantee full anonymization of the biological material especially in circumstances under which different databases are linked together. It is important that the concept of anonymization is clarified in the document.

In Sweden the prerequisites for withdrawal of consent, are currently under consideration in the revision of the Swedish Act on Biobanks.

Fetal DNA in pregnant women's blood
Another issue related to withdrawal of consent concerns samples containing biological materials from different persons. New research within prenatal diagnosis has shown that blood samples from pregnant women contains biological materials from the fetus. This will enable a complete genome sequencing of the future child, by analyzing a blood sample from the pregnant woman. Biological materials from pregnant women are therefore particularly sensitive from an integrity point of view. This also highlights the question whether the future child also should be informed about previous blood samples and also be given the rights referred to in article 16.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (1) specifies that '*When a person has provided consent …., the person should retain the right to withdraw or alter the scope of that consent'.* This is problematic because the right to alter the scope of consent is not absolute while the right to withdraw is. There are not clear mechanisms for altering the scope of consent, this may vary from project to project and in many cases it is not ethically justified for individuals to alter the scope nor is it feasible for research to meet the requirements of the altered scope if data have already been provided for use under the scope of the original consent. The description of rights with regard to altering the scope of the consent should be modified to reflect these issues.

State data protection inspectorate of the Republic of Lithuania

In paragraph 1 of Article 16 of Working document it is proposed to add words "clear, free-of-charge and easily realizable" after words "should retain the".

It is proposed to foresee provisions concerning the destruction/nondestruction of results of biomedical research received after carried out biomedical research when the person concerned withdrew given consent.

EUROPEAN UNION

European Medicines Agency (EMA)

Article 16.1
Please consider that if the biological material has been used to manufacture an ATMP it may not be possible to destroy.

CHAPTER IV – Use of biological materials in a research project

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

General comments :

Scope:
Clarify the title/scope of this chapter (ref. « Further use of… », in accordance with exclusions of Article 2.2.

Research falling outside the scope of consent may be authorised by law
It is suggested as a general rule that research on biological materials should only be undertaken if it is within the scope of the consent or authorisation given by the person concerned (Article 17 para.1.). Everyone agrees that when someone has explicitly said no to a certain purpose or to other purposes than the one consented to, one should respect that. However, often the scope of the consent in association with previously collected samples is unclear, or just silent about possible purposes. Going back for a renewed consent has a cost in that there will be drop outs and many samples will not be used, thereby decreasing the scientific value of a study and therefore not fully respecting the rights of access to preventive health care and the right to benefit from medical treatment attainable through medical research. Regulatory frameworks usually assign to ethical review boards the right to select appropriate information and consent procedure, as well as the possibility to approve research without (renewed) consent (waiver). This circumstance should be clearly reflected in the recommendations.

Exemption clause:
The use and storage of material beyond the scope of the person's consent must be clearly limited to some defined exemptions and shall only be possible on the basis of national legislation assigning ethics committees the competence to scrutinize thoroughly any research beyond the consent of the donor, – without prejudice to other competences of ethics committees (art. 18).

Article 17 – General rule

1. Research on biological materials should only be undertaken if it is within the scope of the consent or authorisation given by the person concerned.

2. i. If the proposed use of identifiable biological materials in a research project is not within the scope of prior consent or authorisation, if any, given by the person concerned, consent or authorisation to the proposed use should be sought and, to this end, sufficient efforts should be made to contact the person concerned. The wish of the person concerned not to be contacted should be respected.

ii. Where the attempt to contact the person concerned proved unsuccessful, these biological materials should only be used in the research project subject to independent evaluation of the fulfilment of the following conditions:
a. evidence is provided that sufficient efforts have been made to contact the person concerned;
b. the research addresses an important scientific interest and is in accordance with the principle of proportionality;

c. the aims of the research could not reasonably be achieved using biological materials for which consent or authorisation can be obtained;
d. there is no evidence that the person concerned has expressly opposed such research use.

3. Anonymised biological materials may be used in a research project provided that such use does not violate any restrictions placed by the person concerned prior to the anonymisation of the materials and subject to authorisation provided for by law.
Anonymisation should be verified by an appropriate review procedure.

4. Biological materials from persons not able to consent may only be used for research having the potential to produce [real and direct benefit to their health or, in the absence thereof,] benefit to other persons in the same age category or afflicted with the same disease or disorder or having the same condition.

BIOBANKS

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para.1.
Including opt-out material. See comments under art.13.1.
The term "person concerned" which is used in different contexts, should be clearly defined, as suggested above in the general comments as it is the subject of several important rights.

Para. 2.ii.
Proposal for textual clarification :
To add « and » at the end of each letter (a; b; c; d).

Para. 2.ii.a.
What is evidence and what is sufficient -emails, phone records, registered letters...? This may lead to very different practices, propose to follow 22.1 of the current recommendation.

Para. 3.
Proposal for textual changes
Anonymisation should be verified by any existing competent authority according to an appropriate review procedure.

Depending on the meaning of "authorisation" we propose to add the sentence "This should not exempt from the other requirements provided by the law regarding independent ethical review".
Last sentence: "technically verified by a competent authority".

Does use of anonymised samples safeguard human dignity? Why build up a strict procedure for use of identifiable samples, but keep it light when anonymised? Is the recommendation mostly about data protection? Then it is unnecessary, as privacy regimes already exist as binding law.

Again "Anonymised":
There is no appropriate anonymisation of biological material/samples and anonymisation of the meta data requires **information and consent** of the donor in case the material is continued to be used after anonymisation, since it retails the loss of fundamental rights, e.g. the right of withdrawal.

Comment: Para. 2. 3. And 4. are the responsibility of the competent Ethics Committee.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Article 17.2.i, "the wish of the person concerned not to be contacted should be respected".

Article 17.2, “anonymisation should be verified by an appropriate review procedure”, which kind of procedure and which authority should conduct this review? Can a waiver also be providedin case such conditions are applicable for the whole group included in the proposed study.

In order to guarantee the possibility to use residual biological materials that have been removed and stored without informed consent, such use should not only be possible with informed consent, but also after authorisation by an Ethics Committee or other competent body (such as a data protection authority, once verified the scientific validity of the proposed research). The text of article 17 could be modified to clarify that the authorisation of an Ethics Committee can be sufficient for the use of residual biological materials, as follows:

1. Research on biological materials should only be undertaken if it is within the scope of the consent given by the person concerned or authorization by an Ethics Committee or other competent body.

i. If the proposed use of identifiable biological materials in a research project, is not within the scope of prior consent or authorization, if any, given by the person concerned, consent by the person concerned or authorization by an Ethics Committee or other competent body to the proposed use should be sought and, to this end, sufficient efforts should be made to contact the person concerned. The wish of the person concerned not to be contacted should be respected.

Swedish National Council of Biobanks (NBR)

Article 17.2
Research falling outside the scope of an earlier given consent (as well as falling outside the scope of an earlier ethical approval) should have to undergo a new ethical vetting where the new purpose and research is explained. If the ethical review board approves the new purpose they should also decide upon the requirements concerning what information and consent regulations that shall apply.

That is, we do not agree with Article 17.2.
Research projects are very different and it is often not possible to find specific rules of this kind that are applicable to all situations. We need professional and well compounded ethical review boards which can assess the adequate ethical and legal requirements for each project.

Article 13 and 14 paragraph 3, and 17 paragraph 4. We do not agree with the recommended restriction of the use of samples. Samples taken for one purpose or disease may be very important as control material for other diseases or if the donor later in life develops another type of disease. We believe that there is a risk of discrimination if one, on a general basis, excludes certain groups of people from possible important research. An ethical review board should approve the new purpose and the research project.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO)

Article 17.1
This point should advise scientist not to write a consent for a discret "project". Ideally, the consent should be general, allowing research in any project authorized by the competent ethical comittees. Otherwise, the paperwork required can take longer than the actual project. In some instances can be impossible to use important biological samples.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 17
This promotes the idea that anonymisation is an antidote to consent (which it isn't) and also that going back to obtain a revised consent is always necessary. Applying a waiver of the need for consent by an ethics committee is another way to fulfill protection of individuals. The section 2ii a-d appears to make it a requirement that all attempts to recontact a person have been made when in fact such contact may itself be unethical in some circumstances. Para 4 should be deleted.

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

According to Article 17, biological materials can only be used for the purpose in which the subject has given his/her approval. If the researcher has accounted for a specific issue, it cannot be used in another relevant issue within the same topic without having to ask the subject and obtain the consent. We find this a heavy procedure which does not encourage good research. Therefore, there is a need to rewrite parts of Article 17.
It should be the responsibility of the Research Ethics Committee to assess whether the new research project is within the scope of the original consent and to evaluate the requirements as laid down in ii a-d.

Article 17, paragraph 2
In case of no consent: material obtained from a clinical biobank, i.e. material originally collected for diagnostic/treatment purpose, does generally not present with consent for usage in future research. According to the Danish rules, it may be used without consenting if the conditions for a research ethics committee
providing permission to exemption from consent is fulfilled (for example tissue from pathology departments).

Article 17, paragraph 4
The Danish legislation holds an additional requirement: provided the research project could not be of similar utility if only involving persons able to consent. Should this be included here?

Dr Astrid Stuckelberger, Institute of Global Health, Faculty of Medicine, University of Geneva

No 2 in general
To my view, a fundamental discussion should take place whether it is ethical not to ask the person each time his/her biomaterial is used and for what purpose and duration.

2 – ii . I strongly disagree with the first sentence – if the person has not been contacted, the material should not be used!!!
this is a violation of biological human rights in my opinion. It could also set a precedent for each and every use of biomaterial: each time someone is unreachable…we assume the person consents! Which is counter-ethical…
Even the point a, evidence that 'sufficient efforts have been made to contact the person' …is not enough! It should be a consent stricto sensu.

Dr. Amin El-Heliebi, Dr. Karine Sargsyan, Biobank Graz, Medical University Graz

Article 17.2.ii, d
The evaluation should be verified by an ethics committee or competent body.

Article 17.3
...provided for by law, local (country wide) ethic regulations, an ethics committee or competent body.

Dr Imogen Evans, UK

Para 2 ii, line 1 should read "proves" unsuccessful.
Line 3, would be better to say "safeguards" rather than "conditions".

Para 3. From the research perspective, the restriction placed by this paragraph would simply preclude such samples being used at all. In other words, it is unrealistic to contemplate a system whereby anonymised materials might be stored together with associated information stating any restrictions placed on their use. This would add such a considerable logistical level of complexity and cost for researchers that they would simply use materials without such restrictions.

Para 4. Line 2. The word "direct" in square brackets should be omitted - as noted under Article 14, this requirement is unrealistic.

EuroSIDA Steering Committee

Article 17.1
Observational research on large cohort datasets collected from routine care of participants and supplemented with collection of biological specimens for future research by nature generally address not yet identified research questions (at the time of participant consent) since the projects run over many years and the field of research develops during the conduct of the cohort studies; this makes defining the scope of the research challenging and often result in participant consents with a very broad formulated and general scope.

Article 17.2.i
For bio-specimen repositories related to cohort studies – often internationally conducted and involving thousands of participants re-consenting participants is an overwhelming task, and will eventually lead to compromised scientific output from the collected samples, i.e. fewer scientific issues will be addressed.

If renewed consent will be required for new research projects using already collected samples, this will lead to suboptimal use of the bio-specimens – which is in potential conflict with patients' consent to donate specimens for future research. The effort and cost invested in collecting and storing specimens for future research is considerable and therefore suboptimal utilisation of stored specimens is critical.

Article 17.2.ii.a.
In multinational large cohort studies this is a huge operational task – please see comments above

Article 17.2.ii.b.
It is unclear to us who will decide whether this is in accordance with the principle of proportionality

Article 17.2.ii.c.
Same as for 17-2b

Karolinska Institutet, Sweden

Research falling outside the scope of consent may be authorised by law
It is suggested as a general rule that research on biological materials should only be undertaken if it is within the scope of the consent or authorisation given by the person concerned (article 17). Everyone agrees that when someone has explicitly said no to a certain purpose or to other purposes than the one consented to one should respect that. However, often the scope of the consent in association with previously collected samples is unclear, or just silent about possible purposes. Going back for a renewed consent has a cost for the person concerned in that there will be drop outs and many samples will not be used, thereby decreasing the scientific value of a study and therefore not fully respecting the rights of access to preventive health care and the right to benefit from medical treatment attainable through medical research. Regulatory frameworks usually assign to ethical review boards the right to select an appropriate information and consent procedure, as well as the possibility to approve research without (renewed) consent. This circumstance should be clearly reflected in the recommendations.

KU Leuven Faculty of Medicine, Belgium, Belgium

In **Article 17.3**, we believe that ensuring that anonymised biological materials are used in a way that does not violate any restriction placed by the person prior to the anonymisation of the materials and subject to authorization provided by law, although a laudable goal, will be particularly difficult to implement.

Article 17.4
When it comes to the removal of biological materials from persons not able to consent for storage for future research, as described in the Article 12, we believe that putting the phrase “real and direct benefit to their health or, in the absence thereof” in square brackets makes the meaning of this paragraph unclear and it does not adequately stress that such removal may be conducted primarily for the benefit of the person concerned. For the above mentioned reasons it would be desirable to remove the square brackets from this sentence, as well as from the same sentence in Article 14 paragraph 3 and Article 17 paragraph 4.

Patrick GAUDRAY (à titre personnel), Directeur de Recherche au CNRS, Membre du Comité Consultatif National d’Ethique, France

There is a degree of “naiveté” in maintaining the illusion that a biological sample can be reliably and definitively made anonymous at a time when DNA sequencing makes it possible to identify unambiguously any individual. This is especially significant where (Chapter IV, Article 17.3) the text suggests that it would be possible to use an anonymous sample in a research project authorised by law. It could also be pointed out that it should be impossible

to trace the consent of the individual if details of his or her identity have been permanently erased. This point is returned to in Chapter V, Article 20.4 which refers to the requisite traceability of an anonymised sample. This apparent contradiction should be clarified.

PFIZER-UNIVERSITY OF GRANADA-JUNTA DE ANDALUCÍA CENTRE FOR GENOMICS AND ONCOLOGICAL RESEARCH (GENYO), Spain – Private/Public Partnership

Article 17.1
This point should advise scientist not to write a consent for a discret "project". Ideally, the consent should be general, allowing research in any project authorized by the competent ethical comittees. Otherwise, the paperwork required can take longer than the actual project. In some instances can be impossible to use important biological samples.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

See comments to articles 12 and 14
Proposal
Article 17 bis
When, according to articles 12 and 14, a sample removed and stored from a person not able to consent is going to be used for research, an ethics committee will consider both the need to inquire if that person has attained the capactity to consent and the need to ask for his / her consent.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

We think the Recommendation needs to recognise that research falling outside the scope of consent may be authorised by law in certain countries. Everyone agrees that when someone has explicitly said “no” for a certain purpose or for other purposes than the one consented for, this should be respected. However, often the scope of the consent in association with previously collected samples is unclear, or just silent about possible purposes. As noted in our response to article 12, seeking renewed consent may have a cost for both researchers and participants, where there could be drop outs leading to a decrease the scientific value of a study and therefore not fully respecting the rights of access to preventive health care and the right to benefit from medical treatment through medical research. We support the move towards better on-going communication with participants using new ICT technologies and in the future would like to see re-contact becoming more common. However, such models are relatively new and at the moment some flexibility is required whereby regulatory frameworks usually assign ethical review boards the right to approve appropriate information and a consent procedure, as well as the possibility to approve research without (renewed) consent. This circumstance should be clearly reflected in the Recommendation.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

Paragraph 2 has outlined the rule that restricts use of identifiable biological material in a research project that is not within the scope of the informed consent and recommends for the research group to obtain consent to the "revised" project goals. In some cases, requiring an attempt to contact study participants first would be an unreasonable burden on researchers and waste precious resources due to the long timeframes, sometimes more than 20 years, between sample collection and the potential use. In addition, the process of obtaining secondary consent could possibly infringe upon the rights of the person that may not want to be re-contacted. Requiring researchers to provide evidence that sufficient efforts have been made to contact a person is too stringent and in some cases may require enormous resources. We recommend in such cases, that an IRB/EC be allowed to determine whether the conditions have been met for a waiver of consent.

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support this article in general and believe it partly satisfies our concerns relating to Articles 13 &14.

We respectfully suggest that the Committee on Bioethics consider the following amendment:

"….evidence is provided that sufficient efforts have been made to contact the person concerned" should be amended to say

"….evidence is provided that sufficient efforts have been made to contact the person concerned or that it is impractical to contact the persons concerned".

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

If the proposed use of identifiable biological materials in a research project is not within the scope of prior consent or authorisation, if any, given by the person concerned, consent or authorisation to the proposed use should be sought and, to this end, sufficient efforts should be made to contact the person concerned.

Regeneron Pharmaceuticals, USA

Rationale: This document should more clearly differentiate between "non-identifiable" and "anonymised". While we recognize these terms are sometimes used interchangeably, they are not necessarily synonymous. Therefore, we suggest utilizing the definitions outlined in ICH E15 or make reference to it.

If a sample is truly anonymised, it cannot be traced back to the subject. It should also be recognised that, technically, genetic data can be traced back, although it may be difficult to do so. If a sample is truly anonymised it would render research/analysis futile because it offers no correlation to the clinical data. It should also be noted that if samples are truly anonymised, it would be impossible to inform a subject of any new health information that is identified in the future. If samples are not anonymised, they can be made non-identifiable by utilizing double coding. In addition, access to the coding could be restricted such that even the site monitors do not have access to the double coding.

In order to respect subject confidentiality and privacy while attempting to advance knowledge

and potential treatments from biomedical research, we propose de-identifying data instead of truly anonymising their information by following the principles outlined in ICH E15. In situations where more stringent de-identification processes may be advisable, we recommend double-coding which will maintain subject privacy while still allowing for a correlation to clinical data.

ETHICS COMMITTEE

Comité de Etica (CSIC), Spain

Article 17.2.ii
If the sample has been legally donated and a clinic ethics committee guarantees the adequate use, the research project shouldn´t be relevant.

Irish health research board (HRB)

Articles 12, 14, 17.4
In the HRB's view, these Articles capture the balance between protection of research participants and enabling research well. The HRB has no further comments on the proposed text.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (2) outlines the steps towards obtaining consent if new research is undertaken that falls outside the scope of the original consent or authorization. With the increasing use of of new genomic technologies (i.e. genotyping and sequencing) in very large collections, there is increasing ethics approval for using opt-out approaches as opposed to the collection of new, active consent. Given proper ethical oversight, the use of such opt-out approaches should be incorporated into article 17.

The comment about Article 12, Paragraph (3) also applies to Paragraph (4) for Article 17. There should be no restrictions on use based on age or affliction.

Paragraph (3) states that 'Anonymisation should be verified by an appropriate review procedure'. Please clarify what constitutes an appropriate review procedure.

European Union

European Commission (DG JUSTICE)

Article 17(2): the additional condition should be added, that personal information from the biological material in question should be kept separately from the other information, as long as the research project can be performed in this manner (cf. Article 9(2)(c) of the proposed Regulation);

Articles 12(3), 14(3) and 17(4) (removal and storage of biological materials from persons unable to consent and their usage in research projects): we suggest to consider framing the conditions for persons unable to consent by: "when it is necessary to protect the vital interests of that person or of any other person" (cf. Article 9(2)(c) of the proposed Regulation);

European Medicines Agency (EMA)

Article 17.2
Please consider that this could be challenging to implement as the purpose of the research may evolve with time, for example when a cell line is initially established for a specific purpose which is changed at a later stage.

OTHERS

Prof. Henriette Roscam Abbing, Netherlands

Art. 17.2: 'if any' is not clear: prior consent/authorisation has been given or not.
(NB: The use of web technologies to involve patients in decisions on the envisaged research(es) (= dynamic consent) possibly could make art. 17. 2. i redundant. If I understand well, this is also foreseen in art. 21.7)

Art. 17.3 Similar remark as under 13.3 and 14.5

Article 18 – Independent review

1. Research should only be undertaken if the research project has been subject to an independent examination of its scientific merit, including assessment of the importance of the aim of the research, and verification of its ethical acceptability. National law may additionally require approval by a competent body.

2. Member states should apply the principles concerning ethics committees contained in chapter III of the Additional Protocol concerning Biomedical Research (CETS No. 195) to the review of the research project within the scope of this Recommendation.

3. Review procedures may be adapted to the nature of the research and the extent to which the persons from whom biological materials have been removed could be identified from these biological materials.

BIOBANKS

3C-R, réseau français de biobanques

Proposed wording of Article 18.1

Research should only be undertaken if the research project has been subject to an independent examination of its scientific merit, including assessment of the importance of the aim of the research and verification of its ethical ***and legal*** acceptability. National law may additionally require approval by a competent body.

Proposed wording of Article 18.2

Member States should apply the principles concerning ethics committees ***and protection of persons*** contained in Chapter III of the Additional Protocol concerning Biomedical Research (CETS No. 195) to the review of the research project within the scope of this recommendation.

Proposed wording of Article 18.3

Review procedures may be adapted to the nature of the research and the extent to which the persons from whom biological materials have been removed could be identified ~~from these biological materials~~.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

General comment / Definitions
Does the term « approval » is different from the « authorisation » referred into this text? If it is, need to write approval in several articles (see above in general comments the need of definition).
Some interpretations of "scientific" exclude research that eventually aim at commercial product/service/benefit (which many universities and research units want as well as companies). Commercially motivated research should be allowed (with appropriate information and consent procedures) to facilitate getting new innovations to the market. This is not to say that the research should not be made with valid scientific methods or that the results would not need to be made available.

Para. 1.
Proposed specifications
Research should only be undertaken if the research project has been subject to an independent examination of its scientific merit, including assessment of the importance of the aim of the research, verification of its ethical acceptability and legal compliance. National law may additionally require approval by a competent body.

Para. 3.
Proposal for textual clarification
Review procedures should be adapted to the nature of the research and the extent to which the persons from whom biological materials have been removed could be identified from these biological materials.

ACADEMIA

EuroSIDA Steering Committee

Article 18.1
Again for large multinational investigator driven cohort collaborations the general cohort study conducted on a continuous bases for years will off cause have the general scope approved by independent ethics review, however, within the general scope specific analysis projects will be developed over time as the scientific field develops – the current proposed regulation does not sufficiently reflect the variation within research studies: a differentiation of requirements for interventional randomised controlled studies and large investigator driven observational research studies should be made.

Patrick GAUDRAY (à titre personnel), Directeur de Recherche au CNRS, Membre du Comité Consultatif National d'Ethique, France

Chapter IV, Article 18.1: the reference to the "importance of the aim of the research" is extremely vague. It should be made clear what is meant by the word "importance": for science, for medicine, for application prospects, etc.? Is it being used as a synonym for relevance?

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basic tenant of this article.
As noted in our comments to Articles 2 and 7, we consider it important to avoid an unintentional gap in the coverage of independent review that excludes the processes of donor identification, recruitment, removal of biological materials from the body and subsequent storage prior to use in a research project. We, therefore, suggest that all processes starting with donor identification, recruitment and removal of biological materials be included in the definition of research and included in the requirement for independent review, as these are activities where significant ethical issues reside.

We respectfully request that the Committee on Bioethics consider these points.

ETHICS COMMITTEES

Irish Health Research Board (HRB)

The HRB suggests some re-wording of this Clause to: 'Research should only be undertaken if the research project has been subject to an independent examination to include scientific merit, an assessment of the important of the aim of the research, and verification of its ethical acceptability'. The reason for this suggestion is that whilst all HRB-funded projects are undergoing a full scientific review, pilot and feasibility studies will not necessarily have this full process behind them. They rely on research ethics committee approval alone, yet they are critical in obtaining funding for the full project. The ethics committee will assess scientific merit at a high level, and this should cover the situation described.

OTHERS

Iciar Alfonso Farnós, Consultant in Clinical Pharmacology, Spain

Our recommendation is that the research protocol must be submitted for consideration, comment, guidance and approval to the concerned **research ethics committee** before the study begins, as it´s recommended in the Ethical Principles of the Declaration of Helsinki.

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

Initial capitals for Chapter in 18 (2). Always use Member States, with initial capitals.

Article 19 – Availability of results

1. On completion of the research, a report or summary should be submitted to the ethics committee or the competent body.

2. Appropriate measures should be taken to make public the results of research in reasonable time.

BIOBANKS

3C-R, réseau français de biobanques

Comment on Article 19.1

Is it really the role of ethics committees to receive and archive all research results?

Proposed wording of Article 19.1

~~On completion of the research,~~ A report or summary ***of the research*** should be submitted to the ethics committee or the competent body ***under the conditions established by national law***.

Comment on Article 19.2

It is not always possible to make specific research results public, especially where intellectual property has to be protected; researchers, whether academic or industrial, cannot disclose their results in such cases. Similarly, in some cases a scientific publication may be brought out only several years after the use of biological materials, which may make it difficult to make the results public "in reasonable time". Article 9 of the recommendation could suffice to ensure that the public is informed, or the wording could be changed to open up the possibility of only publishing general results.

Proposed wording of Article 19.2

Appropriate measures should be taken to make public the ***general*** results of research in reasonable time.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para.1.
Increasing bureaucracy for ERB's without any rationale / Ask for specification or deletion
It is suggested in article 19 that scientists should submit a report or a summary of the research results to the ethics committee. It is not at all clear what these committees should do with such a report and what use it may have.
Ethics committees etc. /bodies may not have this kind of role and have no use for or power to react to any reports. EC/authority filing should not be used to legitimise not making results publicly available. Propose this to be deleted or at minimum include a reference e.g. "if so required under applicable law" or something similar or give the results back to the repository. (BBMRI.SE)

> *Discrepancies on this last proposal of deletion:*
>
> There is already a legal obligation for researchers to submit a report to the Ethical committee in several States (E.g. Belgium). (BBMRI.BE)

Para.2.
Proposal for specification and harmonisation
This seems weak and not publishing results is a major ethical issue. WMA Declaration of Helsinki Art 36 states that "Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports." Propose the recommendation to be aligned with the declaration. Reference to reasonable time is good (and missing in the declaration). In addition, a credit should be made to the repository used in publication.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Article 19.1: "on completion of the research, a report or summary should be submitted to the ethics committee or the competent body". We recommend addition of the words "in accordance with local requirements"
Could it be helpful to clarify what “available results” actually mean: what is the extent of available results? Do they include, among other things, results derived from the development of patents or licences?
Furthermore, please see the comment reported on article 14, paragraph 2.

Swedish National Council of Biobanks (NBR)

Article 19.1
We find it difficult to understand the benefit of this increased bureaucracy. What is the purpose? How are the ethical committees supposed to handle this information?

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 20.4
How would one do this if they have been anonymised? This appears to contradict several other statements in this document.

EuroSIDA Steering Committee

Article 19.1
To reflect the differentiation of research studies between interventional RCTs and non-interventional continuing research studies a revised formulation is proposed: research defined as ‘all research originating from samples at completion of the study rather than on completion of the individual research projects.

Karolinska Institutet, Sweden

Increasing bureaucracy for ERB’s without any rationale
It is suggested in article 19 that scientists should submit a report or a summary of the research to the ethics committee. It is not at all clear what they should do with such a report and what use it may have.

KU Leuven Faculty of Medicine, Belgium, Belgium

Article 19 on availability of results provides, in paragraph 2, that “Appropriate measures should be taken to make public the results of research in reasonable time”. We consider this phrasing to be particularly weak, since it ignores the complexity of related issues, such as the commercial exploitation of biobanks and the protection of intellectual property rights.

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

Article 19.1,2

The responsibility : is it with the researchers or the biobanks to make the data available ? If a biobank does not have a clause at the onset to request return of research outcome from materials used , it would be hard to make results available.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

We support the zeitgeist towards transparency of results and back the dissemination of summary results and data. Where secondary research has made use of external biobanks, registries or research collections we would like to see researchers report back to the interested communities. However, where reporting to ERBs is concerned, it is not at all clear what an ERB would do with a report from scientists, or what use it may have.

This work has been supported by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreements 305444 (RD-Connect), 305121 (NeurOmics), and 305608 (EURenOmics).

INDUSTRY

Danish Association of the Pharmaceutical industry (Lif)

We support the basic tenant of this article, but consider it necessary to include a provision that respects the need for confidentiality of proprietary and privileged information where applicable.
We respectfully request that the Committee on Bioethics consider this point.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

Articles 19-20 address availability of results and governance. EFPIA agrees that it is important that efforts are made to inform the wider public about the results of research. Together with our US sister association, we have introduced new guidelines on the sharing of clinical trial data with include encouragement to users of industry data to pursue publication. We have been able to make these commitments in a way which balances transparency with the need to protect commercially-confidential information and would welcome inclusion in the working document of some recognition of the need to protect proprietary data.

Finally, we recognize that access to these materials ultimately depends on societal endorsement of research. As noted above, it is important that in parallel with enabling research we consider how to advance public accountability.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

We agree that results of research should be transparent and disclosed in a timely manner as consistent with the rights, obligations, and legitimate research needs of the entity conducting the research. However, we suggest that this article be amended to acknowledge the need to

protect proprietary or confidential information. Such protections are vital to the advancement of medicine.

ETHICS COMMITTEE

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 19 section 1: TUKIJA does not see the point in submitting reports or summaries to the ethics committees since as a general rule the ethics committees do not oversee research practice. It is more evident that the report or summary of the results may be helpful to biobanks and it also needs to be published.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (1): at the completion of research what is the purpose of submitting a report to the ethics committees? Who would submit this report and what would the ethics committees do with it? Consider dropping this requirement as it adds extra bureaucracy and has no specified purpose.

CHAPTER V – Governance of collections

BIOBANKS

3C-R, réseau français de biobanques

The addition of an article (at the beginning of Chapter V) so as to recognise the key role played by Biological Resource Centres, or biobanks, in managing biological materials used for research purposes in the field of human health. These BRCs are recognised in international documents[11] that could serve as a basis for certain of the recommendation's provisions.
Proposed additional article at the beginning of Chapter V

Bodies managing collections (BRCs and biobanks) shall be recognised and authorised in accordance with the provisions of national law. This recognition shall be based on a study by the Ethics Committee and take into account governance, organisation, security, traceability of biological materials and quality management.

ACADEMIA

Karolinska Institutet, Sweden

Governance principles should apply also to broadly consented collections
In line with what has been argued above governance principles should not include requirements that the purpose of a collection should always be specified.

PROFESSIONAL ORGANISATION

[11] OECD Best Practice Guidelines for BRCs: 2007

European Society of Human Genetics (ESHG)

ESHG agrees with Articles 20-24.

ETHICS COMMITTEE

Irish health research board (HRB)

The HRB welcomes the introduction of this Chapter and is in agreement with the Articles set out in the document.

Swedish Central Ethical Review Board

In Chapter V, which deals with "Governance of collection", we suggest that it should be inserted into the recommendation that Member States ought to legislate on sanctions for breaches of the rules.

Article 20 – General principles

1. The person and/or institution responsible for the collection should be designated and this information should be publicly available.

2. The purpose(s) of the collection should be specified. The principles of transparency and accountability should govern its management, including, where appropriate, access to and use and transfer of its biological materials and disclosure of information.

3. Any change of purpose of a collection should be subject to independent examination and, where necessary, may require that appropriate consent or authorisation of the persons concerned be requested.

4. Each sample of biological material in the collection should be appropriately documented and traceable, including information on the consent or authorisation.

5. Quality assurance measures should be in place, including conditions to ensure appropriate security and confidentiality during establishment, use and, where appropriate, transfer of elements, of the collection.

6. Procedures should be developed for any transfer of the whole or part of the collection as well as for the closure of the collection; these should be in accordance with the original consent or authorisation.

7. Information about the management and use of the collection should be made available to the persons concerned and should be regularly updated, with a view to facilitating, where appropriate, the exercise of the rights laid down in Article 16.

8. The conclusions of the research should be made available to the persons concerned in reasonable time, on request.

9. Reports on past and planned activities, including information about access by third parties, should be published at least annually.

BIOBANKS

3C-R, réseau français de biobanques

Comment on Article 20.3

It would probably be helpful to define the "purpose" so as to avoid any ambiguity concerning the nature of changes necessitating fresh consent. So as to avoid debate on the definition of the word "purpose" (switching from a medical to a scientific purpose, transfers between research projects, changes made to a wide-ranging research programme and so on), the article might simply refer to the information given to the person.

Proposed wording of Article 20.3

Any change of purpose of a collection, ***as described in the initial consent information***, should be subject to independent examination and, where necessary, may require that appropriate consent or authorisation of the persons concerned be requested.

Comment on Article 20.8

As mentioned in the comment on Article 19.2, access to research findings is not always possible in view of the protection of scientific results prior to publication or filing of a patent.

Comment on Article 20.6

It seems difficult to anticipate the transfer or destruction of a collection in the initial consent or authorisation, especially if the destruction is accidental.

Proposed wording of Article 20.6

Procedures should be developed for any transfer of the whole or part of the collection as well as for the closure of the collection~~; these should be in accordance with the original consent or authorisation~~.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 1.
Proposal for textual changes
"The person and/or institution responsible" should be changed in "The person and the institution responsible", as person may change and the collection should always refer to the institution that has the final responsibility of the collection**.**

Para.2.
Governance principles should apply also to broadly consented collections
In line with what has been argued above governance principles should not include requirements that the purpose of a collection should always be specified.

Para.6.
Proposal for textual clarification
This paragraph should be divided in two distinct paragraphs to detail a little bit more, one for the question of transfers, the other for the question of collection/biobank closure.

Proposed add
…and for providing material for research from the biobank/collection.

Proposed textual changes:
…"should be made available on request to the persons concerned…"

Questions
Can we always anticipate the closure of a collection at the time of procurement (e.g. cohorts)? What to do in such a case?
What kind of procedures "for the closure" of the collection should be developed? E.g. Procedures planning the fate of the stored and used human biological samples in case of definitive biobank closure / final stopping of biobank activities.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Article 20.1
"1. The **person** and/or institution responsible ...". It is recommended to note that person may change in relation to, for example, retirement, work change, disability etc. Whenever a person is responsible, it should always be clarified if and which institution has the actual responsibility of taking over the collection.

Article 20, paragraph 7 stipulates that information about the management and use of the collection should be made available to the persons concerned and should be regularly updated. In order to clarify at which point in time this information should be made available, the words 'on request' could be added at the end of the paragraph, similar to art. 20.8.

Swedish National Council of Biobanks (NBR)

Article 20, paragraph 2. The purpose of the sample collection can be well described but not always specified.

ACADEMIA

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

Article 20, paragraph 4
In case of a common biobank/storage facility, the facility itself may not hold the original consent. It is the responsibility of the clinician/researcher to obtain consent before collection of the material and to store the original consent, not necessarily of the administrator of the biobank.

Article 20, paragraph 6
Any transfer of whole or part of a collection as well as closure of a collection must further abide by national legislation incl. rules as set by data protection agencies.

Dr Astrid Stuckelberger, Institute of Global Health, Faculty of Medicine, University of Geneva

It seems that the issue of human rights and potential discrimination based on biomaterials use might be useful to include at some point.

Pt 4 = I suggest that more details be given such as the dose of the biomaterial, the duration envisaged for use, how many times/studies, or for each studies, information/consent will be seeked, etc

I suggest that systematically (and not if needed) a clause to re-confirm the acceptance of potential use/re-use of the biomaterial should be proposed.

Pt 7 = mention should be made that the person can stop the given consent at any time of the research/procedure with immediate effect! (same as usual research)

Dr Imogen Evans, UK

Para 3. It is totally impractical to think that the consent or authorisation of people who have donated samples to a collection should be consulted as individuals about any change of purpose. This simply would not work. Any changes should be approved by a pre-established system/mechanism of collection oversight.

Para 5. Line 2. Use of the word "elements" is rather strange. Is this intended to mean "samples from" ?

Para 6. Line 2. To what does the phrase "in accordance with original consent or authorisation" refer? The original consent from individuals? The authorisation for setting up the collection?

Para 8. The practicality of this should be fleshed out in the explanatory report. In practice, and certainly for large collections, individuals should be advised where they might find the (collective) information on a website. There is unlikely to be the research management capacity to handle Individual requests for information.

Patrick GAUDRAY (à titre personnel), Directeur de Recherche au CNRS, Membre du Comité Consultatif National d'Ethique, France

There is a degree of "naiveté" in maintaining the illusion that a biological sample can be reliably and definitively made anonymous at a time when DNA sequencing makes it possible to identify unambiguously any individual. This is especially significant where (Chapter IV, Article 17.3) the text suggests that it would be possible to use an anonymous sample in a research project authorised by law. It could also be pointed out that it should be impossible to trace the consent of the individual if details of his or her identity have been permanently erased. This point is returned to in Chapter V, Article 20.4 which refers to the requisite traceability of an anonymised sample. This apparent contradiction should be clarified.

Prof. Alexander Tonevitsky, Head of the Department for Translational Oncology at the Hertsen Moscow Research Oncology Institute

Article 20.8
I would recommend to indicate more precisely how soon the conclusions of the research should be made available to the concerned person, instead of "reasonable time".

Prof. Cassiman, University of Leuven

The owner of the samples/data of a bank should be defined e.g. problems with the prostate cancer bank in the US….

Guarantees for the continuity of the bank when the initiator leaves or dies…should be provided by the bank from the start..

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

Paragraph 4: In line with other comments in this submission, where the collection purpose is specified it should also explicitly state that the collection may additionally be used for purposes outside this.

Otherwise, we welcome these principles as a contribution to good governance. Guidance on transfer and closure policies in paragraph 6 are timely and necessary to ensure biological materials' collections are not unnecessarily destroyed, unused or inaccessible and to provide transparency around management for interested parties. We believe paragraphs 7-9 are an important development in the partnership between collection holders, interested publics, disease groups and participants and we view the provision of information and ongoing communication about outcomes as crucial to promote openness in the pursuit of common goals.

INDUSTRY

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

Article 20.3
Any change of purpose of a collection should be subject to independent examination and, where necessary, may require that appropriate consent or authorisation of the persons concerned be requested.

Article 20.7
Information about the management and use of the collection should be made available to the persons concerned and should be regularly updated.
It may be impractical or unduly burdensome to re-contact persons concerned in order to carry out any of the above requirements. Significant time may have elapsed and/or there may no longer be a direct or even indirect link between the holder of the biological material and the donor of the biological material. Further, if the persons concerned did not initially indicate willingness or desire to be re-contacted then the act of re-contacting to seek additional permission or notify of changes could result in undue stress or burden on the person concerned. We ask the DH-BIO to qualify these statements to reflect that seeking to re-contact should be undertaken as feasible and under advisement of an appropriate ethical body. In addition, where re-contact is deemed not feasible by the researching entity, we ask that alternate options provide a waiver of consent requirements, including approval by an authorised body (e.g. Ethics Committee). We note that this requested qualification would harmonise Article 17.2 with Article 20.3, where it is stated that an independent review should occur first and then, if necessary, efforts be made to contact the subject for consent. We

would also support greater weight being given to the role of ethics committees in the review and approval of research proposals and the appropriateness of re-contact.

Industry Pharmacogenomics Working Group (I-PWG) and the International Pharmaceutical Privacy Consortium (IPPC)

Governance (Articles 20-24)
We generally concur with the governance articles as described and note the following exception:
Article 20.9 describes the expectation to publish an annual report describing past and planned activities as well as access by third parties. This may be difficult to implement in a meaningful way specifically with regard to the pharmaceutical biobank and collections obtained for clinical trial research due to the number of trials conducted and the global nature of the studies. Please note, IPPC and I-PWG member companies make a practice of publishing human subject research in peer reviewed journals and thereby achieve publicity of valuable research while protecting the proprietary value of each company's research results and scientific processes.

We thank you for your consideration of our comments and would welcome the opportunity to discuss these issues with you. Please do not hesitate to contact us with any questions.

Regeneron Pharmaceuticals, USA

Article 20.1
Suggested Revision: Similar to the proposal offered for Comment #9 above, we propose reverting back to the previous biobanking definition, which would improve the clarity of this working document by specifying and aligning it with the ethics requirements and clinical research standards applied to population biobanking for (pharmaceutical) research. We further propose that the term "publicly available" be clarified.

Rationale: For clinical trials, regulations in many countries currently dictate that information be publicly available (i.e., the study Sponsor). Similar to the previous comment, we interpret this clause to refer to the principles of biobanking and align the definition of "collection" in the context of research biobanking.

Articles 20.8, 21.1
Suggested Revision: We propose that this guidance highlight that it is acceptable that physicians are provided with un-interpreted reports or data of genetic results. The physicians would then be responsible for interpreting and communicating any information to a subject or providing counseling. We expect that physicians will validate any results communicated to subjects.

Rationale: These sections are interpreted by the team to mean that researchers must provide individual results back to subjects upon request. Currently, Regeneron is aligned with this in spirit, that information pertaining to the safety of the subject should be communicated to the subject via the healthcare provider.

It must be noted that this genetic research is not often conducted as a clinical laboratory test for the purpose of providing information to guide care of patients. This will be research information related to the cause of human disease and to understand how to improve the use of drug treatments. It is unlikely that any information provided in this research will have any direct health benefit to subjects, but it may help society in general. As such, no conclusions would be provided about the genetic information. Instead, national law may allow physicians to have access to the research DNA data and this can be arranged. It must

be understood that much work would need to be performed by physicians to interpret this data and to confirm any observations before they are reported back to a subject.

One particular concern, given the global nature of clinical research, is the return of exploratory results that are not generated by a Clinical Laboratory Improvement Act (CLIA) certified laboratory or utilizing CLIA or CE tests (e.g. whole-exome sequencing). In the US, subject results are only to be provided by a CLIA certified lab. When Sponsors do not utilize certified labs for genetic research, they should not be expected to provide data or results directly to subjects, Where local law requires, results may be made available upon request to the individual subject's physician or healthcare provider.

On the other hand, in the EU, we are not aware of a central accreditation requirement across all member and/or non-member sates. We recognize that labs that do provide results to subjects and patients have their basis in ISO lab standards (i.e., ISO 15189). Sample testing for genetic research is a specialty service in a niche area dominated by academic institutions and the pharmaceutical and biotechnology industry. For the EU, we reiterate our position that it should not be expected that the results are standardised, and there should not be a requirement that Sponsors and researchers provide results directly to subjects.

We propose a recommendation captured under "Suggested Revision above". Consequently, it should be recognised that these are not standardized tests across industry and are not aligned to the process followed by CLIA certified laboratories.

Articles 20.9, 24.2.ii, 24.2.v

Suggested Revision: We propose reverting back to the previous biobanking definition. Additionally, we propose that this working document is clarified by specifying and aligning it with the ethics requirements and clinical research standards applied to population biobanking for (pharmaceutical) research.

Rationale: The principles within this guidance do not provide a framework of the content of such reports and to whom these reports should be provided. We also recognize that the language on population biobanking that was captured in the previous version of this guidance was removed. We interpret the current language captured in this working document to be applicable to research biobanking. By addressing it simply to 'collections' it has far reaching impact beyond perhaps that which was intended.

By reverting back to the previous biobanking definition, the meaning of the principles set forth in the relevant articles and paragraphs within this working document will minimize confusion and the number of potential misinterpretations. If our interpretation is not correct, however, we request that clarification be provided to specify the minimum criteria for these reports including the frequency of reporting and to provide some general provisions as to whom the report should be submitted.

ETHICS COMMITTEE

Comité de Etica (CSIC), Spain

Article 20.9.

Determine where reports and information will be published.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (3) needs further clarification on several points. It states that "*Any change of purpose of a collection should be subject to independent examination and, where necessary, may require that appropriate consent or authorisation of the persons concerned be requested*."
What is required for 'independent examination'? Who does 'persons concerned' refer to since this pertains to both consent or authorization?
Paragraph (9) indicates that an annual report should be published. Who should prepare and publish this report and where should it be published?

Article 21 – Individual feedback

1. Clear policies should be developed on feedback concerning findings that are significant for the health of the persons arising from the use of their biological materials.

2. Feedback should take place within a framework of health care or counselling.

3. The wishes of individuals not to be informed should be observed.

BIOBANKS

3C-R, réseau français de biobanques

This article could be integrated in Article 9 "Public information".

Comment on Article 21, paragraphs 2 and 3

These two paragraphs pose the problem of a person who does not wish to be informed but whose family is affected by the results and in need of special follow-up (medical surveillance, counselling should they wish to have children).

Proposed wording of Article 21.2

Feedback should take place within a framework of health care or ***genetic*** counselling ***under the conditions established by national law***.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para. 1.
Proposal for textual clarification
1. Clear policies should be developed on feedback concerning results and/or incidental findings that are significant for the health of the persons arising from the use of their biological materials.

Very good to require a policy, but not develop an obligation.

Para. 2.
Proposed add:
Important to add something like only validated and clinically actionable results can be communicated.
In addition, research biobanks and clinical biobanks have different capacities.

Para. 3.

Proposal for textual modification
The subject of return of results is fashionable and the dust has not settled on “best practice”, if it ever will. For example there is a current line of thought, which says that if the information is actionable, the donor must be informed even if he has asked not to be, as it is unethical to stay silent when you know that specific personalized action could be taken to reduce serious health risks to an individual. No shortage of experts will argue the contrary. The point here is not to say who is right, just to say that there is no agreement today on best practice, certainly not on the one recommended in this paragraph.
We recommend changing this paragraph to say that the policy of the collecting organization with respect to return of results must be clearly stated in subject information sheets at the time of consent.

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

With regard to feedback of research results, in a hospital, the laboratory tests are performed in a routine setting where established procedures are in place and are validated (checked), this avoids mix-ups and contamination problems. However, medical research is still experimental and does not always follow these same strict procedures. Also it takes years, and several studies, to confirm research results and to prove they are medically relevant. This means there are variable risks, since research results may not be correct or medically confirmed and this kind of information is not always suitable to give back to the donor. So what a researcher discovers from the sample and data may be of little value to the donor directly. Feedback options are entirely depending on the risk involved for the participant, if a biobank can decide to feedback results through the treating physician. In case the research tests are not performed in a routine setting, where established procedures are in place, which are validated (checked), aimed at avoiding mix-ups and contamination problems, it is not advisable to even ask for feedback. However there are research programs that make use of tests performed in a routine laboratory, where the right procedures are in place, then it could be possible to allow feedback of results through the treating physician.
Another comment points out that the subject of return of results is fashionable and the dust has not settled on “best practice”, if it ever will. For example there is a current line of thought which says that if the information is actionable, the donor must be informed even if he has asked not to be, as it is unethical to stay silent when you know that specific personalized action could be taken to reduce serious health risks. However, there is no agreement today on best practice to be followed. It could be recommended to change this paragraph in order to say that the policy of the collecting organization with respect to return of results must be clearly stated in subject information sheets at the time of consent.

ACADEMIA

Associate Professor Nikolajs Zeps, St John of God Subiaco Hospital, Australia

Article 21.3 is not workable. It is impossible for a person to know what they do or do not wish to be informed about, and selection at time A could be judged to be not ‘informed’ if it subsequently arose at time B that the condition was treatable and life saving. I do not believe it is practicable or desirable to limit any potential to feedback at only one time in the consent process.

Dr Imogen Evans, UK

Para1. The wording here differs from that of Article 27 of the additional Protocol concerning Biomedical Research. Was this intentional? How would one define "significant"?; this usually has a statistical connotation.

PATIENT ORGANISATION

Joint Response by the Patient and Ethics Council and the Patient Advisory Council of RD Connect, NeurOmics, EURenOmics in conjunction with the Interdisciplinary Scientific Committee of the International Rare Disease Research Consortium (IRDiRC) and Eurobiobank

Articles 21 – Individual feedback; 22 – Access; 23 – Transborder flows; 24 – Oversight

We are pleased to see an explicit outline of these standards, to which we already aspire. In particular the specifics of paragraph 24, which assign duties outlined earlier in the Recommendation will be helpful to collection holders, researchers and participants.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

The return of individual research results and incidental findings in the context of research is the subject of considerable controversy. The decisions to be made about whether or not to return findings, which if any findings should be returned, and how to best return the findings are context specific. A one size fits all approach cannot be used. Research is not conducted with the same level of rigor as for health care purposes and initial findings are often later found to be wrong. The explanatory memorandum should include a discussion of the issues, in particular whether "significant" would relate to findings that only have a validated diagnostic test or not and whether hereditary health markers would be communicated that are not significant to the health of the person who donated, but potentially relevant for blood relatives. Nonetheless, it is important that whatever the policy on the return of individual findings, it be clearly communicated to the participants in the informed consent process and document. We recommend addition of the following sentence to follow Article 21, item 1: "These policies should be clearly communicated to potential participants during the informed consent process."

INDUSTRY

Regeneron Pharmaceuticals, USA

Articles 20.8, 21.1

Suggested Revision: We propose that this guidance highlight that it is acceptable that physicians are provided with un-interpreted reports or data of genetic results. The physicians would then be responsible for interpreting and communicating any information to a subject or providing counseling. We expect that physicians will validate any results communicated to subjects.

Rationale: These sections are interpreted by the team to mean that researchers must provide individual results back to subjects upon request. Currently, Regeneron is aligned with this in spirit, that information pertaining to the safety of the subject should be communicated to the subject via the healthcare provider.

It must be noted that this genetic research is not often conducted as a clinical laboratory test for the purpose of providing information to guide care of patients. This will be research information related to the cause of human disease and to understand how to improve the use of drug treatments. It is unlikely that any information provided in this research will have any direct health benefit to subjects, but it may help society in general. As such, no conclusions would be provided about the genetic information. Instead, national law may allow physicians to have access to the research DNA data and this can be arranged. It must be understood that much work would need to be performed by physicians to interpret this data and to confirm any observations before they are reported back to a subject.

One particular concern, given the global nature of clinical research, is the return of exploratory results that are not generated by a Clinical Laboratory Improvement Act (CLIA) certified laboratory or utilizing CLIA or CE tests (e.g. whole-exome sequencing). In the US, subject results are only to be provided by a CLIA certified lab. When Sponsors do not utilize certified labs for genetic research, they should not be expected to provide data or results directly to subjects, Where local law requires, results may be made available upon request to the individual subject's physician or healthcare provider.

On the other hand, in the EU, we are not aware of a central accreditation requirement across all member and/or non-member sates. We recognize that labs that do provide results to subjects and patients have their basis in ISO lab standards (i.e., ISO 15189). Sample testing for genetic research is a specialty service in a niche area dominated by academic institutions and the pharmaceutical and biotechnology industry. For the EU, we reiterate our position that it should not be expected that the results are standardised, and there should not be a requirement that Sponsors and researchers provide results directly to subjects.

We propose a recommendation captured under "Suggested Revision above". Consequently, it should be recognised that these are not standardized tests across industry and are not aligned to the process followed by CLIA certified laboratories.

ETHICS COMMITTEE

Comité de Etica (CSIC), Spain

Article 21.1
It will be very difficult due to confidentiality provisions.

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 21: TUKIJA finds the document a bit contradictory in that in some parts of it the persons cannot be identified and in others they can, for example, in this article. Section 2: TUKIJA supports that feedback should take place within a framework of health care or counselling. However, it is not clear what follows from it and how it is accommodated.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

Paragraph (1) refers to 'significant for the health of the persons'. What are the criteria by which something is judged to be significant? Furthermore, this paragraph should address how the policy in article 21 conforms to original consent.

It is recommended that feedback plans are reviewed and approved by an ethics committee or a similar competent body to avoid potential information-related risks.

EUROPEAN UNION

European Medicines Agency (EMA)

Article 21.1
Please add: as stipulated in the informed consent procedure

OTHERS

Iciar Alfonso Farnós, Consultant in Clinical Pharmacology, Spain

In our opinion it would be important to include a paragraph about these topics:

- To make reference to the possibility that any means should be taken to avoid or reduce the potential injury
- It would be necessary the assessment of clinical validity and utility

Article 22 – Access

1. Clear conditions governing access to, and use of, biological materials should be established.

2. Member states should take measures to facilitate appropriate access by researchers to collections of biological materials.

3. Transparent access policies should be developed and published, including arrangements for oversight of access and transfer procedures.

4. Appropriate access mechanisms should be developed to maximise the value of collections. These should include traceability of the uses granted by the collection.

BIOBANKS

3C-R, réseau français de biobanques

Proposed wording of Article 22.4

Appropriate access mechanisms should be developed to maximise the value of collections. These should include traceability of the uses granted by the collection***'s manager***.

Comment on Article 22

The traceability of movements of biological materials and access conditions should be governed by a contractual agreement. This is a requirement of Article 23 on "Transborder flows", but should apply to any transfer of materials between two bodies (with distinct legal personality).

It is proposed that a paragraph 5 be added to Article 22 (corresponding to paragraph 3 of Article 23).

European, Middle Easterna and African Society for Biopreservation and Biobanking (ESBB)

Article 22.1
Clear conditions governing access to, and use of biological material should be established and publicly made available.
In particular, minimal demands, access rules allowing external requests, including requests originating from outside institute, should be considered.

ACADEMIA

Dr Imogen Evans, UK

It would be more logical to reorder the paragraphs. Para 3 seems to be the more general instruction and should come first, followed by the existing para 2 then the current para 1.

KU Leuven Faculty of Medicine, Belgium, Belgium

Furthermore, in order to harmonize trans-border exchange of biological samples, access arrangements employed across member states should be harmonized. **Article 22** on access could highlight such a need and recommend overarching principles that should be observed in course of designing access arrangements, e.g. a frame work of access committees or Material Transfer Agreements/access agreements.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

Comment
Art 6 b Unesco International Declaration on Human Genetic Data.
"(…) Ethics committees at institutional or local levels should be consulted with regard to their application to specific research projects".
Access implies a transfer which involves a legal relationship that should be documented in the same conditions that transborder flows in article 23.

Proposal
Article 22 – Access
1. Clear conditions governing access to, and use of, biological materials should be established, **including the need of the evaluation by an ethics committee.**
2. Member states should take measures to facilitate appropriate access by researchers to collections of biological materials.

3. Transparent access policies should be developed and published, including arrangements for oversight of access and transfer procedures.

Transfer procedures will be examined by an independent ethics committee as stated in article 22.1. The transfer of samples should be documented in an agreement between the sender of the biological materials, on the one hand, and the recipient, on the other. Appropriate consent or authorisation, including, where appropriate, any relevant restriction established by the person concerned, should be taken into account.

4. Appropriate access mechanisms should be developed to maximise the value of collections. These should include traceability of the uses granted by the collection.

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

Article 22.2
Appropriate access to the biobanks may not always be facilitated at the ‘’state’’ level but all academic institutions or hospitals or relevant organizations within a state should make this policy so that the real purpose of biobanks to catalyze research can be realized.

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

We regard access to biological materials as a responsibility of the “biobank”. A list of the biobanks on the competent authority’s website, with an overview of their activities and aims, should be sufficient to guarantee such access;

Article 23 – Transborder flows

1. Biological materials should only be transferred to another state if a comparable level of protection is either ensured by the law of that state or by legally binding and enforceable instruments adopted and implemented by the persons involved in the transfer and further processing.

2. The transfer of the biological materials should be done under appropriate safety and confidentiality conditions.

3. A documented agreement between the sender of the biological materials, on the one hand, and the recipient, on the other, should be signed. Appropriate consent or authorisation, including, where appropriate, any relevant restriction established by the person concerned, should be included in the agreement.

BIOBANKS

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Proposal for an add into paragraph 2
“Biological material should only be transferred under the highest level of protection adopted between the two states”.
E.g: Dengue virus is BSL3 in France, whereas BSL2 in UK. Transfer from France can only be done if the UK end-user owns a BSL3 facility.

Proposal for two new paragraphs 4 and 5
4. All the necessary measures should be taken to document and ensure the traceability of the transfers.

5. Transfers should not result in the impossibility for the person concerned to exercise its rights pursuant to applicable law. Appropriate measures should be planned within the transfer agreement.

ACADEMIA

Dr Imogen Evans, UK

Para 1. The Recommendation Article 16 referred to "and associated personal data". Surely that phrase should be retained here?

Para 3. Lines 1 and 2. The words "one the one hand" and "on the other" are redundant.

Lund University, Sweden

Article 23 is about transborder flow. You could emphasise that similar legislation does not in itself provide adequate protection for individuals. It is possible that some countries have very good legislation in this area, but where the interpretation and/or enforcement of the law are wholly unacceptable. Only looking to the legislation can be detrimental to the individual. What should be done in these circumstances is to require individual consent in order to send biological material to other countries, and to give individuals the opportunity to specify which countries in particular their material can be sent to. They should also, if they so wish, have the right to deny any such request.

Prof. Kelly Tilleman, PhD, Universitair Ziekenhuis Gent

Article 23
When researchers already have the information that the scientific research is going to be carried out in cooperation with other centres, even more in other countries, this might also be something that might be included in chapter III – Information and consent: art. 11 – Information 1. ii : any relevant conditions governing use of the materials *(including possible transborder use of the material in a research setting)*.

Pilar Nicolás Jiménez. Interuniversity Chair in Law and the Human Genome, University of Deusto, University of the Basque Country

Comment
A mechanism to know and ensure a level of protection as well as the institution in charge of this evaluation should be determined.

The need to ensure an adequate protection should refer to the future research as well as to the collection procedure in the case of samples coming from other countries.

Proposal
Article 23 – Transborder flows
1. Biological materials should only be transferred to another state if a comparable level of protection is either ensured by the law of that state or by legally binding and enforceable instruments adopted and implemented by the persons involved in the transfer and further processing.

Biological materials from other state should only be used if a comparable level of protection has been observed in the collection of the sample.

When examinig the level of protection, the ethics committees will take into account the ethical examination of the collection procedure or the ethical examination of the future research, as well and the conditions stated in the material transfer agreement.

2. The transfer of the biological materials should be done under appropriate safety and confidentiality conditions.

3. A documented agreement between the sender of the biological materials, on the one hand, and the recipient, on the other, should be signed. Appropriate consent or authorisation, including, where appropriate, any relevant restriction established by the person concerned, should be included in the agreement

Prof.Dr.Meral Özgüç, Hacettepe University Faculty of Medicine, Department of Medical Biology, DNA Cell Bank for Rare Diseases, Turkey

Article 23.1,2
Transborder flow should include biological material and/or data and this should be also carried on in other articles when relevant.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

Is Article 23 intended to also apply to transfers from member states to non-member states (i.e. outside Europe)? If so, should this article refer to “jurisdiction” or “country” rather than [member] “states”? In addition, it would be helpful if the explanatory memorandum that will accompany this document provide some examples of the types of legally binding and enforceable instruments that could be used to ensure a comparable level of protection for the transfer of biological materials to another state or jurisdiction.

ETHICS COMMITTEE

Finnish National Committee on Medical Research Ethics (TUKIJA)

Article 23.2 is beautifully put but does not give much guidance of how it is achieved.

Swedish National Council on Medical Ethics (SMER)

Article 23 states circumstances under which biological materials should be transferred to another country. Transborder flows raise questions concerning how to deal with circumstances when countries differs on what they define as biologically identified materials or when the ethical review process differs between the countries. The protection of the individual is not ensured if the application of the law and the ethical review differs. It can be discussed whether the individual has to consent when transferring the biological materials to other countries.

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

Care should be taken that the administrative burdens for those managing the collections of biological material do not become too onerous, so that scientific research is not hampered;

Norwegian Institute of Public Health (NIPH)

Paragraph (3) refers to the sending of biological materials and indicates that “Appropriate consent or authorisation, including, where appropriate, any relevant restriction established by the person concerned, should be included in the agreement.” Often, the researcher has

obtained the consent but the samples are sent from a biobank. How is the consent then included in the agreement? This should be clarified.

European Union

European Commission (DG JUSTICE)

In **Article 23(1)** addition: "including appropriate safeguards with respect to the processing of personal data" (see Article 42(1) of the proposed Regulation);

European Medicines Agency (EMA)

Article 23
What about primary cells from non-European origin?

Article 23.3,2
Please consider that the possibility of regional rules facilitating this should be foreseen.

Article 24 – Oversight

1. Any proposal to establish a collection of biological materials should be subject to an independent examination of its compliance with the provisions of this Recommendation.

2. Each collection should be subject to independent oversight which is proportionate to the risks involved for the persons whose biological materials are stored in the collection. Such oversight should aim in particular at safeguarding the rights and interests of the persons concerned in the context of the activities of the collection.

Oversight mechanisms should cover, at a minimum:
i. the implementation of security measures and of procedures on access to, and use of, biological materials;
ii. the publication of reports on past and planned activities, including information about access by third parties, at least annually;
iii. the change in the risks to persons whose biological materials are stored in the collection and, where appropriate, revision of policies;
iv. appropriate information to the persons concerned of changes in the management of the collection in order to be able, where appropriate, to exercise the rights laid down in Article 16; and
v. the development and implementation of feedback policies, including regular review.

Oversight mechanisms should be able to adapt to possible evolutions of the collection and of its management.

BIOBANKS

3C-R, réseau français de biobanques

Proposed wording of Article 24.2

Each collection should be subject to independent oversight which is proportionate to the risks involved for the persons whose biological materials are stored in the collection. Such oversight

should aim in particular at safeguarding the rights and interests of the persons concerned in the context of the activities of the collection.
Oversight mechanisms should cover, at a minimum:
i. the implementation of security measures and of procedures on access to, and use of, biological materials;
ii. the publication of reports on past and planned activities, including information about access by third parties ***if that does not breach pre-existing confidentiality clauses***, at least annually;
iii. the change in the risks to persons whose biological materials are stored in the collection and, where appropriate, revision of policies;
~~iv. appropriate information to the persons concerned of changes in the management of the collection in order to be able, where appropriate, to exercise the rights laid down in Article 16; and~~
v. the development and implementation of feedback policies, including regular review.

Biobanking and Biomolecular Resources Research Infrastructure BBMRI-ERIC

Para.1.
Proposed add
...as reflected in the applicable law" - the recommendation cannot override legislation.

Para. 2.
Proposal for textual changes
i. security, confidentiality measures…

Concern :
ii. the publication of reports on past and planned activities, including information about access by third parties, at least annually;
This kind of rule could lead to violate confidentiality in the context of partnerships with thirds. Concerned persons are informed about the possibility of thirds to access their human biological resources but what is the meaning of publishing this information, and to what extend this can be useful.

Proposal for textual changes
ii. …and transfers at least annually.

ACADEMIA

Deans of Faculties of Health and Medical Sciences (Aarhus University, University of Southern Denmark, Aalborg University, Copenhagen University)

Oversight should be performed by national bodies (research ethics committees and data protection agencies).

Dr Imogen Evans, UK

It would be preferable to place this article on Oversight at the start of the Chapter.

Para 2 oversight mechanisms iii. The phrase "change is risks to persons whose biological materials are stored.... is unclear. What was this intended to convey?

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

We agree that a collection of biological materials should be subject to oversight for safeguarding identifiable samples and data. It would be helpful if this statement could be expanded for clarification rather than suggesting "independent examination" of compliance as this may be interpreted differently across states.

Biological specimen collections are subject to constantly evolving legal, ethical, and societal values in addition to scientific innovations, and therefore we suggest the statement "Oversight mechanisms should…" be changed to "Oversight mechanisms must be able to adapt ".

INDUSTRY

Regeneron Pharmaceuticals, USA

Articles 20.9, 24.2.ii, 24.2.v
Suggested Revision: We propose reverting back to the previous biobanking definition. Additionally, we propose that this working document is clarified by specifying and aligning it with the ethics requirements and clinical research standards applied to population biobanking for (pharmaceutical) research.

Rationale: The principles within this guidance do not provide a framework of the content of such reports and to whom these reports should be provided. We also recognize that the language on population biobanking that was captured in the previous version of this guidance was removed. We interpret the current language captured in this working document to be applicable to research biobanking. By addressing it simply to 'collections' it has far reaching impact beyond perhaps that which was intended.

By reverting back to the previous biobanking definition, the meaning of the principles set forth in the relevant articles and paragraphs within this working document will minimize confusion and the number of potential misinterpretations. If our interpretation is not correct, however, we request that clarification be provided to specify the minimum criteria for these reports including the frequency of reporting and to provide some general provisions as to whom the report should be submitted.

MINISTRY/NATIONAL AGENCY

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

Care should be taken that the administrative burdens for those managing the collections of biological material do not become too onerous, so that scientific research is not hampered;

Norwegian Institute of Public Health (NIPH)

Paragraph (1) indicates that independent examination should take place but does not stipulate who would carry out this independent examination. This should be specified.

The specification of what should be covered by oversight mechanisms indicates that this is at a minimum. The procedure for requiring which activities should be covered by oversight mechanisms should be made clear. A simplified and comprehensive way to address this

would be to state that “Oversight mechanisms should be put in place to cover all activities and documentation of the collection’.

European Union

European Commission (DG JUSTICE)

Article 24.2

The oversight mechanism should also cover appropriate measures to ensure and be able to demonstrate that the processing of personal data is performed in compliance with the data protection rules (see Article 22(1) of the proposed Regulation). In point i) we should add: the implementation of security measures and of procedures to ensure a level of security appropriate to the risks presented by the research activities and the nature of the personal data to be protected, in particular on access to... (cf. Article 30(1) of the proposed Regulation).

CHAPTER VI – Re-examination of the Recommendation

Article 25 – Re-examination of the Recommendation

This Recommendation should be regularly re-examined after its adoption, notably in the light of the experience acquired in the implementation of its guidelines.

Academia

Dr Astrid Stuckelberger, Institute of Global Health, Faculty of Medicine, University of Geneva

Post-mortem use should be mentioned as it has been a polemic for sperm bank too.

PROFESSIONAL ORGANISATION

International Society for Biological and Environmental Repositories' (ISBER)

We commend the Council of Europe for the plan to regularly re-examine the Recommendation after its adoption in light of the experience acquired in the implementation of its guidelines. It will be important to assess the impact of the Recommendation on all relevant stakeholders, such as academia, small and large biotech companies, pharmaceutical companies, etc. and for different European initiatives (e.g. BBMRI and EATRIS). It will also be important to monitor the impact on the transborder flow of specimens and international collaborations. Such a re-examination will be critical to ensure that the Recommendation allows important research to proceed, while protecting the rights and welfare of research participants.

Finally, we note that this document does not discuss the important issue of ownership. This is a very complex issue that may be outside the scope of the current document and timeframes for its development. In addition, it may be difficult because of cultural differences about ownership of biospecimens. Nonetheless, the development of consistent guidelines and processes for sample ownership across biobanks in Europe and within other countries around the world has the potential to increase sample donations, improve sample optimization and enhance utilization which would advance the development of innovative medical therapies. ISBER members would be happy to contribute to any future effort to resolve this issue should an appropriate body decide to take this on.

MINISTRY/NATIONAL AGENCY

Norwegian Institute of Public Health (NIPH)

The recommendation should also be re-examined in light of new methodologies and knowledge that might impact the procedures outlined in the recommendation.

OTHERS

Sev S. Fluss, Formerly Chief, Health Legislation, and Administrative Officer to the Director-General, WHO, currently Senior Adviser at CIOMS

"provisions" rather than "guidelines" in Article 25.

OTHER SPECIFIC COMMENTS

ETHICS COMMITTEE

Swedish National Council on Medical Ethics (SMER)

Recommendation concerning sanctions if the regulation is not followed
The document should also include a recommendation to the member states to enact legislation with sanctions in case the rules are violated.

Dr Astrid Stuckelberger, Institute of Global Health, Faculty of Medicine, University of Geneva

- Post-mortem use should be mentioned as it has been a polemic for sperm bank too.

- Again, arrest/dismiss at any time should be offered/mentioned systematically

- Future development of the material and results should communicated hand in hand with continuous information to the user (which should always be asked). At any time the biological material beholder should be able to require information, stop the procedure and be able to request to retreat/destroy his biological material.

[we can only imagine if the biomaterial is further developed in stem cells and organs that will be transplanted to future patients, the person should have the priority of use for his/her family for example..]
This contract should be much clearer than it is mentioned in the timing, disclaimer, retreating/non-consent at anytime, use of his own biomaterial developed for his own benefit, be continuously informed if requested (after being offere these options).

In general, the case of pandemic and Syracuse principle in line with the obligation of the WHO International Health Regulation (IHR)* does not seem to be considered in this document. The Question is : is there any link that should be made mentioned such as " the ethical committee will work in full concordanced, fullfillment and respect of IHR and United Nations Human Rights obligations/Conventions.

*nb: IN the context of a collaboratin between WHO, the University of Geneva, Georgetown University and Preatoria University, during 3 years we have been developing an on-the job training for MOH/focal points of IHR in the country offices of WHO or the governements. And among other topics, I was appointed to develop the perspective of ethics and human rights education with case studies (infectious (Ebola/Rift Valley), foodborne disease, chemical and radionuclear events) – it is clear to me that the labs and CDC have to take biological material samples to create a vaccine, but in the prevention of disease, a lot of biomaterial is also seeked for research that could prove for maleficient as well as beneficient purposes…

Anyway,just let me know if this is relevant and you need more material.

In general, it also seems that the text is a bit behind the incredible development of the 'ultraconnected world' and some precautionary ethical measures in the communication of biomaterial and transmission with new means should be taken into consideration already today in a way or another (wifi, transmutation, gps, distance analysis and use).

Agence fédérale des médicaments et des produits de santé (AFMPS), Belgique

- Certain concepts could be defined (“residual material”, “collection”, …);
- Consideration might be given to making a provision which prohibits storage and/or use for scientific research without an adequate and appropriate portion of the biological material being on the one hand used and on the other hand kept in reserve for the donor’s benefit so that the donor’s diagnosis or treatment may be established, finalised or supplemented.