12 August 2014

Dear Secretary Lwoff:

On behalf of the International Society for Biological and Environmental Repositories (ISBER), I am pleased to submit the following comments on the Working Document on Research on Biological Materials of Human Origin to the Committee on Bioethics of the Council of Europe.

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.

Chapter I-Object, scope and definitions

Article 3: Identifiability of biological materials

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

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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). 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.

Article 6: Prohibition of financial gain

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.

Chapter III-Information and consent

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

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

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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.

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

Paragraph 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?

Article 13: Storage for future research of residual biological materials

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

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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.

Chapter IV- Use of biological materials in a research project

Article 17- General Rule

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.

Chapter IV- Governance of collections

Article 21 – Individual feedback

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."

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Article 23: Transborder flows

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.

Article 24: Oversight

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 ".

Article 25: Re-examination

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.

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