Comments on the World Medical Association Declaration on Ethical Considerations Regarding Health Databases and Biobanks

The International Society for Biological and Environmental Repositories (ISBER) appreciates the opportunity to submit the following comments on the World Medical Association Declaration on Ethical Considerations Regarding Health Databases and Biobanks.

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 repositories and biobanks involving human biological materials, the great majority of ISBER members focus on the management of biobanks and repositories of human tissues and associated data 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 specimen biobanks is extensive and longstanding, 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, that were published in *Biopreservation and Biobanking*, April 2012, reflect the collective experience of its members and have received broad input from other biobank professionals. ISBER's membership is global and includes thought leaders worldwide with expertise in bioethics issues related to biobanks. With this expertise, we believe ISBER is in a unique position to contribute to the World Medical Association Declaration on Ethical Considerations Regarding Health Databases and Biobanks.

We wish to thank the World Medical Association for the invitation to submit the following comments for further consideration and would happy to discuss them with the WMA Working Group and provide additional information if it would be helpful.

General Comments:

ISBER agrees that the protection of individuals whose data and specimens are used for purposes other than individual patient care is important and that informed consent should be obtained if possible. However, respect of autonomy must be considered along with other ethical principles, such as justice and the social value of research and other uses of specimens and associated data. As we explain in further detail below, some of the provisions of the Declaration as written would hinder or prohibit some important research, quality improvement, and quality assurance and control activities involving human specimens and data. This reduction in research, in itself, is an ethical problem.

1. The document does not directly address the risks involved with the use of human specimens and health data. The announcement of the request for comments states that:

   "*In analysing the already existing scenarios for the use (and abuse) of health data and biobanks, the work group came to the conclusion that the major risk scenarios do not result from science, but from the commercial, administrative or political use of such data. Limiting our guidelines to research only would have left us blind to the imminent risk of*

abuse from outside the field of medicine: commercialisation, cost-cutting and potential political abuse."

If the major risk from the use of health databanks and biobanks does not come from science as the announcement acknowledges, but from the commercial, administrative or political use of such data, the Declaration should include provisions that focus on specifically minimizing those risks. For example, there is no mention of commercial uses and "selling" of specimens and data or the use of agreements such as Data Use Agreements that would prohibit re-identification of individuals whose specimens or data are used in research. Furthermore, the document makes an assumption that there is inherent danger in unauthorized persons seeing health information about an individual. However, while anti-discrimination laws may be less than optimal, little evidence exists that misuse is occurring. The risk of unauthorized access is low and the harms that may result from such access is also low, particularly when good governance and oversight mechanisms are in place.

2. The scope of the document appears to be quite broad. It applies to data in Health Databases and human biological material in Biobanks that are used for research or for other purposes. It applies to any use of health information beyond the individual care of patients. Greater clarity is needed regarding what kinds of health databases and biobanks the Declaration applies to. Does this include research databases and biobanks in which any identifiable health data are collected and maintained? Does it include only those databases and biobanks that are created for the purposes of healthcare but are then used for other purposes? Does it also include databases and biobanks that also contain health information but are created specifically for research or other purposes? Are patient's electronic health records held in a healthcare "management system" a health database? Does it apply to extracted datasets? What does "health information" include? Does it include any/all information with a health care basis that is recorded by a health care professional? Does it also include lifestyle and environmental exposure information? Some examples of the types of information and types of health databases and biobanks that are intended to be covered by this document would be helpful.

3. As described in the specific comments below, definitions should be provided for key terminology throughout the document (e.g. anonymised and non-identifiable data, and biological data", anonymous and pseudo-anonymous data, broad consent, conditional broad consent, blanket or open consent). Without additional clarity regarding these terms, it is difficult to understand how to apply the provisions and what the implications will be for health databases and biobanks.

4. The broad scope of the document is problematic with regard to application of some of its provisions. For example, in some countries, disease registries are maintained that do not require individual consent. Their purpose is to collect information for government health statistics and/or clinical audit for public health purposes; however, their use would be hindered by the current proposal. In addition, disease registries and electronic medical records systems are governed by national and local laws which may be in conflict with the policy as written.

5. As explained further below, one of the major concerns regarding this document is the very narrow provision for a waiver of consent. Such a narrow waiver provision is extremely problematic with regard to the use of specimens that may be collected during the course of routine care. It would significantly inhibit research use of pathology

archives in cases where the research use could not be anticipated at the time of specimen collection, and when it is difficult to obtain a new consent. It may also introduce bias in research and other activities (such as quality assurance and improvement) that can result in harm to patients if patient care is based on flawed results.

6. A variety of additional existing documents provide guidance for human biological materials, health databases and biobanks. These include the Council of Europe Working Document on Human Biological Materials (The Organisation for Economic Cooperation and Development Guidelines for Human Genetic Research Databases and Biobanks http://www.oecd.org/science/biotech/guidelinesforhumanbiobanksandgeneticresearchdatabaseshbgrds.htm), and best practices from the National Cancer Institute (NCI Best Practices for Biospecimen Resources, http://biospecimens.cancer.gov/practices/) and the International Society for Biological and Environmental Repositories (http://www.isber.org/?page=BPR). These documents provide comprehensive guidance for the global research community regarding research biobanks and databases containing health data. It is not clear how the WMA Declaration comports to these other guidelines or existing national regulations. We note that regulations and guidelines vary globally as they apply to health databases and biobanks and that regulations and policies are currently in flux. These include proposed changes to the US Federal Policy for the Protection of Human Subjects ("Common Rule") and the EU data protection regulations in Europe. Of note, as explained below, Paragraph 19 is in conflict with the WMA Declaration of Helskinki (October 2013).

7. Finally, defining ethical considerations for all uses of health databases and biobanks may be outside the domain of physicians in clinical care relationships. Consideration should be given to limiting the Declaration to the secondary use of medical records systems created for healthcare purposes, particularly given the problems with the broad scope of this document.

Specific Comments:

Preamble:

Paragraph 4 - The Declaration states that it is "intended to cover any use of health information beyond the individual care of patients." This would therefore apply not only to research uses, but also quality assurance, quality improvement, public health purposes, medical education and other important uses. It could also be interpreted to include all audits, use of registries (e.g. disease registries, registries for organ donations), and even government (national or local) health department "owned" databases. As explained further below, the application of some of the provisions of the document, as written, to some of these activities would be highly problematic.

Paragraph 7 – The Declaration states that "Biological material refers to a sample obtained from an individual human being, living or deceased, which can provide biological information, including genetic information, about that individual." While we agree, in general, with this definition, we believe that for the purposes of this document, as written, the provisions should only apply to biological materials from living individuals because it is impossible to obtain consent from deceased individuals. See further discussion of Paragraph 19 below.

Paragraph 8 and 9 – As previously indicated, a definition is needed for "anonymised and non-identifiable data and biological data" as well as anonymous and pseudo-anonymous data. There

is great variability in these terms and their usage in the field as well as in legislation and policies globally. We suggest that the WMA consider including the definitions in ICH-E15, "Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories" (see http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002880.pdf).

Paragraph 9 - We suggest that it may be more useful to state that wherever possible, custodians of health databases and biobanks should take steps to limit unauthorized access to information that can be readily re-identified. This can be achieved in a number of ways including anonymisation or coding.

Paragraph 11 and 12 – These appear to be missing from the document.

Ethical Principles

Paragraph 15 - This Paragraph stipulates that individuals should be informed about the persons who will have access to the health database or biobanks. Is this intended to mean classes of individuals (e.g. researchers) or more specific information (researcher name, etc.)? In many cases, it will not be possible to specify the individual(s) who will have access to the specimens and data in advance; only certain classes of individuals. We therefore suggest that this paragraph be clarified to mean classes of individuals.

Paragraph 16 – This Paragraph states that "Individuals have the right to solicit and be provided with information about their data and its use as well as to request necessary corrections of mistakes or omissions." Does this mean general uses? How much information is it necessary to provide about the uses? This Paragraph provides an example of the problems with the scope of the document and how the document does not clearly delineate the distinction between secondary use of healthcare databases for research or other non-clinical purposes and the research use of specimens and healthdata from biobanks that may be created solely for research purposes. In addition, it does not distinguish between the use of aggregate level information and the use of individual-level data. In at least some countries, individuals have the right by law to request a general accounting of how their healthcare data has been used and disclosed. Given the difficulties of providing access to individual-level data obtained during the course of research, particularly in biobank setting, we suggest that this article be limited to healthcare data and suggest modifying it along the following lines:

> *Paragraph 16: "Individuals have the right to solicit and be provided with general information about the use of their healthcare data by their healthcare provider in an appropriate manner as well as to request necessary corrections of mistakes or omissions."*

Paragraph 17 - Many disease registries do not require notification of the patient/health care consumer and they generally do not offer an opt-out option or withdrawal at a later date. However, there may be global differences with regard to these registries. How can you withdraw if you do not know you are included in a database, or are aware of its existence? This point may need to be interpreted through national law on a country-specific basis.

Paragraph 18 – This Paragraph states that a conditional broad consent is acceptable and that blanket or open consent is not ethically acceptable. We support the notion that consent for research may be broader than a specific study. However, this Paragraph is unclear as written for a

number of reasons. For example, the terms "conditional broad consent", "blanket" or "open consent" need to be defined, especially since there are no uniform, widely-accepted definitions of these terms. What does it mean to provide "all principle information about future use"?

This Paragraph states that "blanket or open consent for future use of health data or biological material not envisaged at the time of collection is not ethically acceptable." Would this apply even if the sample and/or data can be fully anonymized?

The statement that blanket or open consent is not acceptable defies the principle of autonomy. Shouldn't it be acceptable for a person to choose to do what they like with their own samples and give authority to others as they wish? Wouldn't it be ethically acceptable for an individual to give the authority for decision making on specific uses of their data and specimens to an ethical review board? We suggest modifying this Paragraph along the following lines : "In contrast, blanket or open consent for future use of health data or biological material not envisaged at the time of collection is not ethically acceptable without the approval of an accredited and competent ethical review committee," or similar wording.

This Paragraph also requires that all uses of health data or biological material be explicitly approved by a dedicated, independent ethics committee. Would this be a requirement for uses of even de-identified specimens and health data from an identifiable health database or biobank? If so, it would seem that this requirement would burden ethics committees for what would be minimal risk research and divert their ability to focus on the review of higher risk studies involving interventions.

Paragraph 19 – As mentioned previously, the provision for a waiver is too narrow. Informed consent can only be waived in the event of a clearly identified and immediate threat to public health where anonymous data will not suffice.

Informed consent and right to privacy, confidentiality and self-determination are important principles and we believe that informed consent for use of identifiable data and specimens should be obtained whenever possible. However, there is a need to balance these principles with the social value of the use of human biological material and health data for important research, quality assurance (QA), quality improvement (QI), medical education and public health purposes (e.g. disease registries). The effect of such a narrow waiver of the informed consent requirements would mean that much important research and other important uses such as QA or QI could not be performed because the individual may be deceased or unable to be located. Furthermore, valuable archived collections of human biological material (e.g. residual material from pathology archives) would not be able to be used for research or other important purposes (QA/QI) unless broad consent had been obtained at the time the specimen was collected. We note that many important discoveries have been made from the research use of previously existing, archived specimens for which it would have been difficult or impossible to obtain consent; for example, the development of tests to predict response to therapies for breast cancer.

Additionally, if prospective consent were required for research use of all identifiable health databases and biobanks without the ability of an IRB/ethics review committee to waive consent under appropriate circumstances, research, hospitals, and outpatient clinics, would have to establish research-consent infrastructures in the patient service setting. This kind of infrastructure would require appropriately trained staff to obtain consent at each entry point to the hospital system. It would be costly and infeasible for some hospital systems, particularly smaller, community hospitals. This could have the effect of hindering minimal risk research, particularly research on underserved populations or other resource-poor settings. It may also introduce bias

into important research using health data or human specimens and lead to incorrect conclusions. This could ultimately result in harms to patients if decisions about care are based on flawed and/or biased research. The same is true of important QA/QI activities that are low risk and may not currently require informed consent.

Furthermore, the narrow waiver provision is inconsistent with most ethical codes that permit waiver of consent by ethics committees under strict conditions balancing the public interest in the research with the personal interest in autonomy and privacy. This includes the WMA Declaration of Helsinki (October 2013) that permits a waiver of consent when obtaining consent is impossible or impracticable:

> *Paragraph 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."*

We strongly encourage the broadening of the waiver provision in Paragraph 19 to be consistent with the Declaration of Helsinki in order to unnecessarily inhibit important, low risk activities and balance personal interests of autonomy and privacy with public health benefit.

Paragraph 20 – This Paragraph is problematic with regard to the scope of this document. In some jurisdictions, dedicated independent ethics committees do not approve the establishment of health databases and biobanks used for some purposes besides research (such as public health registries). We are concerned not only about the impact of this requirement on these activities but also about the possible unintended consequence of significantly expanding the mandate of ethics committees designed to review and approve research activities. Will ethics committees be able to take on the additional responsibilities outlined in these areas of the declarations? How will adding more responsibilities to ethics review committees support more rapid research advancement for patients? What does it mean to have a "dedicated" independent ethics committee? Is this Paragraph referring to an Ethics Committee for a single biobank? Biobanks may support many studies and multiple ethics committees may be involved. Additionally, research biobanks may be reviewed by ethics committees that review other types of research. It is therefore not clear how this provision would apply to these situations.

Paragraph 21 – Does this Paragraph apply only to the use of identifiable data or does it also apply to the use of de-identified data or specimens obtained from a Health Database or Biobank containing identifiable data or specimens?

Paragraph 22 – We suggest changing the last sentence to include the term data, to acknowledge populations who consider that the information/data,is of equal value to the material, for example indigenous peoples.

> *"Protections for ownership of materials, rights and privileges must be considered before collecting and sharing the material and data.*

Paragraph 25 – This Paragraph states that an appropriately qualified physician should be appointed to safeguard Health Databases or Biobanks with responsibility for ensuring compliance with this declaration. However, it is not clear why a physician must have the responsibility for overseeing compliance with the requirements in the document. In fact, a physician may not be the most qualified person to do so, particularly if the biobank is established for research purposes.

We suggest modifying this provision to indicate that an appropriately trained individual must oversee the health database or biobank. This individual should have training in privacy, confidentiality and research ethics. A steward with the appropriate training would be sufficient, coupled with ongoing oversight of identifiable health databases and biobanks for research purposes by a research ethics committee.

Paragraph 26 – We agree that a system of governance and oversight is absolutely essential for the ethical establishment, operation and use of health databases and biobanks. While we agree in principle with the provisions of this Paragraph, it is not clear what is meant by "governance arrangements". Further clarification would be very helpful. Consideration should be given to re-writing the Paragraph along the following lines:

> The governance framework for a biobank or health database should clearly outline:
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> Paragraph 26.1. as written but combine with 26.2
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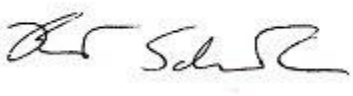
> Paragraph 26.2 Who is responsible for the management of the Health Database or Biobank
>
> Paragraph 26.3 Standard operating procedures for all processes regarding the appropriate and ethical collection, storage, dissemination and usage of sample and health information.
>
> Paragraph 26.4 Policies regarding access and security
>
> Paragraph 26.5 Policies regarding the longevity of the resource and what will happen if and when the facility closes.
>
> Paragraph 26.6 – 9 as written
>
> New Paragraph; 26.10 – plans for sustainability
>
> New Paragraph; 26.11 – disposition of the specimens and data at the end of the consent period, in the event a biobank or database is terminated or no longer scientifically useful.

Paragraph 27 – Would this statement be more appropriate for inclusion in the Preamble than Ethical Principles?

On behalf of the International Society for Biological and Environmental Repositories (ISBER),



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For any questions, feel free to contact ellyce@isber.org.