

## POLICY

# International Charter of principles for sharing bio-specimens and data

Deborah Mascalzoni<sup>\*,1,2</sup>, Edward S Dove<sup>3</sup>, Yaffa Rubinstein<sup>4</sup>, Hugh JS Dawkins<sup>5,6,7,8</sup>, Anna Kole<sup>9</sup>, Pauline McCormack<sup>10</sup>, Simon Woods<sup>10</sup>, Olaf Riess<sup>11</sup>, Franz Schaefer<sup>12,13</sup>, Hanns Lochmüller<sup>10</sup>, Bartha M Knoppers<sup>3</sup> and Mats Hansson<sup>1</sup>

There is a growing international agreement on the need to provide greater access to research data and bio-specimen collections to optimize their long-term value and exploit their potential for health discovery and validation. This is especially evident for rare disease research. Currently, the rising value of data and bio-specimen collections does not correspond with an equal increase in data/sample-sharing and data/sample access. Contradictory legal and ethical frameworks across national borders are obstacles to effective sharing: more specifically, the absence of an integrated model proves to be a major logistical obstruction. The Charter intends to amend the obstacle by providing both the ethical foundations on which data sharing should be based, as well as a general Material and Data Transfer Agreement (MTA/DTA). This Charter is the result of a careful negotiation of different stakeholders' interest and is built on earlier consensus documents and position statements, which provided the general international legal framework. Further to this, the Charter provides tools that may help accelerate sharing. The Charter has been formulated to serve as an enabling tool for effective and transparent data and bio-specimen sharing and the general MTA/DTA constitutes a mechanism to ensure uniformity of access across projects and countries, and may be regarded as a consistent basic agreement for addressing data and material sharing globally. The Charter is forward looking in terms of emerging issues from the perspective of a multi-stakeholder group, and where possible, provides strategies that may address these issues.

*European Journal of Human Genetics* (2015) 23, 721–728; doi:10.1038/ejhg.2014.197; published online 24 September 2014

## INTRODUCTION TO THE INTERNATIONAL CHARTER OF PRINCIPLES FOR SHARING BIO-SPECIMENS AND DATA

Sharing data and bio-specimens is essential for the discovery, new knowledge creation and translation of various biomedical research findings into improved diagnostics, biomarkers, treatment development, patient care, health service planning and general population health. The growing international agreement on the need to provide access to research data sets to optimize their use and fully exploit their long-term value has been articulated in many documents, including the OECD Principles and Guidelines for Access to Research Data from Public Funding, the Toronto Statement, and more recently the Global Alliance for Genomics and Health's White Paper.<sup>1–3</sup> Contemporaneously, the ambitious aims set out in the International Rare Disease (RD) Research Consortium (IRDiRC.org), which seeks to develop 200 therapies and to diagnose most RDs by 2020, and the decision of the European Commission asking all members states to develop a national plan for RDs,<sup>4</sup> provide further impetus. Although sharing of data and samples is thought to be beneficial for most health-related research, it is of highest importance for RD research because of the scarcity of research participants, samples, data, resources and researchers for any given RD.

Ideally, data and bio-specimens should be made widely available to the most inclusive and ethically responsible research community, but there is often resistance by institutions and individuals who fear that they will not receive recognition for their investment in building collections. Real and perceived risks of discrimination of vulnerable patients groups because of health-related data sharing also exist and must be considered in any legislation or guidelines. Collecting data and storing biological samples in accordance with ethical and scientific standards requires intellectual, institutional and economic resources and, critically, the participation of patients and the wider community including otherwise healthy volunteers.

All data and material sharing agreements should be ethically robust and mindful of the responsibilities owed to the donors to make best ethical use of the samples and data consistent with their consent.

Researchers face very different requirements for data and sample sharing. Data Transfer Agreement (DTA) and Material Transfer Agreement (MTA) are often written in legal terms, and so are not easily understood by scientists or institute administration officers who serve as a conduit for these agreements. Hence the need to provide a simplified overview of basic principles and a practical template

<sup>1</sup>Center for Research Ethics and Bioethics Uppsala University, Uppsala, Sweden; <sup>2</sup>Center for Biomedicine, EURAC Research, Bolzano, Italy; <sup>3</sup>Centre of Genomics and Policy, McGill University, Montreal, Quebec, Canada; <sup>4</sup>Office for Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA; <sup>5</sup>Office of Population Health Genomics, Department of Health, Perth, Western Australia, Australia; <sup>6</sup>Centre for Population Health Research, Curtin Health Innovation Research Institute, Curtin University of Technology, Bentley, Western Australia, Australia; <sup>7</sup>School of Pathology and Laboratory Medicine, University of Western Australia, Nedlands, Western Australia, Australia; <sup>8</sup>Center for Comparative Genomics, Murdoch University, Murdoch, Western Australia, Australia; <sup>9</sup>EURORDIS, Rare Disease Europe, Paris, France; <sup>10</sup>PEALS (Policy, Ethics & Life Sciences) Research Centre, Newcastle University, Newcastle upon Tyne, UK; <sup>11</sup>Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany; <sup>12</sup>Pediatric Nephrology Division at Heidelberg University Hospital, Heidelberg, Germany; <sup>13</sup>Institute of Genetic Medicine, Newcastle University International Centre for Life, Newcastle upon Tyne, UK

\*Correspondence: Dr D Mascalzoni, Center for Research Ethics and Bioethics, Uppsala University, Husargatan 3, BMC, Entrance A11 Box 564, SE-751 22 Uppsala, Sweden. Tel: +46 18 471 61 97; Fax: +46 18 471 66 75; E-mail: deborah.mascalzoni@crb.uu.se

Received 13 June 2014; revised 1 August 2014; accepted 20 August 2014; published online 24 September 2014

(the MTA/DTA). The principles are equally valid and applicable for Access Agreements (AAs).

The Charter, together with the template for general MTA/DTA, constitutes an enabling tool to improve the governance and audit of sharing data and specimens across multiple international settings. It is written in simplified language to make it accessible and usable by scientists and other stakeholders, and provides a consistent set of principles that will improve interoperability nationally and internationally.

The Charter has been developed to provide a common overview and foundational framework of the practice of sharing, and to frame a minimum list of the terms needed to achieve an equitable and ethically grounded data sharing agreement through multi-stakeholder engagement and consensus, including patient representatives, clinicians, researchers, institutions and government agencies. This Charter is the result of a careful negotiation of different stakeholder's interest: that includes a stakeholders workshop held in Brussels in October 2013. During the 2-day workshop, RD patient representatives, legal experts, ethical experts, industry representatives and scientists debated the issues and produced consensus positions that informed the Charter. The model is the result of further analysis and is built on earlier consensus documents and position statements, which provided the P3G general legal framework and generic MTA.<sup>5</sup> The Charter has then been considered by the RD Connect Patient Ethics Council and RD Connect Patient Advisory Council, which endorsed the Draft Charter as the patient consulting bodies of RD Connect.

The MTA/DTA provides a clear and simplified template that can be applied to different research contexts. It follows the Charter's principles and incorporates them in a mutual template agreement between researchers (or institutions) that comprise best practices and values. Ideally, both the provider and recipient should not only fulfil legal requirements but also comply with ethical and quality assurance mechanism recommendations to achieve the highest ethical standards. Therefore, the suggested items constitute a best practice guideline.

The following five principles<sup>6</sup> for the custodianship of bio-specimen repositories and data, constitute the common premise for the Charter:

- Respect for privacy and autonomy: custodianship implies protection of participants' privacy. Privacy protection measures should be in place and informed consent must provide provisions for future as yet unspecified research using data and bio-specimens.
- Reciprocity: custodianship also implies giving back. Feedback of general results should be channelled to institutions and patients.
- Freedom of scientific enquiry: custodianship should encourage openness of scientific enquiry, and should maximize data and bio-specimen use and sharing so as to exploit their full potential to promote health.
- Attribution: the intellectual investment of investigators involved in the creation of data registries and bio-repositories is often substantial, and could be acknowledged by mutual agreement.
- Respect for intellectual property: the sharing of data and bio-specimens needs to protect proprietary information and address the requirements of institutions and third-party funders.

As described by Knoppers *et al*,<sup>7</sup> the sharing of personal data is a form of data processing, in accordance with the EU directive 95/46/EC on personal data protection. The processing of personal data requires authorization from a data protection authority or an ethics review board, unless directly permitted by law. Health-related personal data are classified as sensitive, implying that confidentiality laws apply and that processing requires consent from the data subject or permission

by law (on consent, see below). Different types of data are associated with different degrees of intellectual investment by the researchers, which should be reflected in sharing agreements. The sharing and integration of data across research groups and national borders implies that data (and metadata) must be sufficiently equivalent. As suggested by the DataSHaPER platform for harmonizing data collection in epidemiological research, the level of equivalence with regard to primary information collected (eg, serum cholesterol level) and qualifying factors that may affect the interpretation of data (eg, whether the subject had been fasting before measurement) is likely to be context- or consortium specific.<sup>8</sup> Issues about the quality of data accordingly have to be separately addressed by each party before sharing and being described in an MTA/DTA.

Wherever possible, the complete anonymization of data and bio-specimens should be avoided, based on the principle that this would make it impossible to add relevant data as science progresses, and precludes re-contacting donors and data subjects to communicate future medical discoveries that may benefit them.<sup>9</sup> This also reflects RD patients' views on the need to optimize data value in order to seek results for patients and for the benefit of the broader community. Similar considerations and issues concerning the anonymization of data in large cohort population databases and biobanks have been expressed more recently, and form an integral part of the consensus being developed internationally;<sup>10,11</sup> for a discussion, see also.<sup>12–15</sup> Donors of bio-specimens and data should therefore be informed that confidentiality will be taken seriously with the help of strict coding measures, as described below, but that there is no guarantee of complete anonymity because of the nature of the research and advances in technology.

At the time of the collection of data and bio-specimens, their future specific use may be difficult to anticipate or may only be described in very broad general terms, for example, for cancer research, RD research or medical research. The question about the acceptability of broad consent<sup>16,17</sup> has been deeply debated in the ethics and legal literature,<sup>13–15,18–20</sup> and there is some consensus on its acceptability<sup>21,22</sup> provided proper on-going ethical and legal oversight are in place (approval by ethics review boards for every single project is mandatory).

The need to re-contact and involve patients in research though, may also lead to the development of patient centric approaches to consent that provide a dynamic interaction. A number of patient centric consent strategies exploiting online technologies have been developed to help address the limits of a pure broad consent approach. Obviously longitudinal population projects are in constant contact with their participants but dynamic consent models<sup>14,15,22</sup> offer an alternative way to overcome the tension between broad and specific consent also in non-longitudinal research such as clinical trials, by ensuring on-going information and participant involvement after general consent has been provided at the time of bio-specimens collection. Different research platforms and legal frameworks may require more detailed consent, but for the sharing procedures related to prospective sampling and data acquisition we propose and outline a minimal requirement strategy. Therefore, we further propose that templates for informed consent in research projects of an epidemiological character can be accepted if based on the notion of broadly described purposes for future research, provided this is subject to ethics approval and supported by a policy of regular updates to donors and a clear option to withdraw. In fact, even when the purpose is described only in general or broad terms, information regarding the process of research may be specific on the relevant issues, for example, that the research project implies the sharing of data across research groups and national

borders, that complementary information may be added through linkage to different registries' medical records, that it involves genetic analyses and collaboration with both academic and commercial partners, whether or not there is any provision for return of research findings, etc. So to overcome the lack of detailed research information at the time of consent, we suggest an integrated approach entailing broad consent coupled with provision of on-going information about the general development of project, for instance by proper communication with the participants/donors through email, phone, a newsletter, patient organizations contacts and regular website updates dedicated to them.<sup>22</sup>

A sizeable number of samples currently exist in clinical biobanks as well as patient data registries for which there is little or no expressed consent for research, data/material sharing to other groups especially industry, or where the scope of the consent may be unclear. These samples may have been collected at a time when research ethics had not been developed to the standard they are now. In RD, there may not be an opportunity to obtain an equivalent sample or data set for research. Rules and recommendations regarding information and consent procedures need to take into account the complexity of patient perceptions as well as the different characteristics of different cohorts and collections.<sup>23,24</sup>

In order for researchers to be able to share samples and data of this kind, a common framework of how to manage informed consent concerns is needed. Legal frameworks may differ between countries making it possible in some countries to use archived samples and data without explicit consent, while researchers in other countries are obliged to obtain new consent. However, this does not necessarily constitute an obstacle for sharing across borders as each institution needs only to adhere to their national legal requirements on the information and consent procedures in order to satisfy the ethical requirements necessary to send samples and data abroad.<sup>25,26</sup> A recipient in another country can then use them either in a joint venture together with the sender or for MTA regulated projects, even if sampling and acquisition of data is differently regulated in that country, provided the objectives of the research are the same. Approval of these single projects by an ethics review board is always required.

Respect for autonomy, in the sense of having a direct say on how one's samples and data will be used in some cases may involve re-consent where according to the ethics committee the scope of the original consent may preclude the suggested research use. This is particularly relevant where the development of new techniques could not have been anticipated when the samples were first collected. Although ethics review is always requested for every single project, a general requirement to obtain new informed consent in all cases may be impractical and would also involve a potential for selection bias because of drop outs, decreasing the scientific value of the data and the sample collection.<sup>27,28</sup> The potential psychological impact on the research participants of re-contacting and re-consenting should be considered, although neglecting to inform patients on this basis should never be the default position and should be carefully evaluated in order to avoid paternalistic approaches.<sup>14</sup> RD research may be particularly vulnerable to selection bias because the number of available samples and data are intrinsically low for each condition, ultimately jeopardizing research, which is in the interests of all parties. However, careful consideration of the time, effort and other resources required to adequately re-consent patients should be given, as low numbers of patient research participants may also result in benefits of re-consent with low drop-out rates. The actual balance and trade-off between respect for autonomy and optimizing provision of new

treatment opportunities should be sensitive to and recognize the needs of the RD community and the wider public.

Where legal provisions requiring informed consent were in place at the time of sample/data collection, re-consent or notification with an opt-out option, should be pursued. A clear distinction should be made between collections in which a previous consent was obtained and where a question was not asked, and one where a patient actively declined an option or in which the information provided excluded some options (eg, 'your data will not be shared with any commercial organizations'). In these instances, re-consenting or notification with opt-out should be also pursued. For some older cohorts, the researcher may still find re-consent achievable within reasonable efforts, using this also as an opportunity to update or collect new data. Other projects may be particularly vulnerable to drop outs and one may want to use a scheme with notification and opt-out, thus still respecting the autonomy of participants.

Where it is determined that re-contacting patients is unfeasible or when inclusion of small sample numbers from across a large number of collections and registries are of outmost importance or when samples are held in older collections, an acceptable option could be a waiver on re-consent. This option is not feasible in every legal system and requires an adequate assessment of the reasons for asking for a waiver to the ethics review board. Optional re-consent as well as notification with an opt-out clause or general waiver of re-consent for specific cases may create some efficiencies and still maintain ethically responsible and practical ways to access samples an data spread across many sites globally. Where a waiver for re-consent is required, a careful explanation of the reasons that lead to this solution should be provided to the ethics review board. The permission by the ethics board to use the samples should specifically state the permission to share abroad and foresee genetic analysis where appropriate. The sharing of data and bio-specimens without consent needs to be compliant with the appropriate legal framework.

In the case of bio-specimens and data from minors or collected when the person was a minor, re-consent or notification with opt-out clause should be always pursued. Data and bio-specimens from deceased persons should be anonymized and used with ethics approval. Some legal systems may impose specific restrictions (eg, UK's Human Tissue Act 2004).

Institutions and organizations may have legitimate proprietary interests associated with data collected by researchers.<sup>9</sup> Biobank research infrastructures and data collections require investments and intense labour, and therefore a legitimate institutional interest based on the need to protect local investments exists. There is also another layer of institutional interest: the integrity of a research endeavour that has collected data based on original and promising hypotheses.<sup>29-31</sup> The effective dissemination of research results is thus associated with established criteria for acknowledging intellectual contributions and originality through rules of authorship and intellectual property rights. Custodianship implies the duty of recognizing the role of research institutions and their legal and ethical duties to participants and patients. There is agreement that general aggregated research results should be either on open access databases or at least disseminated to institutions and patients.

With regard to biobanks where the amount of samples may be limited, it is recommended that the samples are used only for studies reviewed by a competent and well-balanced data access committee so as to ensure good scientific quality. This is motivated primarily by ethical concerns for the protection of patient interests of reaping the fruits of their donated samples in terms of truly improved diagnosis and treatment opportunities. Data collections do not face scarcity but

clinical quality registries are dependent on the trust of patients and therefore good communication processes are required to maintain this trust. Also, the submission of new data and reports using clinical registries that are of low scientific quality may jeopardize the trust and willingness of patients to consent and to continuously contribute data. To this end, caretakers of the clinical registry should also be granted a right to assess the quality of an application to acquire data for a study, as a parallel to an intellectual property right, because they have invested both personal intellectual and institutional resources in order to create the registry. They should be the rightful protectors of the integrity of the clinical registry in this sense. In practice, most networks of bio- and data repositories do have some kind of scientific evaluation committee to make these kinds of decisions, and we believe for good reason. The protocols of investigators who request access to clinical registries or biobanks should be vetted by a representative data access committee for scientific quality and the bona fides of applicants should also be authenticated, for example, through checking on their background and institution affiliation with the institution or university signing the MTA/DTA as co-responsible for the scientific integrity of the applicant.

The Charter briefly outlines the guiding principles for data and bio-specimen sharing together with the MTA/DTA that encloses these ethical principles in a template model. The Charter, developed within the framework of international research consortia projects, aims to provide a tool to be used for effective, ethically grounded sharing in the international context.

## CHARTER OF PRINCIPLES FOR SHARING DATA AND BIO-SPECIMEN

### Guiding principle

1. Sharing data and biological samples (bio-resources) is essential for accelerating biomedical research projects that will provide benefits to current and future patients.

Research conducted through biobanks and registries is more effective if access to sufficient data is granted, and the use of data is maximized through data sharing. Ensuring secure data and sample sharing ethically and legally protects bio-resources, as well as the donors and all the partners involved in research.

### Sharing data and bio-specimens

2. DTA/(MTA: DTAs and MTAs should always be used to govern data/material transfer between parties.

DTAs and MTAs are legal contracts that help ensure that the parties signing the agreement will comply with a set of rules defined by the involved parties. These documents state the scope of the use of data or bio-specimens, the limits posed by the informed consent used for the original collection, special limitations, duration of sharing and use, and other special conditions including donors' expectations, etc.

### Security and privacy regulations

3. Data and bio-specimens shall always be collected, stored and exchanged in a secure manner, through secure channels. Double coding and encryption are highly recommended for data handling. The type of data and bio-specimens provided to researchers should be described clearly in the DTA or MTA.

4. Data sharing should only occur when proper ethics review board approvals are in place (approval for the collection of the materials and approval for the single research projects).

5. Anonymization of data and bio-resources should generally be avoided because it will make it impossible to add individual-level data

as science progresses, and precludes re-contacting donors to communicate future medical discoveries that may benefit them.

6. Donors should be informed that the confidentiality of their information will be protected through secure technology and strict coding measures, but that there is no guarantee of complete confidentiality because of the evolving variety of techniques and technology advances in genome and gene sequencing that may lead to the potential identification of the individual.

7. Sharing occurring in international contexts should ensure that fundamental privacy interests are respected. The processing of personal data abroad requires authorization from a data inspection authority or by duly authorized institutional review board (IRB) unless directly permitted by law (general authorizations).

The European Medicines Agency has recommended a strict nomenclature, which we have adapted here with regard to both bio-specimen and data (Hansson<sup>31</sup>):

- Identified data and bio-specimens: data labelled or linked to the individual in a way that makes them directly identifiable (name and surname or social security numbers).
- Coded data (may be single or double coded): personally identifying information is removed from data and bio-specimens and replaced with a code. In the case of double-coding, two or more codes are assigned to the same donor's data held in different data sets, with the key connecting the codes back to the donor's direct identifiers held by a third party and not available to the researchers.
- Anonymized data and bio-specimens: data and samples that have been identified earlier or coded, but the identification, or the code and the code key have been destroyed, and thus there is no longer any link to the individual.
- Anonymous data and bio-specimens: there are no links to the individual donor, the data and bio-specimens were never associated with identifiers, and the risk of identification of individuals is very low. There may be general descriptions such as 'man, aged 50–55 years, cholesterol level 240 mg per 100 ml.'

For all above-mentioned categories, it is assumed that international and national regulations on access, informed consent, coding and data protection apply.

Health-related personal data are classified as sensitive, implying that data protection and confidentiality laws apply and that processing requires consent from the data subject or legal permission. Data sharing of personal data is a form of data 'processing', in accordance with National and International Regulation such as the EU directive 95/46/EC on personal data protection or in the US, HHS Regulations for the Protection of Human Subjects (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102>) and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, 45 CFR 164.514(b).<sup>2</sup>

### Ensuring the scientific use of data and bio-specimens

8. Without distinction, access and use of data and samples should always be based on the scientific validity, quality and potential of the request. Those who contribute, collect, curate and annotate samples/data, however, should have first rights to publish within a given time period (usually no longer than 1 year).

9. In addition, the identity and bona fide of the requestors should be authenticated. Proper attribution and intellectual property should be accorded as appropriate, and the security of the data and samples should always be ensured.

In recognition of the contribution of the samples and data of patients, research participants and their families, the protocols of those requesting access for use should be vetted for their scientific validity and quality.

#### Acknowledgment of the bio-resources and data providers

10. The sharing of data and bio-specimens should follow criteria for the acknowledgement of intellectual contributions and originality through rules of authorship and intellectual property rights.

Many consider data collections and genomic databases a public good contributing to the improvement of public health, often serving as an incentive for governmental spending. This in itself will motivate the sharing of data and bio-specimens. However, it does not exclude the recognition of the interests of the researchers who have invested a great deal of intellectual effort in establishing the databases, registries and bio-specimen collections. An analogous example is the publication of scientific results, which can also be seen as instrumental to public health. However, unlike the sharing of data and bio-specimens, the dissemination of research results is associated with established criteria for the acknowledgement of intellectual contributions and originality through rules of authorship and intellectual property rights. We suggest five categories that should reflect different ladders of merit and following levels of recognition as proposed in the table below:

- Data included in official governmental administrative databases

These sets of data should be available for research. As they are created for public interest they should not lead to authorship or special recognition.

- Data from health quality registries organized by researchers/clinicians

These registries are normally organized within the national health-care systems and should in principle be publicly available for research. However, there is often a dedicated group of doctors/researchers who invest intellectual as well as material resources in collecting and systematizing data. This should be recognized in the acknowledgements of an article that builds on the collected data but not lead to authorship. There may be a fee-for-service for providing access to the data.

- Descriptive data directly accessible through health records or available instruments

These data should in principle be openly available with due reference to the original source of the instrument. Some instruments are also made publicly available for a fee.

- Hypothesis-generated data and bio-specimens collection available after screening or within a specific project, or processed data

Should in principle be available, but the principal investigator (PI) and researchers in the project should have time to explore and confirm preliminary findings. There may be a fee for service for providing access to the data. Normally, the conditions for the sharing of data should be part of the original agreement with the funder and be subject to the review process of the scientific journals. Requests for data and bio-specimens could include an offer of co-authorship to the PI when significant contribution to

the acquisition, analysis or interpretation of data is made and acknowledgements to the consortium or the biobank.

- Processed data: for example, GWAS data, omics data, whole-genome sequence data

The processing of bio-specimens to obtain data is a considerable investment by the institution and reflects a significant contribution to the acquisition, analysis and interpretation of data. Therefore, requests for data and bio-specimens could include an offer of co-authorship to the PI or the consortium and a note in the acknowledgements.

- Acknowledgement for biobanks/data providers

Biobanks are infrastructure created with the purpose of providing data and bio-specimens for research purposes. Authorship may not be a proper recognition mean. A recommended way to recognize the role of the data/bio-specimen provider is through the emerging bio-resource research impact factor (BRIF). As described by P3G, BRIF is 'a tool to calculate the research impact of bio-resources based on a unique digital resource identifier and on a metrics algorithm somewhat analogous to the journal impact factor.' Further information on BRIF can be found on the P3G website at <http://www.p3g.org/brif-bioshare-pilot-study>.

The kind of acknowledgment foreseen for the use of bio-resources and data should be clearly defined. For all categories, it is assumed that European and national regulations on access, informed consent, coding and data protection apply.

It is recommended in appropriate cases that when data from a common database is analysed, the results should be fed back to the common database. In order to recognize intellectual contributions, the researcher/research group who carried out the analyses should be entitled to a period of exclusivity of use of the results in order to explore their potential. Following the tradition of a 'grace period' in association with balancing publication interests versus investigating patentability, 6 months to 1 year of such exclusive use should be usually granted.

#### Quality of data and bio-specimens

11. Quality of data and bio-specimens must be ensured by the provider.

The quality of data and bio-specimens must be ensured in accordance with international standards. The integration of data across research groups and national borders implies that data must be sufficiently equivalent. As suggested by the DataSHaPER platform for harmonizing data collection in epidemiological research, the level of equivalence with regard to primary information collected (eg, serum cholesterol level) and qualifying factors that may affect the interpretation of data (eg, whether the subject had been fasting before measurement) is likely to be context- or consortium specific. Accordingly, issues concerning the quality of data have to be sorted out separately by each consortium before sharing.

#### Informed consent

12. Informed consent: informed consent to the general scope of the research project is mandatory. If broad consent is used, regular updates on the development and the aggregated results of the project/biobank are recommended, as they serve as reminders of on-going participation and keep the participants involved. Informed consent should also offer the clear option for the participant to

withdraw from the research. Ongoing ethics oversight by proper review or ethics review boards is recommended.

At the time of data and sample collection, future research use may be difficult to anticipate or may only be describable in very broad general terms, for example, for 'cancer research', 'rare disease research' or 'medical research'. Therefore, broad consent with ethics approval, with the right to withdraw from the study, is acceptable if there is a continuous flow of information on project developments. We therefore suggest that templates for informed consent in research projects of an epidemiological character may be based on broad consent if they are supported by a commitment by the PI/project to provide regular updates in a timely and sufficiently comprehensive manner. Information especially relevant for data sharing should be disclosed in the information sheets.

In the information provided, it should be clearly specified whether or not:

- the research project reasonably anticipates the sharing of data across research groups and national borders.
- complementary information may be added through linkage to different data registries, medical records, etc.
- the project involves genetic analyses.
- the project involves collaboration with both academic and commercial partners.

Participants should be allowed to have some options to express choices, or at least be provided clear information on the policy for return of incidental findings, the destination of data and bio-specimens after death or in the case of the termination of the project, and the involvement of relatives in research. A description of the communication of information strategy flowing from the project should be provided, and should include the general development of project timelines and newsletters or website updates dedicated to the donors.

#### Use of previously collected data and samples

13. For the use of previously collected data and bio-specimen where consent is absent or not fit for purpose, we recommend a case by case assessment by an ethics board. According to national legal requirements, either re-consent or a notification with opt-out schemes should be required in order to enable the institution to use and share internationally. This is especially important where minors (at the time of the collection) are involved. In some cases – where re-contact of patients is unfeasible and disproportionate to benefits (very old collections) – a waiver for re-consent can be granted by an ethics review board (please refer to national legal requirements). In this case, a clear outline of the reasons for requiring the waiver should be provided to the ethics board. A clear distinction should be made between collections in which a previous consent was obtained and where a question was not asked – and – one where a patient actively declined some options, for which re-consent is required.

#### Return of results to sharing partner institutions

14. Any agreement on sharing should regulate:

- Return of results significant for individuals that provided the bio-materials (the source institution remains responsible for that).
- Return of aggregated or other types of results to the source biobank/database.

Results from research may have a specific value for public health and individual health. Custodianship implies recognizing the role of research institutions and their legal and ethical duties to participants and patients. There is also agreement that aggregated research results should be disseminated to institutions and patients; regardless of the kind of policy of return of results adopted, these should be made explicit. Short reports should be provided by the research team to the data providers (institutions, biobanks) in order to ensure awareness of results relevant to their collections or to the donors. These reports may contain a publication list and relevant results important for further research developments or directly relevant to donors.

#### Intellectual property

15. The sharing of data and bio-resources must be done in a way that protects proprietary information and addresses the interests of institutions and third-party funders. These parties may have legitimate proprietary interests associated with data collected by researchers.

The intellectual investment of investigators involved in the creation and maintenance of data registries and bio-repositories is often substantial, and should be appropriately acknowledged.

#### MTA/DTA TEMPLATE

##### Mutual agreement between provider and recipient

Provider of data.....

Recipient of data..... (This must be an institution officially registered by national/regional authorities.)

MTA/DTA must be signed before any exchange takes place

1. *Provider.* Provider..... hereby declares that:

The (name country) ..... from which the human biological material is collected has a legal and ethical framework providing a high level of quality, security and privacy protection concerning medical research involving human biological material; and that health data exchange is in accordance with local regulation (please note that some regulations, such as those from the EU, require compliance with their rules even if the research is conducted abroad).

Data/bio-specimens provided consist of the following: ..... (description including type of material and type of data: primary data and which type, genotypes, aggregate data, etc.)

The bio-specimens provided refer to .... (no. of individuals) and are composed of ..... (no. of tubes and quantity of material referred to the scope).

The material will be de-identified, stripped of all personally identifying information, without any direct means of identification. Bio-specimens will be double-coded (no direct identifier shall be on the tubes).

To ensure the confidentiality and security of the associated data, transfer and processing will be handled safely and associated data will not be transported together with bio-specimens.

To ensure traceability of the material to be de-identified, a code will be applied to the tubes. The mechanism to re-identify the data will remain with the provider.

To ensure exchange and transport security, biosafety (packaging, labelling description of transport means and insurance for bio-specimens) will be observed.

The project from which the data and bio-specimens were collected was approved by a local ethics committee or IRB.

Informed consent for storage and distribution was obtained (enclose a copy of the model in use), and that:

- the informed consent contained the clause necessary for allowing bio-specimens and data sharing abroad (in case of an international project).
- the informed consent allowed the research described in the project description section.

2. *Recipient.* Recipient..... hereby declares that:

- the data will be used solely for the scope of the project described below, and no attempt will be made to sell the data/material or share it with a third party. The data/samples will be used for the following purpose: (description of the biomedical research project of the Recipient (or of the joint project): .....(aims should be clear, including the duration of the project.....)
- authorization from the local ethics review committee or IRB .....(date and copy enclosed).
- when consented to, will ensure the return of results relevant to the health of individuals ..... and .....(description of the type of data that must be returned).
- will not harm the persons who provided bio-specimens by naming the provenience of the bio-specimens unless approved by the Provider.

3. *Terms and conditions (for Recipient).* Conditions of use include:

- no attempt to re-identify the participants
- adherence to use limitations stated in approved application
- no third-party data or sample sharing/selling without authorization from Provider
- primary data must not be patented
- that the use of the material has, for example, medical/public health objectives
- informing the resource of issues related to data integrity and/or the privacy of the participants as applicable
- compliance with original consents and applicable laws and institutional policies
- access granted for a limited time period (eg, 6 months or .....), after which Recipient must reapply.

Documents to be provided by the recipient institution:

1. Authorization from a local ethics committee or a regional or local competent authority for the project for which the data are provided (by Recipient or, in the case of a joint project, by both parties).
2. Documents by the national data protection authority that reference the applicable laws that allow research using sensitive and health data, including genetic data.

4. *Receipt and handling of imported biological material.* The Recipient must document and follow the procedures for the receipt and proper storage of the type of biological material handled.

Provider has to prepare and ship the biological material in accordance with postal regulations, such as IATA (International Air Transport Association) and ADR (European Agreement on International Carriage of Dangerous Goods).

5. *Publication.* Prior review of publications before submission may be required (eg, to ensure the privacy/confidentiality of data and that the results will not cause stigmatization). Recipients should acknowledge the biobank/data provider in any publication/presentation (or other clauses).

6. *Is the material used to be returned or destroyed?* Recipient will comply with the destruction/return of unused bio-specimens and of data related to the bio-specimens at the end of the project or of the duration stated above

Description of the requirement (destruction/return).....

7. *Intellectual property rights.* (Requires a specific agreement case by case. See general Introduction).....

8. *Who controls the data/bio-specimens in the resource?* Control of the bio-specimens remains with Provider, who can at any time demand the return or destruction of data and bio-specimens if a breach in the agreement occurs.

9. *Obligation to report.* Annual..... (or other) and final reports to Provider are required. Reports should include ..... (specify required content).

10. *Responsibilities of the biobank/consortia.* Biobanks and research consortia have the right to terminate/alter this agreement with the researcher/institution, for the safety of the patients/participants or because of any infringements of the obligations stated in the present DTA/MTA. The Recipient understands and agrees that Provider does not bear any responsibility or accept any liability arising from the Recipient's use of the data or bio-specimens.

Time, place and signatures of the persons legally responsible for the institutions involved.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

We thank the RD Connect Patient Ethics Council and RD Connect Patient Advisory Council (Jean Jacques Cassiman, Tracy Dudding, Muriel Gevrey, Emma Heslop, Joseph Irwin, Julian Isla, Sigurður Jóhannesson, Lydia Lemonnier, Chantal Loirat, Dorthe Lykke, Milan Macek, Caron Molster, Kay Parkinson, Odile Perrousseau, Marita Pohlschmidt, Daniel Renault, Peter Reussner, Françoise Rouault, Balthasar Schaap, Inge Schwersenz, Chris Sotirelis, Volker Straub, Oliver Timmis, Johannes van Delden, Marieke van Meel, Elizabeth Vroom, Urban Wiesing) and all RD-connect partners for their valuable inputs. This work has been supported by the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreements no. 305444 (RD-Connect), 305121 (Neuromics), and no. 305608 (EUREnOmics) and RD Connect from the Australian National Health and Medical Research Council APP1055319 under the NHMRC-European Union Collaborative Research Grants scheme'. In addition, DM and MH have received funding from the Innovative Medicines Initiative project BTCure (grant agreement no. 115142-1), the BioBanking and Molecular Resource Infrastructure of Sweden project (financed by the Swedish Research Council), Euro-TEAM, BiobankCloud, BioSHaRE and Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)LPC (313010). BMK and ESD wish to thank the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Quebec Breast Cancer Foundation, and the Ministère de l'enseignement supérieur, de la recherche, de la science et de la technologie du Québec through Génome Québec. The funders had no influence on the design or the writing of the article.

- 1 Global Alliance White Paper. <http://oicr.on.ca/oicr-programs-and-platforms/global-alliance/white-paper>.
- 2 OECD principles and guidelines for access to research data from public funding. <http://www.oecd.org/dataoecd/9/61/38500813.pdf>.
- 3 Birney, Prepublication data sharing, Toronto International Data Release, *Nature* **461**: 168–170.
- 4 European Council (EC 2009/c 151/02) Council recommendation on an action in the field of rare Diseases 2009.
- 5 Knoppers BM, Chisholm M, Kaye J *et al*. A P3G generic access agreement for population genomic studies. *Nat Biotechnol* **31**: 384–385.
- 6 Ness RB. on behalf of the American College of Epidemiology Policy Committee: biospecimen “ownership”: point. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 188–189.
- 7 Knoppers BM, Harris JR, Tassé AM, Budin-Ljøsne I, Kaye J, Deschênes M, Zawati MH: Towards a data sharing Code of Conduct for international genomic research. *Genome Med* 2011; **3**: 46.
- 8 Fortier I, Burton PR, Robson PJ *et al*: Quality, quantity and harmony: the DataSHaPER approach to integrating data across bioclinical studies. *Int J Epidemiol* 2010; **1**–11.
- 9 O'Brien SJ: Stewardship of human bio-specimens, DNA, genotype, and clinical data in the GWAS era. *Annu Rev Genomics Hum Genet* 2009; **10**: 193–209.
- 10 McGuire A, Gibbs RA: No longer de-identified. *Science* 2006; **312**: 370–371.
- 11 Gymrek M *et al*: Identifying personal genomes by surname inference. *Science* 2013; **339**: 321.
- 12 Hansson MG, Gattorno M, Stjernschantz Forsberg J, Feltelius N, Martini A, Ruperto N: Ethics bureaucracy – a significant hurdle for collaborative follow-up of drug effectiveness in rare childhood diseases. *Arch Dis Childhood* 2012; **97**: 561–563.
- 13 Kaye J: Broad consent is informed consent. *BMJ* 2011; **343**.
- 14 Kaye J: From patients to partners: participant-centric initiatives in biomedical research. *Nat Rev Genet* 2012; **13**: 371–376.
- 15 Kaye J: The tension between data sharing and the protection of privacy in genomics research. *Annu Rev Genomics Hum Genet* 2012; **13**: 415–431.
- 16 Lunshof JE, Chadwick R, Vorhaus DB, Church GM: From genetic privacy to open consent. *Nat Rev Genet* 2008; **9**: 406–411.
- 17 Hansson MG, Dillner J, Bartram CR, Carlsson J, Helgesson G: Should donors be allowed to give broad consent to future biobank research? *Lancet Oncol* 2006; **7**: 266–269.
- 18 Caulfield T: Biobanks and blanket consent: the proper place of the public good and public perception rationales. *Kings Law J* 2007; **18**: 209–226.
- 19 Arnason V: Coding and consent: moral challenges of the database project in Iceland. *Bioethics* 2004; **18**: 27–49.
- 20 Mascalzoni D, Hicks A, Pramstaller P, Wjst M: Informed consent in the genomics era. *PLoS Med* 2008; **5**: e192.
- 21 Sheehan M, Martin J: Can broad consent be informed consent? *Public Health Ethics* 2011; **4**: 226–235.
- 22 Mascalzoni D, Paradiso A, Hansson M: Rare disease research: breaking the privacy barrier. *Appl Translational Genomics* 2014; **3**: 23–29.
- 23 Hoeyer K: Donors perceptions of consent to and feedback from biobank research: time to acknowledge diversity. *Public Health Genomics* 2010; **13**: 345–352.
- 24 Steinsbekk KS, Solberg B: Biobanks – when is re-consent necessary? *Public Health Ethics* 2011; **4**: 236–250.
- 25 Budin-Ljøsne I, Tassé AM, Knoppers BM, Harris JR: Bridging consent: from toll bridges to lift bridges? *BMC Med Genomics* 2011; **4**: 69.
- 26 Van Veen EB *et al*: TuBaFrost 3: regulatory and ethical issues on the exchange of residual tissue for research across Europe. *Eur J Cancer* 2006; **42**: 2914–2923.
- 27 Kaijser M: Examples from Swedish biobank research; in: Levin M, Hansson MG (eds.): *Biobanks as Resources for Health*. Uppsala: Uppsala University, 2003, pp 33–50, may be downloaded at [www.crb.uu.se](http://www.crb.uu.se).
- 28 Helgesson G, Dillner J, Carlsson J, Bartram CR, Hansson MG: Ethical framework for previously collected biobank samples. *Nat Biotech* 2007; **25**: 973–975.
- 29 Shamoo AE, Resnik DB: *Responsible Conduct of Research*. 2nd edn. New York: Oxford University Press, 2009.
- 30 Hansson MG, Simonsson B, Feltelius N, Stjernschantz Forsberg J, Hasford J: Medical registries represent vital patient interests and should not be dismantled by stricter regulation. *Cancer Epidemiol* 2012; **36**: 575–578.
- 31 Hansson MG: Ethics and biobanks. *Br J Cancer* 2009; **100**: 8–12.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 3.0 Unported License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/3.0/>