A Role for Research Ethics Committees in Exchanges of Human Biospecimens through Material Transfer Agreements?

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Abstract

International transfers of human biological material (biospecimens) and data are increasing, and commentators are starting to raise concerns about how donor wishes are protected in such circumstances. These exchanges are generally made under contractual Material Transfer Agreements (MTAs). The paper asks what role, if any, should research ethics committees (RECs) play in ensuring legal and ethical conduct in such exchanges. It is recommended that RECs should play a more active role in the future development of best practice MTAs involving exchange of biospecimens and data and in monitoring compliance.

1. Introduction

The global nature of modern genomic and biomedical research requires that biological materials and data are exchanged between researchers, both within and between countries. These exchanges are generally made under contractual Material Transfer Agreements (MTAs). Like other contracts, parties to an MTA are at liberty to include terms negotiated between them, subject to national contract laws, consumer protection laws and other relevant laws aimed at protecting the public interest. However, the parties to an MTA are not the general public, but rather they are universities, specialized research organisations and commercial companies. The materials exchanged are also specialized, ranging from plant germplasm to human biological materials (biospecimens). As a consequence, the parties to MTAs are also likely to be subject to ethical guidelines and funding obligations as well as specific laws relating to the materials (these might include, for example, prohibitions on transfers of human tissue or noxious microorganisms, plants or animals). The ethical dimensions of MTAs are particularly pronounced in the exchange of biospecimens, because of the centrality of consent and privacy. Additional complications arise when the MTA involves exchanges of biospecimens and data between jurisdictions, as questions arise as to which laws and ethical guidelines apply and how they are enforced.

This paper examines the governance framework for collection, storage and use of biospecimens for research purposes, with particular focus on the transfer of biospecimens internationally. The paper poses the following question: what role, if any, should research ethics committees (RECs) play in ensuring legal and ethical conduct in research use of biospecimens and associated data exchanged through MTAs? In particular, the paper asks how the interests of donors and the terms of the donor's consent are properly taken into account and protected in the MTA and subsequent use of the tissue. This paper argues that the oversight role for RECs in relation to MTAs should be expanded to ensure that exchanges of biospecimens and data between countries satisfy internationally recognized best practice standards. Spain and Australia are used as exemplars in discussing how the complications of exchanges between jurisdictions might be resolved. The reason for this choice is that both countries are active in biospecimen research, have well established research ethics review frameworks and together they represent the civil law and common law traditions. It also allows the authors to draw on their own expertise.

2. The Use of Material Transfer Agreements in Exchange of Biospecimens and Data: Towards Standardisation

Traditionally, biological materials have been freely exchanged between researchers, frequently without any legal documentation (Bennett, Streitz, and Gaecel 2007). The 1980s saw increasing engagement between universities and industry and the development of strategies aimed to commercialise the outcomes of research (Rodriguez 2007). These increased activities saw the emergence of more formalisation in the exchange of biological materials with the use of MTAs (Streitz and Bennett 2003). This trend towards formalisation of exchanges of biological materials also reflected increased concerns about their biosafety and provenance (Peel 2005). For example, in Australia, the National Health and Medical Research Council (NHMRC) has stated that MTAs "…are an important mechanism for ensuring traceability of biospecimens and data, and transparency and accountability on the part of biobanks and their users" (NHMRC 2010, 46). Similarly, traceability to the donor and accurate labeling to ensure the proper use of blood and blood products were the major considerations in the decision by the Australian Red Cross Blood Service to use MTAs.

The International Society for Biological and Environmental Repositories (ISBER) defines an MTA as: "a contract that governs the transfer of tangible research materials [including biospecimens] between two organizations, a provider and a recipient, when the recipient intends to use it for his or her own research purposes. The MTA defines the rights of the provider and the recipient with respect to the materials and any derivatives" (ISBER 2012, 147). Given the contractual nature of MTAs, the parties negotiating them are generally free to establish and agree on the terms that will be legally enforceable between them. However, like other areas of contract law, MTAs have become standardised for reasons of efficiency. International agencies provide some guidance as to the terms that should generally be included in MTAs transferring biological materials. For example, ISBER, in promoting uniform best practice standards, lists the common terms that MTAs for the transfer of specimens and data "should address" (ISBER 2012, 147-148).

3. Special Considerations relating to the Exchange of Human Biospecimens and Data

When biospecimens and associated data are collected for research, an essential part of the consent process requires that donors be given information and assurances that their biospecimens will be used in accordance with national ethical guidelines. It is a universal ethical principle that donors should be asked for consent to the collection and use of their biospecimens and data, as specified in Articles 8, 16 and 17 of the UNESCO *International Declaration on Human Genetic Data 2003*. This consent must be given freely and after sufficient information has been provided to the donor. On this basis, if international transfer of biospecimens and data is anticipated at the time of collection, consent should have been given with the full knowledge of this possibility.

Traditional notions of consent to research use of biospecimens are being challenged by the establishment of large-scale biobank repositories, which store collections of biospecimens and data for future research projects, many of which would not have been designed or planned when donors consented to the collection and storage of their biospecimens (NHMRC, 2010). Whilst re-consent from every donor each time their biospecimen is used in a research project may be best practice from the ethical perspective, this is likely to be both impracticable and undesirable from the perspectives of the donor and the researcher. Rather, broad consent to future unspecified research is becoming the internationally accepted norm (Hansson et al 2006). For example, in both Spain and Australia it is possible to give broad consent to unspecified use of biospecimens and data (Romeo, Nicolás and Romeo 2011; Chalmers and Nicol 2008). Some consent documents are more specific, allowing donors to specify that any research using their biospecimens and data must be related to their disease. In these models, donors delegate authority to an REC to act on their behalf. In the alternative, in some instances a tiered approach is employed, allowing people to make a selection from a range of options. Participant-centric initiatives have also been proposed, including one suggestion for a “dynamic” consent model using modern technology, like tablet computers (Kaye et al 2012; Kristin, Bjørn Kåre, and Berge 2013). The dynamic model allows research participants to monitor and make ongoing decisions about how their biospecimens and data are used.

The ethical consent requirements, both generally and for biospecimens and data in particular, are framed in terms of a right to informational self-determination, which implies the capacity to control one's personal information. This right is expressed as an individual's right to know about information concerning them, how it has been obtained and how it is being used by others. This right also extends to the right not to know information concerning them. Article 13 of the UNESCO *International Declaration on Human Genetic Data 2003* states that no one should be denied access to his or her own genetic data.

Some countries explicitly recognise this right to self-determination. In Spain, for example, this right allows citizens to apply for access to their personal data and creates a duty to communicate by the data custodian, as provided in the European Data Protection Directive (Directive 95/46/EC). This right requires biospecimen donors to be informed about the potential uses of their genetic data prior to the consent. Donors must also be asked whether or not they wish to be recontacted about research findings that may be relevant to them or their family. Although there is no explicitly enforceable right to self-determination in Australia, section 3.5.1 of the *National Statement on Ethical Conduct in Human Research* (National Statement: NHMRC 2007a) requires researchers to establish an "ethically defensible plan" when applying to do research using biospecimens and associated data with respect to whether they would disclose individually relevant data. However, whether individually relevant results should be given to a person has to be determined for each new study, by the specific context of the research.

It is difficult to ensure that donor wishes are respected when biospecimens and data are transferred between countries for research purposes, particularly where there are differences in laws and ethical guidelines. This may be problematic with regard to donor access to personal data or recontacting of donors when relevant data are found. In some jurisdictions, including both Australia and Spain, it is ethically acceptable to tell potential donors that they will not be recontacted if there are uncertainties about clinical and/or analytical validity. It has been argued more broadly that it may be ethically permissible not to return individual results on the basis that they may be of uncertain relevance and accuracy, particularly when it is difficult and costly to do so (Bledsoe et al 2012). It would be more problematic, however, to justify such a denial when a donor specifically requests access their personal data (Kaye et al 2013). These

issues need to be considered with some sensitivity when executing MTAs. The same can be said about the effect of the right to withdraw consent or to have stored personal data removed.

4. The Role of Research Ethics Committees in the Exchange of Biospecimens and Data Internationally

As a general rule, MTAs will be signed and executed by institutions rather than individual researchers, and issues relating to the legal enforceability of their terms will be considered by the institution's legal team. However, compliance with national and international ethical standards demands that the institution's REC should also play a role in ensuring the adequacy of the ethical review processes relating to the biospecimens and data. There are two components to these ethical review processes where stored biospecimens and data are made available to other researchers: first, prior ethical approval must have been sought to collection, storage, transfer and research use of the biospecimens and data; and secondly, further ethical approval must be sought for all proposed future research using the biospecimens and data. As noted, these ethical obligations become more complicated when biospecimens and data are transferred between jurisdictions.

The difficulties arising from international exchanges are illustrated in the following case study. Consider a collection of biospecimens and associated data stored in a biobank in Australia for unspecified broad research purposes. In accordance with the initial ethical approval process, the relevant REC may stipulate a condition that the biospecimens and data will only be used for ethically approved research in accordance with Australian standards. A Spanish research team applies to the Australian biobank to use the biospecimens and data for genetic profiling. To release the biospecimens, the Australian biobank must demonstrate compliance with Australian ethical requirements, and, on this basis, the Spanish researchers will need to apply to an Australian REC for approval of their research project. However, this will not be enough, as Spanish ethical guidelines require that the Spanish researchers must also obtain approval from a local (Spanish) REC to carry out their research. This ethical review must be done in the light of any further local restrictions or requirements that the research team must comply with. Furthermore, Article 31 of the Spanish *Royal Decree on Biobanks* prescribes that biospecimens from other countries can only be used for scientific research when they have been collected, stored and

transferred with the same guarantees that are required by the Spanish law (Ministerio de Economía y Competitividad 2011). Similar requirements would apply when Australian researchers seek to use biospecimens and data collected in Spain. In seeking approval from a local Australian REC to undertake the research project, Section 3.4.13-3.4.15 of the National Statement requires that the researchers must be able to prove that the biospecimens and data were obtained under ethical standards equal to those in Australia. However, neither REC reviewing these considerations currently communicates with the other, and there is often no awareness of local requirements of the other REC.

In practice this presents quite an onerous set of requirements, if all of the rules and processes in one country have to be reviewed by the REC in the other country. While trust between RECs or appropriate authorities in different jurisdictions is essential, it will not be not sufficient to comply with national requirements. There is currently no international consensus regarding the criteria for recognising the decisions of RECs in foreign jurisdictions, nor setting common minimum standards in this sense. In Spain, RECs are accredited by a public authority (the regional government). Until recently in Australia, RECs were only required to notify the NHMRC that they had been created. However, recent changes bring Australia more in line with the Spanish situation since RECs may now be certified by the NHMRC. Further, the *Australian Code for the Responsible Conduct of Research* (NHMRC, 2007b) makes compliance with any ethical requirements mandatory, and sanctions such as withholding federal funding from the researchers or their institution can be imposed for failure to comply. These certification/accreditation rules should enhance trust in Australian ethical review processes by RECs in other jurisdictions. They also should provide assurance to those entering into MTAs for transfer of biospecimens between Australia and other jurisdictions that contractual obligations relating to ethical approvals have been complied with. This is important because once approved, the fulfillment of any requirements imposed by either the exporting or importing REC is the duty of the researchers and their institution.

It is, however, necessary to underline that not every country has national ethical guidelines. Moreover, even where ethical frameworks for research involving humans exist, there are significant differences between jurisdictions. Not all have national accreditation frameworks for RECs or frameworks that meet international best

practice (Van Veen et al 2006; WHO 2011). This lack of consistency and certainty in the standard of ethical review across jurisdictions creates significant problems for biospecimen repositories, researchers and RECs alike, in meeting their legal and ethical obligations. It could also undermine public trust in biomedical research, which may have a detrimental effect on public funding and public participation in that research.

The question that arises is: how can appropriate mechanisms be put in place? One solution is to harmonise the ethical and legal requirements between countries. While this has been attempted in the past with minimal success, efforts should continue in the modern globalised research environment (Chalmers 2011). One option is to establish an agreed set of concrete criteria for meeting internationally recognised best practice standards in the ethical review process. There have already been proposals for international recognition of "safe harbors" of ethics review by RECs that comply with international best practice standards (Dove, Knoppers and Zawati 2013). Review processes that follow these standards may have force in other countries as a kind of "*exequatur*" (a term used in private international law whereby a domestic court authorizes the enforcement of decisions of foreign courts). Exequaturs for RECs decisions could be authorized by national ethics bodies, such as the Australian Health Ethics Committee. Another option is the development of a voluntary mechanism for accreditation of RECs internationally.

The MTA parties could play an important role in the implementation of these mechanisms for recognition of REC decisions in other jurisdictions. The MTA could include standard terms, in addition to the ISBER common terms (ISBER 2012, 147-148), about the acceptability of foreign ethical review processes. Such MTA terms would need to be subject to review by each party's REC to ensure that the internationally agreed criteria, discussed above, are met. Additionally, RECs in each country could have a responsibility to check the conditions of the collection and future use of the biospecimens and data have been met, as well as to ensure that there is an ethical commitment of both two parties to the MTA to respect those conditions. RECs could also be more actively involved in the future development of best practice MTAs involving exchange of biospecimens and data, and in monitoring compliance. If RECs take on this expanded role, it should not be done in an idiosyncratic fashion. Policy decisions should be taken by the relevant national authority, in Australia, for

example, by the Australian Health Ethics Committee. There are inevitable resource implications in imposing additional roles on overworked RECs, which will need to be taken into account. There are likely to be other practical considerations that also need to be factored into any new policy direction.

5. Conclusion

To date, in the regulatory context, legislators and law reform agencies have generally not concerned themselves with MTAs to any great extent. They are considered to fall within the exclusive province of private contract law, involving negotiations between parties of equal bargaining strengths. Given the policy drivers towards open science and public benefit, however, good governance of MTA processes becomes as important as it is for research ethics, release of research results and other aspects of public research.

One significant difficulty relating to international transfers of biospecimens and data is that different countries have different governance frameworks for the collection, transfer and use. RECs should play a more active role in ensuring that legal and ethical principles for the appropriate use of human biospecimens are adhered to, both nationally and in an international context. These requirements extend beyond the physical biospecimens themselves, to data accompanying them or generated from them (for example in international genomic projects). If it is agreed that MTAs can, and should, attest to the validity of these ethical review processes, then we propose that an audit of the regulatory instruments that govern MTAs, including laws, ethical guidelines and institutional policies, is both necessary and overdue.

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