REPORT

The ethics of research on stored biological samples: outcomes of a Workshop

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Abstract

Research is often conducted using laboratory samples and data. The ethical issues that arise in a study involving residual samples are considerably different from those arising in a prospective study. Some of these ethical issues concern the risks to confidentiality, individual autonomy, trust in and credibility of the researcher or the research, commercialisation and even the nomenclature involved.

We conducted a workshop at the 5th National Bioethics Conference, 2014, in Bangalore to address some of these issues. There were 35 participants and 3 moderators from the broad fields of medicine, social sciences, bioethics and law. There was general agreement about the need to obtain the approval of the institutional ethics committee (IEC)for research on stored samples. There was no consensus on when waivers could be allowed. What emerged as the probable solution was the introduction of a form of broad or expanded consent at the time of sample collection primarily allowing for research, which could be referred to the IEC when seeking its approval. Custodianship rather than ownership by the facility housing the stored samples and medical data was suggested. Patents and other legal arrangements were considered the best for monetary benefit-sharing. The special feature of this workshop was to bring together the human and social nuances and the practical and legal angles of this area of great scientific potential.

Introduction

Tissues removed from the human body for diagnostic or therapeutic purposes are often stored for varying durations or destroyed as per the regulatory guidelines governing good laboratory practice (1–3). It is well established that stored samples, along with their linked clinical data, are valuable material for the advancement of medical knowledge and the understanding of disease (4–7). However, the use of stored or "residual" samples and linked data raises several questions for researchers, laboratories and organisations housing such samples and for institutional ethics committee (IEC) members. These are as follows.

1. Do such studies involve human participants or not (sample vs person)? Is the IEC's ethical approval mandatory for such research?
2. Are there are any risks to the individuals whose surplus samples or archived medical records are used for research?
3. In a stored repository, who owns the samples and data? Who makes decisions on their use? Who is responsible?
4. Is informed consent from the contributor of the sample required for such research? Is it always feasible?
5. Can an institution/laboratory/bio-repository transfer or sell the samples or data in its possession to another institution wishing to conduct research on them? What should the policies and ethical norms determining this be?

The ethical differences between research with stored samples and stored medical data versus other types of research

1. In stored sample research, the purpose of research is not always known at the time of the collection of the sample. There is, therefore, (i) atime lag between the collection and storage/subsequent use of the sample for research. Hence, specific consent for research may not have been envisaged (3). There is also (ii) adifference between the purpose of the primary collection and storage (usually diagnostic or for a specific research study, eg a clinical trial) and the secondary or extended uses of samples and linked data for research or new research studies (3,8,9).
2. The scale of participants' involvement versus "non-involvement" is another difference. Since there is no direct contact with the person in research on stored samples, doubts are raised about whether the participant is involved at all and if there is a need to protect participants (10). An analysis of the literature shows that the nomenclature of the person reflects the perspective of the researcher; "participant" seems to reflect an exaggerated involvement, "source" seems impersonal and the dismissive "donor" conveys one-way altruism; however, "contributor" acknowledges and respects the person and the material (8,11).
3. As for the scale of risk/harm to the participant, stemming from the above, it is obvious that there is no direct physical harm to the person as there is no direct contact. However, there are the possible risks of psychological

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harm and also socioeconomic impact based on violations of confidentiality and privacy (3,9,12). There is also the possibility that the test results may be clinically significant and "not intervening", even if only through the communication of a test result, would amount to potentially doing harm (maleficence).

4. Likely transfer of samples/data: To achieve the potential outcome expected, pooling of data and larger sample sizes may be required. With databases being more electronic than physical, the storage facility is, in a sense, virtual and hence, without borders and easily transferable (3,13). The transfer of samples to other research locations may be seen as necessary to better "exploit" samples/data (14). In addition, to sustain the facility of storage and manage resources, collaboration with multiple partners (academic and commercial) across multiple sites occurs. This can be many years after the original collection and is likely not to have been envisaged when drawing up the consent document. The motives of the new sites could be very different from those of the primary site of collection and storage, where the relationship with the contributor was based on trust and credibility (15–18).
5. Potential of commercialisation: Multiple levels of "exploitation" of the sample are possible, as in the case of the "HeLa cell line"resulting from Henrietta Lacks' cervical tumour cells or the 'Mo cell line' resulting from John Moore's cancerous spleen cells (19,20). The questions of who the owner of the material is, who should share the benefits and whose rights need to be protected are what make this area of research different from other research (2,7,20,21).
6. Genetic and genomic studies: Collections of stored biological samples and stored medical data are increasingly being used for genetic research. New concepts such as genetic privacy, genetic confidentiality and "genetic exceptionalism" (arising from the uniqueness of one's genes)give rise to complexities that are greater than in other kinds of research (3,7,22,23). Can a person's identity ever be removed from his genetic material? Therefore, can genetic samples ever be anonymised? The findings of genetic research may have a bearing on not just the individual contributor of the sample but his/her entire family and possibly, the ethnic/racial group he /she comes from (12,21,22). Should the disclosure of the findings to family members be mandatory if they are at risk of disease? Would this compromise the autonomy of the individual (12,24)?
7. Responsibility of storage/access/accountability of stored samples and stored data, including databases: While it is the contributor who is the ultimate "owner" of the sample and the data, the ownership of the responsibility of safeguarding his/her interests varies. In unregulated scenarios in which there is no centralised biobank, the responsibility and gate-keeping functions lie with the original holding department, the individual investigator or the medical records department of the institution. There may or may not be an IEC or a centralised bio-repository ethics committee involved. This raises issues related to the governance of the storage and research facilities and systems of accountability beyond the timeframe of individual projects (6,13,24). The concept of "research governance bodies" is illustrated in the UK Biobank, which is based on the principle of "stewardship" (20,25).
8. In India, an additional problem is the low level of health literacy and the inability of the general public to distinguish between treatment and research even in clinical trials, and the idea of research on removed biological material has not entered public consciousness (26).

The workshop

The objective of the workshop at the National Bioethics Conference, December 2014, was to bring together those dealing with stored samples in departments such as pathology and microbiology, those using stored biological samples and stored medical data for research purposes, and IEC members whose role is to protect the interests of research subjects and to collectively understand the challenges faced by these groups and suggest how best to address these issues. The authors of this paper were the facilitators of the workshop and represented these three categories of people.

The entire workshop lasted two hours. The participants were asked to fill in a proforma on their backgrounds, interests and concerns with the topic. This was followed by a brief overview of the potential of research on stored samples and the ethical challenges experienced by a molecular biologist (author 2), a pathologist and IEC member (author 3) and a social scientist and IEC member (author 1). The participants were primarily attendees of the National Bioethics Conference, 2014. The small group discussions that followed centred around three sub-topics and the participants joined the sub-groups voluntarily.

Participants' profile

There were 35 participants, spanning the medical sciences, social sciences, bioethics and law. Table 1 shows the type of engagement of these participants in their disciplines.

Participants' concerns with stored biological samples – research and ethical issues

The analysis of the participants' proformas reflected the following concerns:

I. Storage and retrieval of samples and medical records, including conditions for storage, quality issues and the duration for which storage was permitted
II. The requirement for the patient's consent for research using the person's stored sample and data, and whether there were conditions for exemption or waiver of consent
III. Transfer of samples, sharing of data, and sharing of benefit and intellectual property matters.

The first two concerns were raised mainly by those dealing with biological samples given for diagnostics but useful for

Table 1: Profile of participants

	Pathology	Microbiology	Biochemistry	Public health	Others (medicine, social sciences, bioethics, law)	Total*
Teaching	9	5	1	1	4	20
Research	8	5	1	3	7	24
Clinical work	2	3	1		2	08
IEC members	3	1		1	7	12
Other (students, etc.)	2	1	2	1	3	09

** Total exceeds 35 as many individuals have multiple roles*

Most participants dealt with tissue samples in the form of paraffin blocks and histopathology slides, followed by blood and its derivatives, such as serum, and bacterial and fungal isolates. A few also mentioned clinical data linked with samples.

research (pathologists, microbiologists and biochemists), while the third concern and the second, to some extent, were expressed by IEC members who needed to grant approval for such research. The concerns of basic scientists involved in collaborative research fell in the third category.

The cross-cutting issue was the interpretation of the guidelines and legal frameworks, and the contrasting and sometimes contradictory stands of IEC members within a single IEC or across IECs.

Agreements in and insights from small-group discussions

The participants formed small sub-groups to discuss a cluster of questions. Each group pooled their experiences and views and differing perspectives before coming to a consensus that was presented to the whole group. The following were the insights gained.

Group 1: Is IEC approval necessary for stored sample research? Why / Why not? What are the considerations and requirements for approval?

Initially, while not everyone was convinced that IEC clearance was required for research on stored biological samples, most finally agreed that it was considering the present regulatory context that mandates seeking of ethical approval prior to accessing and using stored samples and data (27). In addition, if the primary purpose of the sample being stored was diagnosis, then the use of the stored material could possibly leave nothing for the primary purpose; hence, as a safeguard, IEC involvement would be required, to protect the patients' interests. Again, if incidental findings emerged that had a direct bearing on the prognosis of the person's health, then it would be necessary to inform the person. How could this be done and would it be ethical to contact the person directly if the IEC had not approved the research in the first place? In sum, the researcher's intrinsic bias or paternalistic attitude would be balanced by a presumed "external unbiased" patient-centric view. This group had mainly IEC members and those concerned with ethics and regulatory matters.

Group 2: Is it necessary to obtain informed consent for research with stored samples and stored medical data? Why/Why not? Are there alternatives?

The group was diverse, with a mix of medical professionals from diagnostic departments, social scientists and public health professionals. They had difficulty arriving at a consensus on when waivers could be allowed.

The primary argument put forward for the necessity of informed consent was so that the person could be informed about the change in purpose of the use of the samples (diagnostic/treatment to research). The change in purpose also signals a change in relationship (patient–doctor to subject–researcher).

In addition, seeking consent acknowledged the person's right of refusal, respected the individual's ownership of the tissue/biological sample and respected his/her personhood. As one said, "If we were to put ourselves into that person's shoes, we would want to know categorically what was being done with one's tissue."

The primary argument for not requiring informed consent from the individual was that the material was "waste" and "once out of me, why should I care?" The supporting argument was one of utility – once the blood was drawn or a tumour excised, it no longer had any utility for that person; hence, there could be no question of ownership or of benefit to that individual. Another argument against so-called informed consent was people's limited understanding of the information conveyed during the consent process, especially those from the low socioeconomic strata in India. This, together with the way informed consent is often obtained, made informed consent a formality at best.

The middle ground was to understand the needs and concerns of individuals and the practical issues of implementation. As far as possible, at the time of collection, the possibility of long-term storage and the potential purpose of storage should be stated and discussed. This was not called "broad consent" by the group, but it seemed to be implied. This consent form could also include options such as, "Do you wish to be informed about the specific research being conducted?" and, "Do you wish to know the general findings of the research?" If, for whatever reason, an individual was not convinced and had some doubts or clearly stated his/her refusal of additional storage or research, then this was to be noted and respected. It was also emphasised that it was not a matter of how much

information was conveyed but the way it was conveyed, with the maximum importance being given to respecting that person and his/her fears and doubts. As the social scientists explained, "People in our context generally do not have the culture of being asked, especially by a doctor who is considered a demi-god, but it is our duty, as responsible researchers, to make them understand."

If consent was not obtained at the time of sample collection, ie the research was on archival tissue and data, then the necessary protection of identity and confidential information should be ensured and approval from the IEC sought. The inability to reach the individuals for consent should be justified and conveyed to the IEC. This would be the case for student research, in which such material is routinely used, for studies on deceased individuals' specimens and data, and for retrospective epidemiological studies involving large numbers where there is no commercialisation involved.

Group 3: Norms regarding storage of samples, transfer to other locations, use by other researchers, buying and selling samples for research

People with a legal background, clinicians and basic scientists were the core of this group. While there was much debate over the legal versus ethical concepts of "ownership", "sample versus data" and "research purpose and diagnostic purpose", it was finally considered reasonable to accept that patients owned their sample as long as it was necessary for their diagnosis or treatment. However, the group was unclear whether they could still be considered "owners" after that point. Examples from organ and blood donation were quoted here. It was felt that the concept of "custodianship", rather than "ownership", was relevant for the organisation housing the stored samples. The custodian was expected to abide by the laws of the land, as well as national and international regulations. There was a greater comfort if the custodian was an academic or not-for-profit organisation which had as one of its objectives the greater good of the public from which the samples were received. The responsibility of the transfer of samples lay with the custodian and transfer would have to take place according to principles that had been laid down. The aspect of funding and the lack of it and the dilemmas this raised for sustaining the infrastructure required for storing the samples, data optimisation and research were important factors.

The transfer of samples required a different understanding in the present day and age, when a stored sample might no longer be a physical specimen or tissue, but electronic, genetic, molecular information which is stored on the cloud and is hence very mobile and "without borders". "Controlling this transfer is trickier than controlling the actual biological material." was how one basic scientist in this group put it.

Patenting was thought of as the best available legal option if monetary benefits coming from commercialisation needed to be distributed. The novel findings of most research studies performed using human biological specimens are typically published in peer-reviewed journals and not patented. While this leads to broader dissemination, many a time there is no further development of the idea/procedure. Patenting permits the licensing of the intellectual property to commercial entities and the royalties from the licensing can be used to further the causes supported by the organisations associated with the bio-bank.However, for academic researchers and academic institutions, publishing the data and putting them in the public domain was considered best; "letting the entire world and society at large exploit it as they see fit" , were the words of most academic researchers in this group.

Further ethical dilemmas

Not all matters could be tackled within the time available in the workshop, and some relevant new areas were raised that require more thought and investigation.

Are there some specific areas where stored samples and stored data research are exempt from IEC clearance? For example, can anonymised data be collected and used without consent to predict trends in infectious diseases and can non-anonymised data be collected without consent if this would prevent significant harm to others? Certain guidelines like that of the Nuffield Council for Bioethics have stated that waivers for consent are possible and have to be sought from authorized ethics committees (28, 29).

How far does the informed consent process provide respect and accountability to the subjects in stored sample research? Will more stringent regulations on informed consent really uphold the ethical and legal rights of research subjects? Do anthropological and similar studies give us any insights that will make it possible to form a relationship of trust and mutual respect?

Do the powers given to the IECs for the protection of the participants' interests make them paternalistic towards the latter and hence, perpetuate a hierarchical attitude?

Does the custodian of the sample/data, viz the institution housing this material, have a moral obligation to have adequate funds and infrastructure to optimally store, maintain quality and sustain research?

Under the Indian legal framework, what are the legal rights of individuals who have supplied their biological material and clinical data as samples for research?

Can patenting help in an equitable distribution of gains among all the stakeholders? Can we develop a framework by which this can be implemented?

Do we have adequate oversight and protection mechanisms in the case of samples and medical records that do not exist in the physical but electronic form, stored in the cloud?

It is clear from these workshop findings that a multidisciplinary approach to understanding the ethical issues involved in research with stored samples and stored data is beneficial and may be essential. It also appears important that all samples used for research and stored beyond a specified period come

under a central regulatory facility, such as a bio-repository ethics committee (25), which is able to address these complex ethical issues.

Given the fact that clinical and epidemiological studies and genetic research are often conducted on stored samples, considerable thought needs to be given to the ethical complexities involved. As science progresses and values change, the ethical premises need to be revisited and revised, if need be.

References

1. National Accreditation Board for Testing and Calibration Laboratories. Specific criteria for accreditation of Medical laboratories. NABL 112, Issue date: 01.02.2008, Amendment date: 16.10.2012 [cited 2016 Mar 17]. Available from: *www.nabl-india.org/nabl/file_download.php?filename... NABL-112...*
2. Ekmekçi S, Nacar O A, Tihan T. Who owns these tissues? General principles on the use of material submitted to pathology departments for healthcare, education and research purposes. *Turk Patoloji Derg*. 2012;28(3):189–94. doi: 10.5146/tjpath.2012.01124.
3. Cambon-Thomsen A. The social and ethical issues of post-genomic human biobanks. *Nat Rev Genet.* 2004;5(11):866–73.
4. Sgaier SK, Jha P, Mony P, Kurpad A, Lakshmi V, Ganguly NK. Public health. Biobanks in developing countries: needs and feasibility. *Science*. 2007;318(5853):1074–5.
5. Paynter RA, Skibola D R, Skibola CF, Buffler PA, Wiemels JL, SmithML. Accuracy of multiplexed illumina platform-based single-nucleotide polymorphism genotyping compared between genomic and whole genome amplified DNA collected from multiple sources. *Cancer Epidemiol Biomarkers Prev.* 2006;15(12):2533–6.
6. Scholtes VPW, de Vries JPPM, de Kleijn DPV, Moll FL, de Borst GJ, Pasterkamp G. Biobanking in atherosclerotic disease, opportunities and pitfalls. *Curr Cardiol Rev.* 2011;7(1):9–14. doi: 10.2174/157340311795677707.
7. Palsson G, Hardardottir KE. For whom the cell tolls: debates about biomedicine. *Current Anthropology.* 2002;43(2):271–301.
8. Hoeyer K. The ethics of research biobanking: a critical review of the literature. *Biotechnol Genet Eng Rev.* 2008;25:429–52.
9. Kapp MB. Ethical and legal issues in research involving human subjects: do you want a piece of me? *J Clin Pathol*. 2006;59(4):335–9.
10. U.S. Department of Health & Human Services [Internet]: OHRP – Guidance on Research Involving Coded Private Information or Biological Specimens, 2008 [cited 2015 Feb 9]. Available from: http://www.hhs.gov/ohrp/policy/cdebiol.html
11. Wendler D, Emanuel E. The debate over research on stored biological samples: what do sources think? *Arch Intern Med.* 2002;162(13):1457–62.
12. Campbell AV. The ethical challenges of genetic databases: safeguarding altruism and trust. *King's Law J.* 2007;18:227–46.
13. De Souza YG, Greenspan JS. Biobanking past, present and future: responsibilities and benefits. *AIDS.* 2013;27(3):303–312. doi:10.1097/QAD.0b013e32835c1244.
14. Zika E, Paci D, Braun A, Rijkers-Defrasne S, Deschenes M, Fortier I, Laage-Hellman J, Scerri CA, Ibarreta D. A European survey on biobanks: trends and issues. *Public Health Genomics.* 2011;14(2):96–103. doi: 10.1159/000296278. Epub 2010 Apr 15.
15. Knoppers BM, Laberge CM. Research and stored tissues. Persons as sources, samples as persons? *JAMA*. 1995;274(22):1806–7.
16. Corrigan OP, Williams-Jones B. Pharmacogenetics: the bioethical problem of DNA investment banking. *Stud Hist Philos Biol Biomed Sci.* 2006;37(3):550–65. Epub 2006 Aug 24.
17. Zhang X, Matsui K, Krohmal B, Zeid AA, Muthuswamy V, Koo YM, Kita Y, Lie RK. Attitudes towards transfers of human tissue samples across borders: an international survey of researchers and policy makers in five countries. *BMC Med Ethics.* 2010;11:16. doi: 10.1186/1472-6939-11-16 [cited 2016 Mar 17]. Available from: http://www.biomedcentral.com/1472-6939/11/16
18. Vaz M, Vaz M, Srinivasan K. Ethical challenges in biobanking: moving the agenda forward in India. *Indian J Med Ethics.* 2014;11(2):79–88 [cited 2015 Jun 19]. Available from: http://ijme.in/index.php/ijme/article/view/1932/4197
19. Skloot R. The immortal life of henrietta lacks. 2nd ed. London: Pan Books; 2011.
20. Haddow G, Laurie G, Cunningham-Burley S, Hunter KG. Tackling community concerns about commercialization and genetic research: a modest interdisciplinary proposal. *Soc Sci Med.* 2007;64(2):272–82.
21. Wallace HM. The development of UK Biobank: excluding scientific controversy from ethical debate. *Critical Public Health*. 2005;15(4):323–33.
22. Boverberg JA. Towards an international system of ethics and governance of biobanks: a 'special status' for genetic data? *Critical Public Health*. 2005;15(4):369–83. doi: 10.1080/09581590500523400.
23. UNESCO, Bioethics Committee [Internet]. International Declaration on Human Genetic Data 2003 [cited 2015 Feb 13]. Available from: http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genetic-data/
24. Caulfield T, McGuire AL, Cho M, Buchanan JA, Burgess MM, Danilczyk U, Diaz CM, Fryer-Edwards K, Green SK, Hodosh MA, Juengst ET, Kaye J, Kedes L,Knoppers BM, Lemmens T, Meslin EM, Murphy J, Nussbaum RL, Otlowski M, Pullman D, Ray PN, Sugarman J, Timmons M. Research ethics recommendations for whole-genome research: consensus statement. *PLoS Biol* 2008; 6(3): e73. doi:10.1371/journal.pbio.0060073.
25. UK Biobank Ethics and Governance framework [cited 2015 Jun 17]. Available at: http://www.ukbiobank.ac.uk/resources
26. Vaz M, Vaz M, Srinivasan K. Listening to the voices of the general public in India on biomedical research—an exploratory study. *Indian J Med Ethics.* 2015;12(2):68–77 [cited 2015 Jun 19]. Available from: http://ijme.in/index.php/ijme/article/view/2221/4738
27. Indian Council of Medical Research. Ethical Guidelines for Biomedical Research on Human Participants. New Delhi: ICMR; 2006 [cited 2016 Mar 17]. Available from: http://www.icmr.nic.in/ethical_guidelines.pdf.
28. Desikan P, Chakrabarti A, Muthuswamy V. Ethical issues in microbiology. *Indian J Med Microbiol.* 2011;29(4):327–30. doi: 10.4103/0255-0857.90154.
29. Nuffield Council on Bioethics, Report on Public Health Ethical Issues, November 2007; pp.63–4 [cited 2015 Jun 19]. Available from: http://nuffieldbioethics.org/report/public-health-2/infectious-disease/