

# Biobanks and human health research: Balancing progress and protections

A Dhai,<sup>1</sup> MB ChB, FCOG (SA), LL.M, PhD; S Mahomed,<sup>2</sup> BCom LLB, LL.M; I Sanne,<sup>3</sup> MB BCh, FCP (SA), DTM&H

<sup>1</sup> Director, Steve Biko Centre for Bioethics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

<sup>2</sup> PhD candidate, Steve Biko Centre for Bioethics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

<sup>3</sup> Managing director; Right to Care. Department of Medicine, Clinical HIV Research Unit, Internal Medicine and Infectious Diseases, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

**Corresponding author:** Ames Dhai ([ames.dhai@wits.ac.za](mailto:ames.dhai@wits.ac.za))

Biobanks are repositories that store human biological materials and their associated data. They are rapidly becoming part of national and international networks and give rise to unique ethico-regulatory issues. Whether consent is informed and whether this term should be used when specimens are collected for biobank research is questionable. Where risks occur, they are usually social and relate to identifiability. Public trust and confidence are important for the success of this type of research. Consensus is growing that governance of biobanks should be harmonised. Controlled specimen and data access agreements are essential. The South African National Health Act (NHA) and its Regulations, that provide the foundation for the legal framework with regard to human tissue and research in South Africa, are silent on the issue of biobanks and the law lags behind while science and technology advance rapidly. The use of biobank assets will lead to significant benefits in human health and should be encouraged while taking account of the associated ethical, legal and social issues and working towards a balance between these two positions.

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The advent of biobanks in the field of science and technology has seen scientists entering a new age in biotechnology research. General ethical considerations, which apply to health research involving human participants, will apply equally to biobank research. However, in addition, there are unique ethical issues specific to biobank research. This is because of the nature of biobank research which has evolved to include an intersection of disciplines and networks. While the unique considerations pertaining to genetic research also apply in this context, with biobanks, international collaborations have emerged on a scale not previously seen. Without doubt this type of collaborative research is pivotal to advancing science, health and well-being. Nevertheless, multifaceted ethico-regulatory and social complexities have surfaced, including concerns around individual and group autonomy, informed consent, privacy, confidentiality, secondary use of samples and data over long periods, data sharing, benefit sharing and differing legal requirements across national boundaries.<sup>[1]</sup> Because biobanks are essential for major advances in health research, a balance is required between the tensions arising from the need for progress towards human health and well-being and ethico-regulatory and social concerns.

In this paper we briefly describe biobanks and the advancement from biobanks to networking and sample and data-sharing. We discuss how the supremacy of informed consent is challenged by this new age research and some of the risks that could occur in the context of biobank research. We highlight the importance of safeguards like specimen and data access agreements and the pivotal role of public trust for the success of this type of research enterprise. The need for ethics in the governance of biobanks is underscored. Pertinent international and local ethics and governance documents

are referred to. The legal void in South Africa (SA) with regard to biobank research is also discussed. While the ethico-regulatory issues relating to biobank research in this paper are not exhaustive, we raise what we consider to be the relevant ones.

## Biobanks – a brief description

Biobanks are repositories that store animal, plant and human specimens. This paper focuses on biobanks that store human biological materials (HBMs) specifically for research purposes. Biological materials, as defined in the Regulations to the South African National Health Act (NHA)<sup>[2]</sup> are: 'material from a human being including DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, small tissue biopsies and growth factors from the same.'<sup>[3]</sup> Biobanks are repositories that store not only organised collections of HBMs usually from a large number of donors but also their associated data, including individual health records and information derived from their analysis.<sup>[1,4]</sup> A well-functioning up-to-date biobank serves to accelerate important advances in health research as it exploits 'state-of-the-art genetics together with big data sets and individual health records to allow for complex and powerful studies'<sup>[4]</sup> on an unprecedented scale. Biobanks collate large numbers of variables and are crucial resources to the understanding of genetic, environmental and lifestyle factors in the aetiology of disease.<sup>[4,5]</sup> However, in SA, biobanks are typically concerned with the storage of specimens and the crucial bioinformatics capacity of these repositories seem to be very much in their nascent stages.<sup>[6]</sup>

The two broad categories of biobanks are:

- those that are involved in large cohort studies where a minimum of tens of thousands of participants is required
- those that are disease specific.<sup>[4]</sup>

The former are usually referred to as population biobanks and they focus on the promotion of population health.<sup>[1,7]</sup> There is a paucity of data on the number and types of biobanks operating in the country. A review documented just over a dozen biobanks in the country and these operate on a smaller scale.<sup>[6]</sup> Not all of them are specific to research. Those that are involved in human health research are usually smaller collections from research projects within academic institutions.<sup>[6]</sup> While the National Health Laboratory Services in SA has attempted to establish a population level biobank,<sup>[8]</sup> this has unfortunately not materialised. The reasons for this are probably multifactorial but in our opinion include bureaucratic hurdles and the lack of a comprehensive ethico-legal framework for biobanks in the country. Although the SA regulatory framework makes provision for tissue banks, these are not biobanks. Tissue banks are defined as ‘an organisation, institution or person that provides or engages in one or more services involving cells and/or tissue from living or deceased individuals for transplantation purposes’<sup>[9]</sup> This definition may clearly include a person who provides or engages in these activities. Moreover, the uses of cells and/or tissues are limited to transplantation purposes only. This inelegant definition differs from the internationally recognised definition of a biobank as described above. Notably, the NHA,<sup>[2]</sup> which provides the foundation and scaffold for the legal framework regarding human tissue and research in SA, is silent on the issue of biobanks. Despite chapter 8 of the NHA being specific to human tissue and chapter 9 to research, none of their regulations provide regulatory direction with regard to biobanks.

### Biobanks, networking and data-sharing

Biobanks are conventionally defined in terms of their institutional or geographical location. With the emergence of new scientific and computer technology development, HBMs and associated data are rapidly and increasingly becoming part of a national and international network of biobanks. Such networking means that biobanks have the greatest potential as resources for translational research.<sup>[10]</sup> Data are shared between biobanks when sample sizes are insufficient to produce statistically significant results. Research potential is therefore fully realised.<sup>[4]</sup> The bigger and more networked the biobank, the greater the power of the research that can be conducted.<sup>[10]</sup> Certain types of research can only be conducted if there is networking between biobanks, e.g. where rare diseases are studied, a single researcher may not be able to collect an adequate number of samples. Moreover, some common diseases, like cardiac disease, are now seen to comprise rare disease subsets characterised by specific genetic polymorphisms. Networking also assists in situations where there are social and logistical difficulties with obtaining HBMs.<sup>[10]</sup>

Several categories of biobank networks have evolved over time. These categories are neither exhaustive nor non-mutually exclusive and include:<sup>[10]</sup>

- ‘Storage’ networks – facilities for storage are shared among biobanks to reduce costs and improve quality.
- ‘Bring-and-share’ storage networks – lower fee structures are offered to researchers to encourage sharing of resources with other researchers.
- ‘Catalogue’ networks – maintains a database that can be accessed by external researchers looking for samples for their research.
- ‘Partnership’ networks – costs and efforts in recruitment are shared.

- ‘Contribution’ networks – relevant specimens are contributed to disease-specific biobanks.
- ‘Expertise’ networks – expertise instead of samples are shared.

South Africa, with its world-class scientists and infrastructure conducive to advancing high-quality, high-tech research, is ideally placed on the continent to integrate these different categories of biobanks and establish networks within the country that would maximise the research potential here. Specimens within these biobanks are from the public and sharing would not only facilitate attaining the desired statistical power and addressing some of the financial and other resource constraint issues, but would be a step in the direction of the common good. Research, conducted with public involvement, is in reality a contract between science and society.

While ethical challenges specific to those of networking and data-sharing between biobanks have arisen, these are not insurmountable and should not impede much needed human health research. One of the greatest concerns is that large-scale networking would result in a total disconnect between participants and researchers and as a consequence, researchers would become less accountable to donor interests.<sup>[10]</sup> Where biobanks have been approved and are subject to oversight by well-functioning, competent research ethics committees (REC), donor interests ought to be taken care of adequately.

### Informed consent

A key problem, resulting in a bottleneck between conventional established research and biobank research, is the issue of informed consent.<sup>[11]</sup> Informed consent is both an ethical and legal doctrine forming a necessary component of health research. Ethical challenges in the context of biobank research often focus on the tensions between individual autonomy or respect for persons and utilitarian justice and the common good.<sup>[10]</sup> We believe that because biobank research involves the contributions of a large number of people, its ethical emphasis should hinge on the utilitarian common good. Due to the nature of biobank research, the focus on individual autonomy and informed consent is seriously challenged. The consent emphasis in classic research ethics is that of individual, first-person consent for sample collection and use for the specific research project that the participant consents to. In addition, the participant consents to storage over a defined period of time. We recommend and encourage researchers to consider storage in biobanks over an indefinite period as such research involves genetic and genomic studies where the intergenerational period is at least 25 years. The consent and sample collection process with biobank research is often separate from the actual research which could be conducted several years later, by a group of different researchers, in different biobanks as compared to when the initial sample collection took place and informed consent was obtained. In addition, the research may involve research questions and methods that could not have been contemplated at the time of sample collection. Specific cell lines could be derived from the samples and these could be duplicated and exchanged through the networks.<sup>[11]</sup> It is therefore questionable as to whether consent for biobank research is at all informed and whether this term should be used when specimens are collected for biobank research. In addition, classic and biobank consent forms respect participant autonomy to the extent of including a withdrawal clause for the specimens that have been collected.

Clearly, with such extensive networking, sharing of specimens, and transformation of specimens into cell lines, withdrawing of samples will not be as easy as it seems on the consent form and this could be perceived as paying 'lip-service' to autonomy. Because of this lack of knowledge of what will happen to the specimens in the future, consent processes must be broad and 'broad' consent, ethically and legally is not the same as 'informed' consent.

Various models of consent have been offered by ethicists and researchers to address the informed consent difficulties encountered in biobank research. These include re-consent, tiered consent and multi-layered consent with secondary use statements.<sup>[1,4,11]</sup> However, these could result in consent exhaustion on the part of the participant and increase the financial costs and administrative burdens of the research. Therefore, we advocate obtaining broad consent from participants and assuring them that there would be REC oversight and approval for future research using their samples and data as the most appropriate way forward. This would be in line with the SA Department of Health's research ethics guidelines which allows for broad consent and defines it as where the 'donor permits use of biological materials for future studies, subject only to further prior ethics review and approval'.<sup>[12]</sup> Depending on the category of the biobank, differing degrees of broad consent could be obtained and range from consent to conducting research in a specific sphere in health, or on a specific disease, to unrestricted consent for future health research use as in population biobank studies.<sup>[11]</sup> International organisations, for example, the Organisation for Economic Cooperation and Development (OECD) advocate this type of broad consent for biobank research.<sup>[13]</sup>

The Draft World Medical Association (WMA) Declaration on Ethical Considerations Regarding Health Databases and Biobanks<sup>[14]</sup> which has been out for open consultation since March this year, states that individuals must be given the choice to decide whether or not their biological materials will be included in a biobank. The consent process needs to include information on the purpose of the biobank, the nature of the material to be collected, who will have access to the biobank, the biobank's governance arrangements and how privacy will be protected. It goes on to state that conditional broad consent is acceptable *if inter alia* all information about future use is provided during the consent process and all use is approved by a dedicated, independent ethics committee. It does not define 'conditional broad consent'. It also does not take into consideration that because of the evolving nature of biobank research it is not possible to provide all information on future use. It would be interesting to see how the WMA defines broad consent. The Draft Declaration states that blanket or open consent for future use 'not envisaged at the time of collection is not ethically acceptable'. This, in our opinion, would serve to cripple biobank research as many studies emanating from biobanks involve research questions and methods not envisaged at the time of sample collection.

## Risks of biobank research

It is important to bear in mind that just as there are societal benefits of biobank research based on the common good, there are societal risks to this type of research. While physical risks of research conducted on samples that have already been collected and stored are rare, social risks need to be safeguarded against.<sup>[1]</sup> The nature and degree of risk will depend on whether the samples are identifiable and

the type of information that is linked to the sample. Potential risks could extend beyond individual participants to their population groups and the general public. Stigmatisation and discrimination, in particular genetic discrimination, which are frequently group-based, implicating both participants and non-participants, are examples of social risks of biobank research. Moreover, when identifiable samples are used in research, disclosure of sensitive information could result in an invasion of the participant's privacy.<sup>[1]</sup>

Confidentiality is the main ethical concern regarding identifiability. It is essential that donors understand the notion of identifiability and the different levels of anonymisation in order to assess the individual consequences of participation.<sup>[15]</sup> In addition, biobank research implies risk for identifiable groups and communities because anonymity of the individual does not necessarily translate to group anonymity. Different terms pertaining to identifiability are used for stored tissue in different guidelines and literature. Moreover, the same terms have different meanings in different guidelines and also, at times, within the same guidelines.<sup>[15]</sup> The latter problem also applies to the SA ethics guidelines. Needless to say, confusion and communication barriers result. A clear indication of levels of identifiability are offered by the following five levels of anonymisation utilised in the European Guidelines:<sup>[16]</sup>

### Anonymous

This is appropriate only for archaeological samples. As it is always possible to identify the donor through DNA fingerprinting, where samples contain any trace of DNA, they are not truly anonymous.<sup>[16]</sup>

### Anonymised

This term denotes storage of biological material alongside associated information like age, medical treatment, etc. However, all identifying material is removed either irreversibly (unlinked anonymised) or reversibly (linked anonymised). Identification of linked anonymised samples is usually by use of a code which researchers and other users of the samples do not have access to.<sup>[16]</sup>

### Coded

Here samples are reversibly linked, anonymised with researchers and users having access to the code.<sup>[16]</sup>

### Identified

These are samples with information allowing identification, e.g. name, address, telephone number, etc. Pathology laboratories usually store samples in the identified form.<sup>[16]</sup>

Population databanks, which are mainly longitudinal in nature, would require linked anonymised and coded samples. Fears regarding problems with recruitment because of the potential for identification of the participant must be balanced with utility and the tangible benefits of such a process. Research with potential participants has shown that such fears could be unfounded.<sup>[17]</sup>

## Controlled sample and data access agreements

Participants and the public must have assurance that the scientific community will use samples and data from these banks correctly. Therefore, to ensure controlled access, sample and data access agreements are advocated towards the provision of liberal, but secure

access of samples and data. While the international guideline on prevention of scientific misconduct (Singapore Statement),<sup>[18]</sup> and the Draft WMA's Declaration on Ethical Considerations Regarding Health Databases and Biobanks<sup>[14]</sup> could have an impact on international laws and practices, they are unclear on how to implement processes to monitor and regulate research integrity.<sup>[19]</sup> Problems concerning these international documents include:<sup>[19]</sup>

- Implementing national laws in an internationally consistent manner is problematic.
- Immediate, practical solutions for problems that could arise within global genomics projects are often not offered.
- An optimal level of protection is not offered as they are not contractual in nature and their interpretation and enforcement could end up being very costly, unpredictable, lengthy and protracted.

It follows therefore, that establishers of biobanks should have strict controlled-access policies in place which should be approved by a REC. Contractual sample and data access agreements which ensure the proper recognition of all in the research production chain and adequate protections of research participants have been recommended.<sup>[19]</sup> The HBM recipient has a responsibility similar to that of a trustee or steward in order to ensure protection of the donated tissues. Material Transfer Agreements (MTAs) are an example of such a contractual arrangement. The University of Witwatersrand's Biobanks Ethics Committee has developed an MTA template which incorporates both ethical principles and legal requirements for use by researchers.<sup>[20,21]</sup> The need for an MTA prior to samples being transferred is a requirement by the Health Professions Council of South Africa (HPCSA).<sup>[22]</sup> The SA ethics guidelines only mention that inter-institutional sharing agreements are required to be confirmed in writing. There is no further guidance to researchers on how and at what stage this should be done. The Draft WMA Declaration is silent on the need for contractual specimen and data access agreements.

### Public engagement and trust

Consultation with the public and ensuring that they clearly understand the functioning of and research conducted by the biobank are some of the key factors towards a biobank's success.<sup>[14]</sup> Ongoing dialogue between the public, researchers and biobank managers is essential as public support in this context cannot be taken for granted. Moreover, public confidence and trust in biobanks research as being done for the common good must be cultivated. This is essential to maximise participant recruitment and retention of samples. Therefore public support is vital to the development of biobanks.

Two thirds of respondents surveyed in a study that was conducted widely throughout Europe had not heard of biobanks and most respondents, once aware of the concept, were generally supportive.<sup>[4]</sup> It would be interesting to know what the SA public's response would be to a similar study. A large-scale survey on the public's knowledge, understanding and attitude towards biobanks has not been conducted throughout SA as yet. In addition, meaningful conversations on biobanks between the public and researchers are lacking. If SA wants to be at the forefront of this cutting-edge research, commitment is necessary on the part of researchers and scientists to build public trust and confidence in these activities.

### Biobank governance

Because of extensive networking between biobanks, there is growing consensus that governance of biobanks should be harmonised, especially if HBMs are to be used broadly.<sup>[4,13]</sup> In particular, there should be harmonisation in the operating procedures and policies for procurement, collection, storage and transfer of HBMs if the objective of the biobank, which is that of fostering research, is to be realised. Oversight for this should be provided by the REC. In terms of the OECD guidelines, the establishment, governance, management, operation, access to, use of the biobank and its protocols and processes for research activities, oversight mechanisms, strategies for ensuring long-term sustainability which also addresses the event that funding is terminated or its nature changed, stakeholder consultation (including the general public), and criteria for sampling and participant selection, should be reviewed and approved by an independent REC.<sup>[13]</sup> The Draft WMA Declaration also requires that an independent REC approves the establishment of the biobank.<sup>[14]</sup> The SA ethics guidelines require that all new repositories have prior REC approval and that the REC should establish procedures to guide this process and the use of the repository.<sup>[12]</sup> A weakness of the SA guidelines, which use the terms repository and biobank interchangeably, is that REC oversight with regard to already established biobanks is not mandatory. The Human Research Ethics Committee (Medical) of the University of the Witwatersrand, the oldest REC in the country and among the first to be established in the world (1966),<sup>[23]</sup> set up its Biobanks Ethics Committee in 2013.<sup>[20]</sup> The mandate of this committee is *inter alia* to review applications for the establishment of biobanks and all research pertinent to the use of specimens from the approved biobanks.<sup>[21,24]</sup> This REC oversight of biobanks was commenced by the REC despite no local directive to do so. Moreover, the REC is guided by the principles of the WMA's Declaration of Helsinki which does not pronounce on biobank oversight.

### Conclusion

The value of biobanks in the health research arena must be appreciated by scientists, the public and policymakers alike. The use of biobank assets will lead to benefits in diagnosis and the treatment of numerous diseases. This should be encouraged while considering the associated ethical, legal and social issues and working towards a balance between these two requirements. The importance of public trust and confidence in this equation must not be underestimated. While advances in science and technology are accelerating, the law in SA unfortunately lags behind. Fortunately though, some institutions have taken their ethics oversight roles seriously and have instituted safeguards, despite the legal hiatus in this regard.

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