The role of research ethics committees in South Africa when human biological materials are transferred between institutions

S Mahomed, BCom, LLB, LLM, PhD; **M Labuschaigne,** BA, BA (Hons), MA, DLitt, LLB, LLD

Department of Jurisprudence, School of Law, University of South Africa, Pretoria, South Africa

Corresponding author: *S Mahomed (mahoms1@unisa.ac.za)*

The role of health research ethics committees (RECs) has evolved dramatically over the past few decades. Novel and specialised research, multicentre trials across borders and commercially sponsored research, coupled with a huge increase in the number and complexity of research protocols, and capacity and resource constraints on the part of RECs, have led to serious breaches regarding the protection of human participants. Research involving the exchange or cross-border transfer of human biological materials (HBMs) requires specialised legal and ethical knowledge relating to multiple governance frameworks. RECs may be required to monitor compliance not only with contractual requirements, but also the national laws and national ethical guidelines and standards of selected jurisdictions, not to mention adherence to international regulatory instruments governing biomedical research generally, and the conditions for the collection and use of HBMs specifically. The South African (SA) legislator's decision to make RECs signatories to the prescribed material transfer agreement (MTA) template is a first step in the right direction, reinforcing the role and responsibilities of RECs, and their duty of care towards human participants in research. In addition, there has to be a transformation of the general mindset, towards accepting ethical principles within legal documents, particularly legal documents that involve the REC and create binding provisions that have a direct impact on participants. It is time that African views and participant protections are respected and accepted with the same vigour commanded by the Western world. In this article, the role of RECs in general is considered, prior to focusing on their responsibilities with respect to HBM transfer. The ethico-regulatory framework for REC functioning is discussed both from global and national perspectives. Also deliberated is the critical role that RECs play in reviewing health research proposals when HBMs are transferred between institutions, and the REC as a party to the SA national MTA template.

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The exchange of human biological materials (HBMs) and associated data between institutions, within countries and across national boundaries, has become a common feature of biomedical research and biobanking activities globally. Previously, HBMs were informally exchanged between researchers. However, as engagement between universities and industry intensified, with an emphasis on commercialising the outcomes of research, issues of biosafety, traceability of samples and data, and transparency and accountability of researchers and biobanks required that exchanges become more formalised.[1]

Material transfer agreements (MTAs) play a critical role in the exchange of these specimens and their associated data. Parties to MTAs are usually research and academic institutions, and private and commercial entities. The terms of these MTAs are governed by, among other regulation, relevant national laws and ethical guidelines relating to consumer protection, health research, protection of research participants and fundamental rights generally. Where HBMs are transferred from one jurisdiction to another, the governance framework for the collection, use and storage of the material becomes more complex. Research ethics committee (REC) oversight in this milieu is critical. In July 2018, the National Department of Health (NDoH) in South Africa (SA) gazetted a national MTA template for use by researchers when HBMs and their associated data are to be transferred outside SA.[2] The MTA can also be used when such transfers are effected between institutions inside the country.

In this article, the role of RECs generally is considered, prior to focusing on their responsibilities with respect to HBM transfer. The ethico-regulatory framework for REC functioning is discussed from both global and national perspectives. Also deliberated is the critical role that RECs play in reviewing health research proposals when HBMs are transferred between institutions, and the REC as a party to the SA national MTA template.

Associated data are integral to HBMs, because most health research on HBMs will also require analysis of their associated data. In this context, inherent in all further reference to HBMs is their associated data.

Research ethics committees – roles and responsibilities from a global perspective

Ethical controversies in research were catapulted to the surface when the unconscionable conduct of medical scientists and doctors was

highlighted at the Nuremburg trials, following the Nazi war atrocities in concentration camps during World War II. The Nuremburg Code that followed was given the status of the first international code at the end of the Nuremberg trials. It consists of 10 characteristics required for acceptable research involving humans, and is among the most widely known of the guidelines for ethics in research. It was, however, silent on ethical review of such research.[3] To address some of the hiatuses in the Nuremberg Code, the World Medical Association (WMA) issued the Declaration of Helsinki in 1964. This version of the Declaration was also silent on ethics review, and it was only 11 years later, in its second version in 1975, that research ethics review was specified.[4] Since its original formulation, the Declaration, which is recognised as one of the most authoritative statements on ethical standards for human research in the world, has been updated seven times, most recently in 2013.[3] The Declaration of Helsinki has been referred to as the most widely accepted guidance document globally on medical research, and has also been incorporated into many national and international legal instruments. On the subject of ethical review, it states in section 23 that a REC 'must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be *duly qualified* … the committee must have the right to monitor ongoing studies' (own emphasis).

Hence it is a global requirement that members of RECs need to apply themselves competently when analysing the ethical aspects of research. Regarding HBMs, the only statement inferred is set out in section 32 of the Declaration, which indicates that: 'For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. *In such situations the research may be done only after consideration and approval of a research ethics committee*' (own emphasis).

As the Declaration of Helsinki contains general information on the ethical principles for medical research involving human participants, and contains limited information on HBMs, the WMA in 2016 adopted the Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks.[5] The Declaration of Taipei sets out the ethical principles and governance arrangements that must be in place where health databases and biobanks are concerned. Section 19 states that: 'the ethics committee must approve use of data and biological material and check whether the consent given at the time of collection is sufficient for the planned use or if other measures have to be taken to protect the donor. The committee must have the right to monitor ongoing activities.' An MTA would be included in the 'other measures'.

The purpose, functioning and roles of RECs are mirrored in other international ethical guidelines to which SA subscribes, for example the Organisation for Economic Co-operation and Development's guidelines on 'Human biobanks and genetic research databases' (2009), and the 'International ethical guidelines for health-related research involving humans', published by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organization (CIOMS guidelines). From the above, it becomes clear that the main responsibility of RECs from a global perspective is to protect potential and enrolled participants in the research process. RECs must also consider potential risks and benefits for the communities in which the research will take place. Essentially, RECs need to promote high standards of ethics in research.

Research ethics committees – the South African ethico-regulatory environment

Constitution of the Republic of South Africa, 1996

It is prudent to begin this discussion with the relevant provisions of the SA Constitution (1996), as it forms the apex of the country's legislative framework. Section 12(2)(c) of the Bill of Rights[6] stipulates that 'everyone has the right to bodily and psychological integrity, which includes the right: not to be subjected to medical or scientific experiments without their informed consent.' This fundamental right is non-derogable, and is often relied upon as the country's first directive to ensure participant protection. However, there are other rights in the Bill of Rights that have a direct bearing on research with human participants and, specifically, where the transfer of HBMs is concerned. The rights to human dignity, equality, freedom and security of the person and privacy are some of the other fundamental rights that are implicated. Furthermore, in accordance with section 31(1) of the Bill of Rights, all persons belonging to a cultural, religious or linguistic community may not be denied the right, with other members of that community, to enjoy their culture and practise their religion. This is particularly relevant where HBMs are concerned, as black African communities attach a deep cultural significance to their blood and human materials in general.[7,8] Therefore, RECs must be able to appreciate and respect all these fundamental rights of participants when reviewing health research proposals.

National Health Act No. 61 of 2003

Chapter 9 of the National Health Act[9] (NHA) outlines the functioning of health RECs (HRECs), and states in sections 73(1) and 73(2) that:

> '(1) Every institution, health agency and health establishment at which health research is conducted, must establish or have access to a health research ethics committee, which is registered with the National Health Research Ethics Council. (2) A health research ethics committee must – (a) review research proposals and protocols in order to ensure that research conducted by the relevant institution, agency or establishment will promote health, contribute to the prevention of communicable or non-communicable diseases or disability or result in cures for communicable or non-communicable diseases; and (b) grant approval for research by the relevant institution, agency or establishment in instances where research proposals and protocol meet the ethical standards of that health research ethics committee.'

Therefore, the roles of a HREC are further mandated through Chapter 9 of the NHA.

Regulations relating to research with human participants

The NHA's regulations relating to research with human participants[10] indicate, in accordance with section 6, that all health research proposals involving human participants must be reviewed by a HREC registered with the National Health Research Ethics Council (NHREC), and must satisfy the requirements of the NDoH's national ethics guidelines and

any additional standards, as determined by the HREC. Section 5 of the regulations also provides a list of what participants should be informed of during the research process. The regulations state that research participants or their legally authorised representatives must be informed of the purpose, methods and procedures including possible randomisation; alternatives to participation; potential harms and risks of harm; expected benefits of the research; the freedom to choose to participate or not or withdraw from the process; the ways in which confidentiality and privacy will be maintained; details of the contact person in case of a research-related injury; reimbursement and/or incentives for participation; sponsor information; potential conflicts of interest; information about approval from the HREC or Medicines Control Council (now the SA Health Products Regulatory Authority); information on insurance in the event of research-related injury for more than minimal-risk research; and the availability of beneficial products or interventions post research. Therefore, when a HREC reviews the health research proposal, it must be able to determine whether the participant has indeed been sufficiently informed of the benefits, risks and terms of participation.

Department of Health national ethics guidelines: *Ethics in Health Research: Principles, Structures and Processes*, 2015

The NHREC was established in accordance with section 69(1) of the NHA. One of the responsibilities of the NHREC, in accordance with section 72(6)(a), is to determine guidelines for the functioning of HRECs, to facilitate best practice. Consequently, the first edition of the NDoH national ethics guidelines was published in 2004, and the second in 2015.[11] Chapter 4 of the guidelines sets out the role, functioning, membership, expectations and processes of HRECs. Section 4.3 indicates that the primary role of a REC is to protect the rights and welfare of participants who take part in sound research. To this end, 'the primary responsibility of each REC member is to decide independently whether the proposed research protects the interests of participants adequately and keeps to exemplary standards in research activities.' With regard to membership, section 4.4 of the guideline makes it very clear that membership should include as many disciplines, sectors and professionals as possible, and at least one member who is legally qualified (section 4.4.1.2). Members should have the necessary qualifications and experience to review and evaluate the science, health aspects, ethics and the layperson's perspective. Members are also expected to familiarise themselves with institutional documents and national and international ethics guidelines. The critical importance of training is also emphasised in section 4.4 of the guidelines, especially for RECs that review high-risk research, which includes research involving the transfer of HBMs. If the membership includes a legally qualified person, one can then infer that the role of such member would extend to applying him- or herself to legal aspects that directly affect the research. It would then make sense that such an individual is able to review contractual documents, including MTAs, as part of his or her mandate.

Health Professions Council of South Africa guidelines

The *Guidelines for Good Practice in the Heath Care Professions – General Ethical Guidelines for Health Researchers*[12] reiterate the provisions of the NHA and the NDoH's national ethics guidelines – that all health research proposals and protocols must be reviewed and approved by an accredited HREC before the research commences. In addition, with regard to data storage and transfer, paragraph 3.4 states that justifiable reasons must be provided to the HREC, and the benefits outlined, in order for data and specimens to leave SA. Paragraph 13.3 indicates that this should only be done after an MTA has been signed and submitted to the HREC. If a HREC is mandated to review and consider all ethical questions regarding the health research proposal, an MTA, which contains ethico-legal principles, is required to be submitted to a HREC. It therefore warrants that the HREC carefully review the MTA.

Critical role of HRECs in reviewing health research proposals that include the transfer of HBMs between institutions

The purpose of MTAs

The purpose of MTAs generally is to regulate the exchange of HBMs and associated data between researchers/institutions, as well as to safeguard the interests of research participants, researchers and their institutions.[13] The HPCSA guidelines and national ethical guidelines require the conclusion of MTAs before HBMs are transferred out of SA.[11,12] The national ethical guidelines, in addition, state at section 3.5.2.3, that 'where data or materials are shared with researchers in other institutions, the recipient institution should agree to comply with the requirements of the donor institution' as well as 'any additional requirements of the recipient institution'. The national ethical guidelines recommend that these inter-institutional sharing agreements are confirmed in writing. The uses of the material, quality of the material, terms and conditions under which the material may be used, third-party transfers, benefit-sharing mechanisms, intellectual property rights and other legal and/or regulatory policies or guidelines that need to be considered are also detailed in the MTA.[2]

The HREC as a party to the SA national MTA template

The role and crucial functions of HRECs are highlighted in legislation, national ethics guidelines and international guideline documents, as described above. These functions are further emphasised in the 2018 SA national MTA,[2] which includes both ethical and legal principles and which makes a HREC a party to the agreement. The obligations of a HREC, as set out in paragraph 6 of the national MTA, do not make the role of the HREC more onerous, but rather emphasise and reiterate the mandated duties of the HREC, specifically where the transfer of HBMs is concerned, to ensure ethical compliance. A HREC is closest in proximity to the research process and able to make an informed decision regarding the ethical, legal and scientific integrity of the terms of transfer. In addition, as an independent committee with a legally qualified person mandated to form part of its membership, there are specific obligations and expectations that a HREC is required to fulfil in order to protect the rights and welfare of participants. A HREC is responsible to act on behalf of participants where the transfer of their HBMs is concerned, and has *locus standi* (standing) to enter into a contract, approve research protocols and sign ethical clearance certificates. It is prudent to note that the legally qualified member(s) of a HREC should work with the chair

of the HREC and other committee members to ensure that the MTA provides adequate safeguards to participants, and to confirm that the HREC itself has fulfilled its obligatory duties in ensuring that the best interests of the participants have been satisfied, before the MTA is signed off by the HREC. Considering the historical exploitation of African participant groups in health research, specifically when HBMs are transferred, it is not surprising that SA is not the first African country to include a HREC as signatory to an MTA. The Tanzanian MTA stipulates that the material remains the property of the provider, and requires the chair of their Medical Research Co-ordinating Committee (MRCC) to countersign the agreement in order for it to be effective. In addition, the MRCC authorises and approves in the MTA the exact type of samples that will be transferred from Tanzania.[14] Malawi also requires that an MTA be reviewed, approved and signed by their National Health Sciences Research Committee.[15]

In addition, any HBM or genetic material transferred or exported remains the property of the Malawian Ministry of Health.[15] It is therefore not a new requirement that a HREC be party to an MTA to ensure ethicolegal compliance and participant protections when HBMs are transferred, particularly in the unique African context.

HRECs in the legal spotlight

It is common practice for MTAs to be signed and implemented by institutions instead of individual researchers, and as a result, the enforcement of MTAs is often left in the hands of the institution's legal services department of the research office. As Chalmers *et al*.[1] observe, compliance with international ethical standards demands that an institution's HREC should ensure that the ethical review process relating to the HBM and the data is adequate both in terms of national and international requirements, not to mention the legal requirements relating to those jurisdictions to which the data or material are exported. Moreover, these institutions may have their own regulatory requirements and standards. Some national jurisdictions, such as Australia and Spain, require that researchers are able to prove that HBMs and data were obtained under ethical standards equal or similar to those in these jurisdictions.[16,17] In SA, similar protections exist in the national ethical guidelines in section 3.5.2.3, as well as the Protection of Personal Information Act No. 4 of 2013, the latter stipulating in section 72(1) that where personal information is transferred to a third party in another jurisdiction, such party should be subject to laws or an agreement offering an adequate level of protection that have similar conditions for lawful processing of the personal information as those in SA.

The call for a more active role of HRECs in the future development of best-practice MTAs involving cross-border transfer of HBMs is not new.[1] McGuinness emphasises that HRECs act as regulatory authorities, with concerns beyond those of ethical deliberation, which is clear from the complexities that current protocols present.[18] The call for a better-defined, more transparent and responsible role for HRECs is also reflected in recent developments regarding the liability of HRECs for injury suffered by research subjects. The case of Gelsinger v Trustees of the University of Pennsylvania[19] involved the death of an 18-year-old participant during his participation in a gene therapy study at the University of Pennsylvania's Institute for Gene Therapy. Named as defendants in this case were the trustees of the university, two hospitals affiliated with the research, the investigators, the company that sponsored the research, the former medical school dean and a bioethicist. Causes of action were stated as wrongful death, assault and battery linked to a lack of informed consent and common-law fraud/misrepresentation linked to the informed consent process. The case was subsequently settled, but the details remain unknown.

In Robertson v McGee,[20] the HREC at the University of Oklahoma Health Sciences Center, Tulsa, had approved a protocol for a phase I study of a cancer vaccine. The majority of the patients who participated in the study had advanced disease (melanoma) and were unresponsive to standard therapies. While 94 patients reportedly received the vaccine during the trial, 26 died during the study whose deaths were not attributed to the vaccine itself. In January 2001, a number of participants and their representatives instituted a lawsuit seeking actual and punitive damages against the hospital, the principal investigator, the pharmaceutical sponsor, a senior university official, the individual members of the HREC and the university bioethicist who consulted with the HREC. The causes of action in the Robertson case were derived not only from medical malpractice and tort law, but also from international human rights standards, notably an alleged 'breach of the right to be treated with dignity',[20] as espoused in the Nuremberg Code and the Declaration of Helsinki. Unfortunately, these issues were never decided by the court because the court held that it did not have jurisdiction over the allegations made in the complaint, and the case was dismissed.

Conclusion

The role of HRECs has evolved dramatically over the past few decades. Novel and specialised research, multicentre trials across borders and commercially sponsored research, coupled with a huge increase in the number and complexity of research protocols and capacity and resource constraints on the side of HRECs, have led to serious breaches regarding the protection of human participants.

Research involving the exchange or cross-border transfer of HBMs require specialised legal and ethical knowledge relating to multiple governance frameworks. HRECs may be required to monitor compliance not only with contractual (e.g. MTA) requirements, but also to the national laws and national ethical guidelines and standards of selected jurisdictions, not to mention adherence to international regulatory instruments governing biomedical research generally, and the conditions for the collection and use of HBMs specifically. HRECs will continue to play an increasingly important, responsible and active role in ensuring that the ethicolegal requirements and principles regarding the collection and use of HBMs are adhered to, both nationally, cross-jurisdictionally and internationally. Although not the focus of this article, it is clear that recommendations are desperately required to improve the efficiency of HRECs through a number of interventions, which may include regular and appropriate training for HREC members and more tailored resources to deal with workload, among others.

HRECs are subject to judicial review, and are generally recognised to have sufficient legal personality to be a defendant in a civil suit. The SA legislator's decision to make HRECs signatories to the prescribed MTA template is a first step in the right direction, reinforcing the role and responsibilities of HRECs and their duty of care towards human participants in research. In addition, there has to be a transformation of the mindset towards the acceptance of ethical principles within

legal documents, particularly legal documents that involve the HREC and create binding provisions that have a direct impact on participants. It is time that African views and participant protections are respected and accepted with the same vigour commanded by those of the Western world. It is imperative that a change in institutional culture occurs in order to ensure that the right balance is struck between the protection of human participants and the promotion of good science.

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