Collection and use of human materials during TB clinical research; a review of practices

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Abstract

Background: Human biological materials are usually stored for possible uses in future research because they preserve valuable biological information, save time and resources which would have been spent on collection of fresh samples and are less burdensome to sample sources. However, use of these materials may pose ethical challenges like disclosure of genetic information about an individual or a community which may lead to dire consequences. Others include, stigma, psychological harm, discrimination or bio-security implications rendering sample sources vulnerable, lack of control over the materials or associated data, storage, who owns them, how they are used, for what, by whom and how benefits are shared if any. We evaluated how the tuberculosis (TB) clinical research protocols that were used to collect and store biological materials for future use conform to the requirements stated in the Uganda national guidelines for research involving humans as participants.

Methods: This was a retrospective review of TB clinical research projects approved by the Uganda National Council for Science and Technology (UNCST) from 2011 to 2015, on whether they fulfilled the requirement for ethical collection and use of human materials. Data was abstracted from review of the project protocols and collected using a template developed based on the informed consent and the Materials Transfer Agreement (MTA) requirements in the national guidelines.

Results: Out of 55 research protocols reviewed most of the protocols, 46 (83.6%), had been used to collect the stored samples (sputum, blood and sometimes urine), 13 (28%) had a section on specimen collection and 24% mentioned ownership of the biological materials.

Review of the consent forms used in the studies that stored materials for future use, only 9% of the protocols had a separate consent form for storage of materials, 4.5% of the consent forms explained the risks, 11.4% explained the purpose of the study while 6.8% mentioned the place of storage for the collected materials.

Conclusion: Many of the studies reviewed did not meet the requirements for collection and storage of biological materials contained in the national guidelines.

Background

Clinical research involves collection of human biological materials aimed at understanding the biology of the individuals in order to design appropriate interventions to address the health needs of the individuals or the wider community. With the exponential increase of collaborative research between the high and low -income countries (LMICs) particularly during the HIV/AIDS era, most of the human biological materials (HBMs) collected during clinical research in these countries are exported to their richer counterparts for analysis and sometimes storage for future use [1, 2]. HBMs are often stored for possible uses in future research because they preserve valuable biological information, save time and resources which would have been spent on collection of fresh samples, and are less burdensome to sample sources [2–5]. Hence

it is increasingly becoming fashionable to collect and store such materials for future potential unknown uses [6–10].

Many times HBMs are exported due to inadequate local scientific, technical and storage capacity, for quality assurance at a central lab especially in collaborative research, by citizens studying abroad and because it is cheaper to analyze and interpret samples in more advanced facilities abroad.

However, as materials are exported, aspects like lack of control over the materials or data, where they are stored, who owns them and how they are used, for what and by whom and sharing benefits, if any, have become topical issues in LMIC settings [11–14]. This is mainly because use of stored human materials may impact negatively on sample sources resulting in challenging ethical issues like disclosure of genetic information about an individual or community which may have dire consequences like, stigma, psychological harm, discrimination or bio-security implications rendering sample sources vulnerable [4, 10, 15].

Over the years, Uganda has made significant progress in research ethics capacity development including enactment of the Uganda National Council for Science and Technology (UNCST) Law, establishment of national ethical guidelines for conduct of research involving humans as research participants, institutionalization of the ethical review processes and relevant human resource development (regulators at UNCST, researchers, ethical review committee members and their staff) [16] In order to try and address ethical issues associated with use of stored human materials the National ethical guidelines for research involving humans as participants were revised in 2007 to incorporate guidance on how human materials can be used ethically including a requirement for a separate informed consent form for storage and future use of human materials and a requirement for Materials Transfer Agreement (MTA) for exported materials [17].

As TB is one of the major causes of morbidity and mortality in Uganda and has been studied extensively, this study sought to evaluate how the TB clinical research protocols conform to the Uganda national guidelines requirements for collection, storage and eventual use of stored human biological samples.

Methods

This was a retrospective study of TB clinical research protocols approved and cleared by the UNCST from 2011 to 2015 to assess their compliance with the requirement for ethical collection and use of stored human biological materials. The achieved TB research protocols were reviewed by the investigator in the presence and assisted by an authorized UNCST staff. Permission to review the protocols was granted by the UNCST after the investigator signed a confidentiality none disclosure agreement. Data was abstracted using templates based on the informed consent and MTA frameworks in the Uganda national guidelines for conducting research involving humans as participants 2007. Additional data was collected by review of the respective research protocols for information describing materials collection and handling. Only clinical research protocols involving TB where reviewed by this study

Data management and Statistical analysis

Data were independently captured by two data entry clerks into an EPIdata system. All the captured data were transferred into the Stata version 12.0, where each variable for every unique questionnaire was compared. This eliminated any data inconsistence as a result of entry. Other data inconsistencies were crosschecked with the source documents.

Statistical analysis

Were assessed on the key contents on the consent and MTA based on the UNCST guidelines 2007 in three key domains i) storage of HBMs, ii) *exchange of HBMs and iii) ownership and use of HBMs.* Data were obtained on a total of 46 protocols for *domain-i* that assessed inclusion of 13 items required for informed consent form for storage of HBMs. A total of 8 protocols generated data on domain-ii that assessed content on the exchange of HBMs using 21 items required for the material transfers agreements (MTA). For domain-iii, 46 protocols were assessed on five items indicating inclusion of information concerning storage of materials (acquisition of materials, storage and Future Use, ownership of samples, exchange/transfer of HBMs both from and to or within country for Research Purposes). All items were coded with the responses as; *1: yes included and clearly indicated, 2: yes included but not clearly indicated, and 3: not included at all*.

Exploratory data analysis was conducted on all variables to enable identification of outliers, missing data and ascertain distribution. Descriptive statistics were generated providing percent/proportions for categorical data when the number of observations was at least 20. For the domain-ii "*exchange of HBMs*" where the number of protocols was only 8, only the number of observation under each coded responses was presented instead of the percent distribution.

Ethical issues:

Ethical review and approval was sought from the Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics Committee Ref number SBS385. Clearance to conduct the study was obtained from the Uganda National Council for Science and Technology (UNCST) Ref. number SS4165. The requirement for informed consent was waived since it was a retrospective review of research protocols achieved the UNCST the National Research Regulatory Agency with no individual human participants involved. A confidentiality agreement was between the investigator and the UNCST was signed before access to research records could be granted. All methods were carried out in accordance with relevant guidelines and regulations. No individual protocol identifying information was recorded.

Results

A total of 55 research protocols met the inclusion criteria and were reviewed. Most of the protocols 46 (83.6%) were used to collect HBMs including sputum, blood, biopsies and sometimes urine; 13 (28%) had a section on specimen collection and 24% mentioned ownership of the HBMs. Table 1.

Table 1: Information in the protocol about collection and use of human materials

Percent of protocols with available information on materials collection

Items	Clearly Included	Included but not clear	Not available
Material acquisition	28.3	47.8	23.9
Storage & future use	13.0	26.1	60.9
Ownership of materials	0.0	24.4	75.6
Exchange/transfer of materials	0.0	20.0	80.0
Exchange/transfer while abroad	0.0	13.3	86.7

Although many of the studies store HBMs for future use, only 9% of the protocols had a separate consent form for storage of HBMs, 4.5% of the consent forms explained the risks associated with storage and use, 11.4% explained the purpose of storage while 6.8% mentioned the place of storage for the collected HBMs. Table 2.

Table 2: Review of the informed consent forms for storage and future use of human materials

Information in the consent forms for TB clinical studies

Items	Clearly Included	Included but not clear	Not available
Storage & Enrol Separated	9.1	11.4	79.5
Storage purpose	11.4	9.1	79.5
Storage quantity	2.3	2.3	95.5
Storage Place	6.8	4.5	88.6
Confidentiality measures	2.3	6.8	90.9
Sample use governance	0.0	2.3	97.7
Storage risk/benefits	4.5	0.0	95.5
Other inform included	0.0	4.5	95.5
Storage future use"	0.0	4.7	95.3
Ugandan Co-PI	0.0	0.0	100.0
No storage penalty	4.5	0.0	95.5
Storage withdraw	6.8	0.0	93.2
REC to review future	0.0	4.5	95.5

Only 8 protocols had their MTAs accessed. Of the accessed MTAs, half (4/8) had a description of the HBMs concerned, 5 had the purpose for transfer and usage of HBMs, 4 had the names of the individuals covered by the agreements while another 4 had information describing the ownership of the HBMs Table 3.

Table 3: Review of the materials transfer agreements

Materials transfer agreements

Items	Clearly Included	Included but not clear	Not available
MTA	8	0	0
Parties involved	7	1	0
Description of materials	4	2	2
Purpose and usage	5	2	1
Users names	4	2	1
Period of use	7	0	1
Description of disposal	4	1	3
Restrictions on usage	2	2	4
Ownership of derivatives	4	2	2
Information on ownership	4	3	1

Discussion

The study set out to evaluate how TB clinical research protocols conform to the requirement by the Uganda national guidelines and found that most of the protocols are non-compliant.

Concerning HBMs collection, majority of the protocols lacked an elaborate section on collection, storage and use. This means that the HBMs collection procedures were not well documented in the protocols which would give way to researchers collecting and handling the HBMs the way they felt. Such undocumented collection and handling can affect the standards of how the HBMs are collected and handled and a potential loophole for possible abuse by the researchers. HBMs collection and use should be part of study procedures in any research protocol intending to collect HBMs and, such procedures are subject to ethical review and approval by the relevant research regulatory agencies before they can be carried out. Non-compliance with the national guidelines requirements had been reported in earlier work which reviewed site monitoring reports in the country [18].

However, all the protocols reviewed had been approved by the Research Ethics Committee (REC) and cleared by the national regulator, UNCST. This means that implementation of the guidelines was not only flawed by the researchers but also the RECs as well as the UNCST. There is a need for retraining of all the concerned parties on the requirements by the guidelines. Although significant capacity in research ethics and associated research regulation has been built significantly in this setting, the quality of ethical review

still needs improvement and this should be a continuous process. The challenge of low quality of ethical review in this setting has been observed in other related work [16].

The requirement for a separate informed consent form for storage of HBMs came in existence following the launching of the revised national guidelines in 2007. This was in response to challenges of whether participants who consent for storage of biological materials as part of the enrolment consent actually understood the consent process and appreciate what their decisions mean. This study was intended to evaluate the compliance by the researchers and the regulator with the requirement for acceptable collection, storage and eventual use of HBMs during TB clinical research. The evaluation was done on research approved and conducted during at least four years (2007 to 2011) after the revised guidelines came into force. The four years allowed for the time change and appreciation of the revised guidelines. However, the results of this study indicate that implementation of the guideline requirements was not adhered to indicating either a lack of knowledge or understanding of what the guidelines require, or a complete disregard of the requirement. This requirement is violated by both the researchers and the regulators, it is most likely that both these parties were ignorant about the existence of that regulatory requirement. It should be noted that presence of guidelines alone may not necessarily translate in ethical conduct of research as observed in previous literature [19]. Additionally, it has been observed that although RECs globally have a mandate to protect research participant interests such as confidentiality, ownership, export, storage and secondary use of HBMs (individual good) with specific consent, regulations and policies, implementation of such policies varied from one REC to another [20, 21]. An additional challenge in the African context relates to traditional perceptions of blood and the body. It is well-documented that blood carries symbolic value for many Africans. Since blood has been associated with strength, superstition, exploitative relations, colonialism and witchcraft, amongst others. There is need to carefully explain the purposes of blood collection in the consent process and during collection [22–27]. Similarly, other commentators have stated that Africans believe that blood obtained ostensibly for research purposes will be used for sorcery [28, 29].

Although it is a requirement that all HBMs exchanged by researchers from one institution to another must be accompanied by a valid materials transfer agreement (MTA), this was not the case with many of the studies reviewed though exchange did occur. In order to export HBMs for research purposes from Uganda to other countries, it is a requirement to have a valid MTA, and an export permit must be sought from the UNCST. No records of such permits were identified during this records review. It was difficult to confirm if the studies reviewed had MTAs and export permits because this was a retrospective review of records which may miss out some of the documentation due to filing or storage issues.

Additionally, the accessed MTAs lacked the required information for a valid agreement as stipulated in the national guidelines Table 3. There should be a requirement that every research regulator, researchers and ethics review committee members undergoes context specific research ethics training periodically with focus on the national guidelines before getting involved in research that aims to collect and store HBM.. Such requirements have been implemented for other purposes like Good Clinical Practice (GCP) training for clinical research.

There is need for continuing training of the ethics committees, researchers and the research regulators on all the ethical requirements as stipulated in the national guidelines as well as updating on any new changes affecting the research ethics. Hence it should be a requirement that every research regulator and researcher should undergo research ethics training with focus on the national guidelines before getting involved in their activities.

Limitations

Being a retrospective review, it is possible that some of the TB research protocols were not retrieved because of challenges for achieving and retrieval of study protocols and associated documents.

It was not possible to observe the actual processes of what took place because the review occurred after most of the studies had been completed.

The findings may not help to improve the quality of the concerned protocols because it is retrospective, though it could serve a lesion for future research.

Conclusion

The requirements by the national guidelines for collection, storage and use of HBMs were not observed by both the researchers, ethics committees, and research regulators in many approved TB clinical research studies.

Declarations

Ethics and consent to participate:

The requirement for informed consent was waived by the Makerere University School of Biomedical Sciences Higher Degrees Research and Ethics Committee because the study was a retrospective review of research protocols and no human participants were involved. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication:

Not applicable.

Availability of data and material:

The data-sets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests:

There is no conflict of interest to declare

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Authors' contributions:

JO Conception of the idea, performed Literature search, study design, data collection, data interpretation, drafting, writing, proof reading and approval of manuscript; BK writing, proof reading and approval. NS conception of idea, performed study design, proof reading and approval. All authors read and approved content of the final manuscript.

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Abbreviations

HBM - Human Biological Materials

LMIC - Low and Middle Income Countries

MTA - Materials Transfer Agreement

REC - Research Ethics Committee

TB - Tuberculosis

UNCST - Uganda National Council for Science and Technology

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