Ethical Viewpoint Paper

Ensuring Procedural Guidance for Research Ethics and Research Integrity in Proposals using Human Biospecimens in Resource-limited Settings

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Introduction

Human biospecimens include tissues, blood and other body fluids and excretions. These are mainly attained from healthy volunteers or patients, either through specific research studies or as residual tissues or biofluids surplus to diagnostic requirements, or postmortem. Recent advancement in scientific research for molecular and genetic epidemiology facilitates using biospecimens as an investigative approach from bench to bedside/community. This is particularly visible as a response to emerging health problems such as COVID-19 pandemic, drug resistance in major infectious diseases and non-communicable diseases that entail challenges in the international ethical framework [1-4]. Concomitantly, adequate compliance to principles of research ethics and research integrity is critical to protect the dignity of vulnerable participants. This is reinforced by observing autonomy, beneficence, nonmaleficence and justice as well as by enriching the credibility and scientific impact of research results in building the trust of the community [5].

For collection, storage, and use of biological materials and collected data, the Council for International Organizations of Medical Sciences (CIOMS) has clearly stated ethical considerations in its guideline number 11 about appropriate consent or waiver, confidentiality, transfer, governance structure, accountability etc [6]. This is further strengthened for clinical research in resource-limited settings [7]. Earlier in the Belmont Report in 1979, similar issues for oversight and governance have been addressed [8]. To date, the National Institutes of Health (NIH) Intramural Research Program has revised its guidelines for human biospecimens in 2021 concerning storage, tracking, sharing, and disposal with emphasis on ethical considerations for leftover/residual samples and pathogen isolates. Leftover specimens are particularly valuable in vulnerable populations such as children, elderly, and pregnant patients, from whom an extra blood draw for research could be challenging or sometimes impossible thereby mitigating the risks and increasing the social value [9].

Towards modification of procedural guidelines in research ethics review

The Institutional Review Boards/Research Ethics Committees (IRBs/RECs) need to modify and strengthen the procedural guidelines in reviewing the research proposals using biospecimens inclusive of left-over/residual samples in accord with recent advances [10-11]. Mainly, the focus is on the procedural decision for the appropriate level of review, the nature of recruitment and collecting data, weighing risks and social values, the level of identifiability of leftover

biospecimens, type of informed consent required, sharing data, exporting or importing biospecimens, material transfer and data use agreements, future research use, and reporting research results [12].

In laboratory medicine, the collection of biospecimens of human research participants (fresh or stored) and related data either retrospective or prospective from multiple sources in a variety of settings could create ethical concerns and practical challenges [13]. Likely determinants in developing countries include weaknesses in legislations and regulatory environment, knowledge gaps, poor infrastructure and lack of resources. In using leftover specimens for research purpose, they still should be deidentified and saved with meticulous control and care to protect patients' privacy and confidentiality. On the contrary, IRB reviews are exempted for the coded biospecimens in laboratories without an access of code keys to researchers or research use of unlinked/anonymize biospecimens inclusive of pathogen isolates which are categorized as 'not human subjects research' [9]. Moreover, in its draft version for benchmarking tools in September 2022, WHO has stated the explicit requirement of legal provisions in Research Ethics Committees to meet the internationally accepted ethical standards for reviews before the research commences. There may be an exemption in studies using previously collected biological specimens or data being specified as low-risk categories [14]. A leftover biospecimen is defined as the remnant of a human specimen collected for routine clinical care or analysis that would otherwise have been discarded. A research sample is a biospecimen collected for research purposes. Nevertheless, quality assurance is central to the use of leftover human biospecimens in research studies.

In the absence of large biobanks for leftover/residual human biospecimens in the public sector, studies are limited or none in resource-limited scenarios including Myanmar that address the viewpoints of researchers, IRB/REC members and research grant assessors concerning complex research ethics oversight requirements [15-16]. Exploring ways and means for improved understanding of advancement in research ethics issues linked to human biospecimens, particularly the use of leftover samples will lead to not only quality research ethics review procedures but also beneficial in the enhanced responsible conduct of research and research integrity by mitigating challenges and limitations.

WHO defines "research with human participants" as "any social science, biomedical, behavioral, or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new knowledge; in which human beings (i) are exposed to manipulation, intervention, observation, or other interaction with investigators either directly or through alteration of their environment, or (ii) become individually identifiable through investigators' collection, preparation, or use of biological material or medical or other records [17]". In line with the given definition of WHO concerning research with human participants, the researchers should attempt to strengthen the ethical guidelines in conducting research involving human bio specimens.

Implications for further research

To date, the COVID-19 pandemic before the end game makes researchers difficult in direct interaction with study participants and access to data collection for human biospecimens. In that case, researchers attempt for more access to left-over materials either to work in a silo or through a collaborative approach that entails ethical challenges apart from technical and administrative requirements. It is imperative to introduce the research intervention that might lead to effective and timely procedural changes in reviewing the research proposals to promote research integrity in resource-limited settings. In dealing with research proposals using human biospecimens, specific objectives should focus to gain insight into the perspectives (awareness, opinions, perceptions) of researchers, IRB/REC members, and research grant assessors in terms of:

(1) research ethics policy and procedures to be followed during the triage in submission for review (full board review, expedited review and exemption from further ethics review);
(2) research ethics principles specifically related to leftover/residual human biospecimens with or without further analyses of pathogen isolates.
(3) challenges in hospitals, clinics, and field settings and potential enhancers.
(4) suggestions to strengthen the current research ethics review procedures.

It is a necessity to promote the awareness of researchers that the initial decision for the level of review at the IRB/REC in general depends on the vulnerability of the study population, data collection: invasive or not invasive; degree of risks for participants by involving in the study (physical risk, social risk, psychological risk, legal risk); intended sources/sites for collecting human biospecimens (operation theatres, hospital wards, clinics, public/private laboratories, community); inclusion of leftover human biospecimens and/or secondary data; inclusion of pathogen isolates; data to be collected prospective or retrospective or both; data to be collected: primary or secondary or both.
Moreover, an improved understanding is essential that under the following conditions, the research proposals could be categorized as "Not Human Subjects Research" and entitled for an exemption from further IRB review process.

(1) Proposed research without an involvement of interaction with living human subjects.
(2) Proposed research involving the use of secondary human biospecimen related data and aggregate level analysis.
(3) Proposed research involving only use of coded or deidentified human biospecimens and/or data.
(4) Proposed research with live surgical tissues being resected for clinical purpose and will otherwise be discarded.
(5) Proposed research involving cadavers, autopsy materials, or bio specimens from now deceased individuals.

Conclusions

By and large, researchers should adhere to the ethical principles for 'Not Human Subjects Research' Projects when appropriate such as scientifically sound design and procedures, informed consent, and privacy and confidentiality protections. The researchers will encounter the myriad of administrative, technical and ethical challenges in planning the source of collecting human biospecimens in general. Priority ranking of those challenges is ambiguous depending on the settings: hospitals, clinics and in the field. However, favourable conditions exist in varying degrees to enhance the researchers in resource limited settings to develop/review the proposals involving use of human biospecimens particularly by observing the standard operating procedures of the IRB/REC and international ethics guidelines, attending research ethics and research integrity training courses and international research ethics conferences and by working in close collaboration with researchers of developed countries and arranging improved access to bio repositories.

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