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Ethical, legal, and social implications in research biobanking: A checklist for navigating complexity

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Abstract

Biobanks' activity is based not only on securing the technology of collecting and storing human biospecimen, but also on preparing formal documentation that will enable its safe use for scientific research. In that context, the issue of informed consent, the reporting of incidental findings and the use of Transfer Agreements remain a vast challenge. This paper aims to offer first–hand tangible solutions on those issues in the context of collaborative and transnational biobanking research. It presents a four-step checklist aiming to facilitate researchers on their compliance with applicable legal and ethical guidelines, when designing their studies, when recruiting participants, when handling samples and data, and when communicating research results and incidental findings. Although the paper reflects the outcomes of the H2020 B3Africa project and examines the transfers from and to the EU as a case study, it presents a global checklist that can be used beyond the EU.

KEYWORDS
biobanking, biomedical research, ELSI, informed consent, personal data, research ethics committees

1 | INTRODUCTION

Biomedical research developments have both scientific and societal value. However, they may only reach the society, after the lawful implementation of ethically sound study protocols which require the direct or indirect involvement of humans[1] and the use of human biological samples. Ethical and regulatory frameworks for sharing human samples and affiliated data between biobanks and other research/industrial parties are essential for a high-level scientific cooperation. In many countries the lack of a national legislative background in biobanking and biomedicine, leads biobanking personnel to seek support from internationally recognized organizations,[2]

[1]Goldblatt, E.M., & Lee, W-H. (2010). From Bench to Bedside: The Growing Use of Translational Research in Cancer Medicine. American Journal of Translational Research. 2(1), 1-18.

[2]Biobanking and BioMolecular Resources Research Infrastructure - European Research Infrastructure Consortium (BBMRI-ERIC). (2021). Guidelines to Good Research. Retrieved May 12, 2023, from https://www.bbmri-eric.eu/elsi-knowledge-base/guidelines-to-good-research/; European, Middle Eastern & African Society for Biopreservation and Biobanking

which promote guidelines for transnational terms of cooperation to maximize the efficiency in biomedical research.

The variety of instruments, which are available for the compliance to the Ethical, Legal and Social Implications (ELSI) requirements in biobanking has led to an inevitable regulatory polyphony. Some tools and documents provide general information (e.g., Global Alliance for Genomics and Health (GA4GH) Framework for Responsible Sharing of Genomic and Health-Related Data)[3] while others provide country- and context-specific guidance (e.g., Research Data Alliance's Recommendations for COVID-19[4] or European Clinical Research Infrastructure Network's (ECRIN) Campus Toolbox[5] that allows to navigate the regulatory and ethical requirements at the country-level for clinical research). Similarly, online training tools are also gaining traction (e.g., Institut Pasteur's course on Biobanking or Training and Resources in Research Ethics Evaluation).[6] There are also mixed approaches, where numerous components such as recommendations, guidelines, supporting documents, templates or webinars among others are brought together (e.g., BBMRI-ERIC's ELSI Knowledge Base).[7]

The existing regulatory fragmentation creates significant challenges for research. Thus, it is necessary to disentangle the fragmented regulatory landscape and focus our efforts towards the creation of common minimum standards (e.g., B1MG Data Access and Use Governance Toolkit),[8] and towards the national or regional standardization at document level (e.g., Informed Consent Template recommended by the Permanent Working Party of the German Medical Ethics Committees)[9] and sub-document level (eg, GA4GH's model consent clauses for rare diseases).[10]

Many issues related to scientific research on biobanks are mostly governed by ethical guidelines as well as soft law instruments adopted by intergovernmental organizations and scientific societies.[11] Most modern national laws are based on the core principles enshrined in these soft law instruments, which although non-binding, inform our understanding of binding legal rules and end up creating expectations for future conduct.[12] Therefore, despite the existing fragmentation in national frameworks, these sets of core principles open the way towards a 'little legal harmonization between countries'.[13]

According to a recent study, there is a high need for professional ethical and legal support within the biobanking community.[14] This paper aims to assist in this cause by decoding the main principles enshrined in ethical guidelines and soft law instruments and guide researchers from the initial stage of designing the study protocol, recruiting research participants and handling samples and data to communicating research results. Researchers are called to address a wide range of challenges, such as those related to the available funding, the size and scale of the research project, the existence or not of a competent Research Ethics Committee (REC), the varied legal landscape across jurisdictions where some countries have specialised regulations on biobanking research and/or data protection, while others do not or partially receive technical assistance by the (institutional) Data Protection Officer (DPO) or tech transfer office. These challenges have a horizontal effect, as they can affect more than one step of the research. This paper aims to provide guidance on navigating the different steps of research and serve as an assisting tool for the non-ethicist audience of the biobanking and biomedical research community.

The outcomes of this paper emerged out of the B3Africa project that focused on biobanking in selected countries across Europe and Africa,[15] however, the lessons learned enabled a comprehensive overview that can be implemented in various research settings.

The structure of the paper comprises a four-step checklist (see Figure 1) that describes what researchers should consider, namely 1) when designing the study protocol, 2) when recruiting participants, 3) when handling human samples and data and, 4) when communicating research results and incidental findings. It must be noted that this guidance is flexible and should be tailored as per research institutions' needs, empowering scientists to exercise their freedom to scientific research.[16]

(ESBB). ESBB Working Groups. Retrieved May 12, 2023 from https://esbb.org/page/WorkingGroups; International Society for Biological and Environmental Repositories (ISBER). (2018). Best Practices: Recommendations for Repositories Fourth Edition. Retrieved May 12, 2023, from https://www.isber.org/page/BPR.

[3]GA4GH. (2019). Framework for Responsible Sharing of Genomic and Health-Related Data. Retrieved May 12, 2023, from https://www.ga4gh.org/document/framework-for-responsible-sharing-of-genomic-and-health-related-data-sharing-v1/.

[4]Research Data Alliance (RDA). (2020). RDA Covid-19 Recommendations and Guidelines. 5th release. Retrieved May 12, 2023, from https://doi.org/10.15497/RDA00046.

[5]European Clinical Research Infrastructure Network (ECRIN). Retrieved May 12, 2023, from http://campus.ecrin.org/.

[6]Institut Pasteur. Course on Biobanking. Fun Mooc. Retrieved May 12, 2023, from https://www.fun-mooc.fr/en/courses/biobanking/; Training and Resources in Research Ethics Evaluation (TRREE). TRREE On-line Training Programme on the Ethics and Regulation of Health Research Involving Human Participants. Retrieved May 12, 2023, from https://elearning.trree.org/.

[7]Mayrhofer, M.T. & Schlünder, I. (2018). Mind the Gap: From Tool to Knowledge Base. Biopreservation and Biobanking. 16(6), 458-462; BBMRI-ERIC. ELSI Knowledge Base. Retrieved May 12, 2023, from https://www.bbmri-eric.eu/elsi/knowledge-base/.

[8]Beyond 1 Million Genomes (B1MG). B1MG Data Access and Use Governance Toolkit. Retrieved May 12, 2023, from https://b1mg-project.eu/work-packages/wp2.

[9]Permanent Working Party of the German Medical Ethics Committees. (2019). Informed Consent Template. Retrieved May 12, 2023, from https://www.akek.de/biobanken/.

[10]Nguyen, M.T., Goldblatt, J., Isasi, R., Jagut, M., Hechtelt Jonker, A., Kaufmann, P., Ouillade, L., et al. (2019). Model Consent Clauses for Rare Disease Research. BMC Medical Ethics. 20(55), 1-7.

[11]Chassang, G., & Rial-Sebbag, E. (2018). Research Biobanks and Health Databases: The WMA Declaration of Taipei, Added Value to European Legislation (Soft and Hard Law). European Journal of Health Law. 25(5), 501-516, 504.

[12]Guzman, A.T., & Meyer, T.L. (2010). International Soft Law. Journal of Legal Analysis. 2(1), 171-225, 174.

[13]Klingstrom, T., Bongcam-Rudloff, E., & Reichel, J. (2018). Legal & Ethical Compliance When Sharing Biospecimen. Briefings in Functional Genomics. 17(1), 1-7, 2.

[14]Goisauf, M., Martin, G., Beate Bentzen, H., Budin-Ljøsne, I., Ursin, L., Durnová, A., et al. (2019). Data in Question: A Survey of European Biobank Professionals on Ethical, Legal and Societal Challenges of Biobank Research. PLoS ONE. 14(9), 1-22.

[15]Bridging Biobanking and Biomedical Research Across Europe and Africa (B3Africa). Retrieved May 12, 2023, from http://www.b3africa.org/. The B3Africa project engaged in capacity building to support equitable collaboration between researchers in low, middle and high income countries. A key goal was defining an ethical and regulatory framework for biobank data sharing between Europe and Africa.

[16]UN General Assembly. (1966). International Covenant on Economic, Social and Cultural Rights. 993 UNTS 3. Retrieved May 12, 2023, from https://www.ohchr.org/sites/default/files/cescr.pdf. Committee on Economic, Social and Cultural Rights. (2020). General comment No. 25 on science and economic, social and cultural rights (article 15 (1) (b), (2), (3) and (4) of ICESCR. UN Doc E/C.12/GC/25, paragraph 13. Retrieved May 12, 2023, from https://documents-dds-ny.un.org/doc/UNDOC/GEN/G20/108/12/PDF/G2010812.pdf?OpenElement.

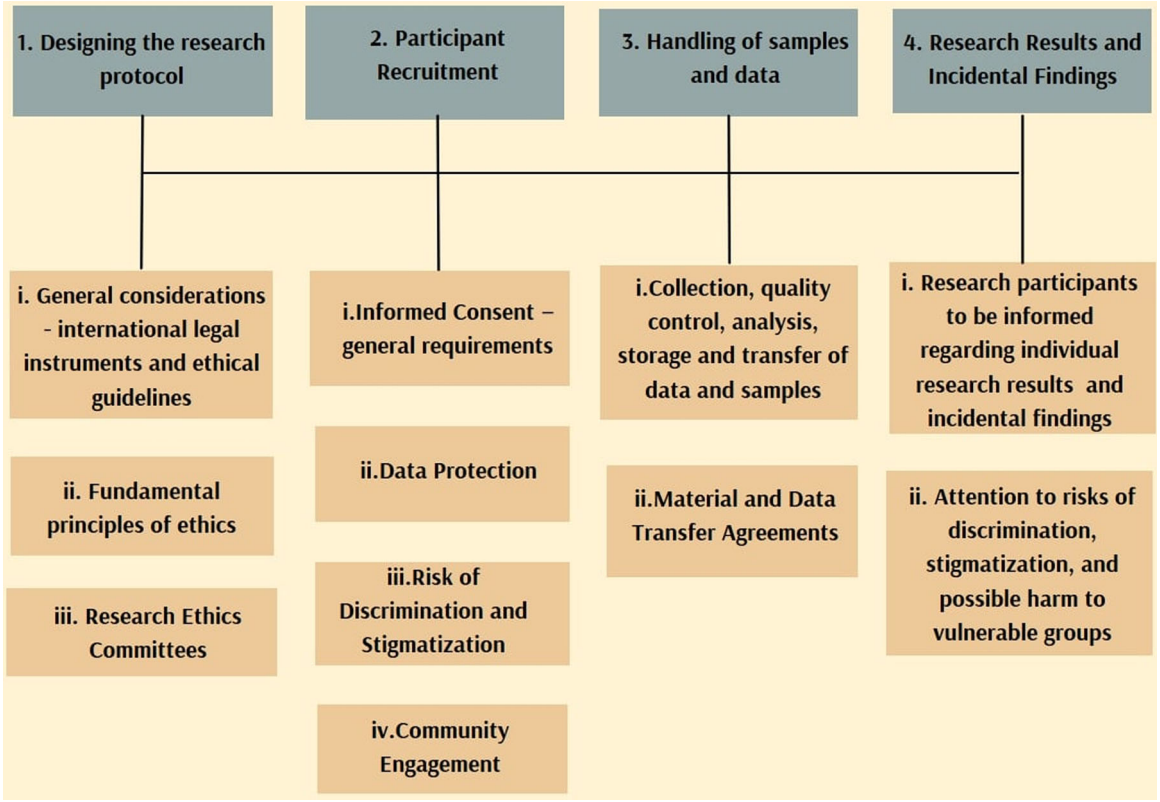

FIGURE 1 ELSI checklist for biobanking research.

2 | FOUR-STEP CHECKLIST

2.1 | Step 1: Designing the research protocol

2.1.1 | General considerations – international legal instruments and ethical guidelines

The balancing of risks and benefits related to a research protocol is a practice that dates to the 1970s.[17] When it comes to biobanking, the risks often concern privacy breaches and misuse of the individual's health and genetic information.

To address the above-mentioned issues in the most effective manner, researchers are encouraged to take into consideration general and sector specific advisory documents, which can be further categorized into hard law instruments, soft law instruments adopted by intergovernmental organizations and scientific societies and ethical guidelines produced by other bodies. For example, the Convention on Human Rights and Biomedicine, also known as Oviedo Convention and its Additional Protocol on Biomedical Research adopted by the Council of Europe (CoE), are regional hard law instruments, legally binding in those countries who ratified them.[18] In the soft law category, we can find the Guidelines on Human Biobanks and Genetic Research Database of the Organization of Economic for Economic Co-operation and Development (OECD),[19] the Recommendation (2016)6 of the Committee of Ministers of CoE on Research on Biological Material of Human Origin[20] and the relevant United Nations Educational, Scientific and Cultural Organization (UNESCO) Universal Declarations, namely the UNESCO Universal Declaration on Bioethics and Human Rights,[21] the UNESCO Universal Declaration on the Human Genome and Human Rights,[22] and the UNESCO

[17]National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The Belmont Report. Retrieved May 12, 2023, from https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html.

[18]Council of Europe. (1997). Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. ETS 164. Retrieved May 12, 2023, from https://rm.coe.int/168007cf98; Council of Europe. (2005). Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research. CETS 195, Retrieved May 12, 2023, from https://rm.coe.int/168008371a.

[19]OECD. (2009). Guidelines on Human Biobanks and Genetic Research Databases. Retrieved May 12, 2023, from https://www.oecd.org/sti/emerging-tech/44054609.pdf.

[20]Council of Europe. (2016). Recommendation of the Committee of Ministers to member States on research on biological materials of human origin. CM/Rec(2016)6 (CoE Recommendation (2016)6). Retrieved May 12, 2023, from https://search.coe.int/cm/Pages/result_details.aspx?ObjectId=090000168064e8ff.

[21]UNESCO. (2005). Universal Declaration on Bioethics and Human Rights. SHS/EST/BIO/06/1, SHS.2006/WS/14. Retrieved May 12, 2023 from https://unesdoc.unesco.org/ark:/48223/pf0000146180.

[22]UNESCO. (1997). Universal Declaration on the Human Genome and Human Rights. BR/2001/PI/H/1. Retrieved May 12, 2023, from https://en.unesco.org/themes/ethics-science-and-technology/human-genome-and-human-rights.

International Declaration on Human Genetic Data,[23] as well as the World Medical Association (WMA) Declaration of Helsinki[24] and the Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks.[25] Ethical guidelines indicatively include the International Ethical Guidelines for Health-related Research Involving Human of the Council for International Organizations of Medical Sciences (CIOMS)[26] and ISBER best recommendations for repositories.[27]

2.1.2 | Fundamental ethics principles in biobanking

The above-mentioned instruments are based on the four fundamental principles of biomedical ethics namely - respect for autonomy, beneficence, non-maleficence, and justice.[28]

Respect for autonomy in the context of biobanking is expressed through providing adequate information to potential research participants, by obtaining their free and informed consent and by ensuring that they have the right to withdraw their consent and have their samples and data deleted from a biobank at any time. To be legally valid and ethically sound, the consent must be the result of an autonomous choice, reflecting the free will of the individual who grants it without being coerced or manipulated. In the context of biobanking, samples and data are usually stored for future research, whose purpose is not yet defined. This requires using specific types of consent– open, broad, or dynamic consent. In an open consent approach, the research subject grants their consent to the future processing of their data and samples giving researchers the flexibility to conduct research on their data and samples within legal and ethical boundaries.[29] Broad consent allows researchers 'to collect biological samples, genomic data and other research subject data for use in unspecified future research projects'.[30] Dynamic consent is defined as a dynamic process which enables the communication and engagement with data subjects through secure digital means, allowing them to revisit and review their consent decisions and their preferences during the life of the research.[31]

According to the UNESCO Universal Declaration on Bioethics and Human Rights, beneficence aims to promote 'the welfare of individuals, families, groups or communities and humankind as a whole' putting as a condition that research should benefit humans and society as a whole.[32] Usually biobank-based research produces few individual direct benefits for the research participants. Nevertheless, with the development of -omics and secondary use of data, important information may be produced in the form of individual research results (IRRs) or incidental findings (IFs).

Non-maleficence in the context of biobanking implies the prevention of risks to an individual's privacy and safety of personal data, as well as individual and group risks of discrimination and stigmatization.[33]

Finally, justice is defined as the 'fundamental equality of all human beings in dignity and rights'.[34] The implementation of this principle means ensuring fair distribution of benefits and burdens by preventing 'ethics dumping' in research in low-, or middle-income settings, development of benefit-sharing frameworks, ensuring transparent governance of biobanks and clear rules for involvement of commercial actors.[35]

All the above-mentioned ethics principles have been operationalized and apply directly to biobanks as indicated below and serve as valuable means to verify whether the research complies with ethical standards.

2.1.3 | Research Ethics Committees

RECs serve as a safeguard in the research process.[36] In certain countries, RECs are set up by law as independent bodies, while in others they are incorporated within the organizational structure of a hospital or research center with their members usually being employees of the institutions. A REC's approval has a particular role in ensuring the risk and benefit assessment. When it comes to biobanks, in certain cases an additional approval for data access is requested from Data Access Committees (DACs). DACs facilitate the procedure of authorized data access based on a biobank's governance model and a positive REC opinion is typically a prerequisite before applying for a DAC approval.

[23]UNESCO. (2003). International Declaration on Human Genetic Data. SHS/BIO/04/1. Retrieved May 12, 2023, from https://en.unesco.org/themes/ethics-science-and-technology/human-genetic-data.

[24]World Medical Association. (1964). Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Retrieved May 12, 2023, from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

[25]World Medical Association. (2002). Declaration of Taipei on Ethical Considerations Regarding Health Databases and Biobanks. Retrieved May 12, 2023, from https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/.

[26]Council for International Organizations of Medical Sciences (CIOMS) & World Health Organization (WHO). (2016). International Ethical Guidelines for Health-related Research Involving Humans. 4th Edition. Retrieved May 12, 2023, from https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf.

[27]International Society for Biological and Environmental Repositories (ISBER), op. cit. note 2.

[28]Beauchamp, T.L., & Childress, J.F. (2009). Principles of Biomedical Ethics. 9th edition. Oxford University Press.

[29]Gille, F., & Brall, C. (2022). Can we Know if Donor Trust Expires? About Trust Relationships and Time in the Context of Open Consent for Future Data Use. Journal of Medical Ethics. 48(3), 184-188.

[30]Hallinan, D. (2020). Broad Consent under the GDPR: An Optimistic Perspective on a Bright Future. Life Sciences, Society and Policy. 16, 1-18.

[31]Teare, H.J.A., Prictor, M., & Kaye, J. (2021). Reflections on Dynamic Consent in Biomedical Research: The Story so Far. European Journal of Human Genetics. 29, 649-656.

[32]UNESCO, op. cit. 21, Preamble.

[33]OECD, op. cit. note 19, paragraphs 1.E and 1.D.

[34]UNESCO, op. cit. 21, Article 10.

[35]Chatfield, K., Schroeder, D., Guantai, A., Bhatt, K., Bukusi, E., Adhiambo Odhiambo, J., et al. (2020). Preventing Ethics Dumping: The Challenges for Kenyan Research Ethics Committees. Research Ethics. 17(1), 23-44.

[36]Helsinki Declaration, op. cit. note 24, paragraph 23; Taipei Declaration, op. cit. note 25, paragraph 19; UNESCO, op. cit. note 21, Article 19; see CIOMS, op. cit. note 26, Guideline 23.

2.2 | Step 2: Participant Recruitment

The balance between the participant's right to data protection and other rights and interests at stake, such as that of scientific research, lies at the center of biobanking research.[37] To achieve this, it is important for researchers to address informed consent, data protection, IFs, genetic discrimination, and stigmatization risk as well as the role of the community engagement appropriately for their studies already during the recruitment phase.[38]

2.2.1 | Informed Consent – general requirements

The Declaration of Taipei, which should be read in the light of the Declaration of Helsinki, is a significant tool for the participants' recruitment in biobanking. In particular, the Declaration's significance stems from its international approach which brings provisions of hard law, e.g., GDPR, together with ethical guidelines and best practices on the storage and management of biological material,[39] enabling that way its application on global scale. The Declaration of Taipei distinguishes two situations; a) where samples and data are collected for a specific research project, 'free and informed consent of the participants must be obtained in accordance with the Declaration of Helsinki',[40] and, b) where samples and data are collected for storing in a biobank for multiple and indefinite future uses, consent is broad. In the first case, each potential participant must receive adequate information.[41] In the second case, additional information must be provided at minimum.[42]

In the process of obtaining informed consent, additional information may be provided to research participants about other aspects such as the participant's insurance, reimbursement, intellectual property issues, data commercialization and conflict of interest. Furthermore, researchers in different contexts should be able to adjust the information provided to address the various ad hoc needs and concerns of participants, such as local values and traditions.[43] Researchers should consider providing consent forms not only in the appropriate (local) language, but also in lay language accommodating various literacy levels.

If a potential participant is not capable to give informed consent, information should be provided 'in a manner compatible to their understanding'[44] and consent should be asked from their legal representatives. A person not capable to give informed consent can be included in research only if the study provides direct benefit to them or the research is intended to promote the health of a group this person represents, and the research cannot be performed with persons capable of granting informed consent while there is only a minimal risk and burden deriving from the research.[45]

The informing process is much more than merely a one-off procedure, as it necessitates that new information should be provided on an ongoing basis and that subsequent inquiries of the research participants should be answered. Such transparency[46] contributes to good governance, and it allows the consent to be 'deep' as broad as it may be.[47]

Approaches on how to proceed with data re-use without jeopardizing the study vary depending on the national legislation[48] Interestingly, some organizations have developed legacy assessment filters to facilitate researchers when dealing with legacy datasets, whose characteristic is that when the data were collected, the individuals were not informed about the potential of data sharing or further processing for research on a disease type different than the original one.[49] The RECs' role in the latter case is crucial since they act as safeguards of the individual's rights ensuring the legality of retrospective research.[50]

2.2.2 | Data Protection

One of the most important aspects of biobanking research involves the samples and data transfers among researchers across the world in various collaborative research settings. Within the context of the B3Africa project, it was found that the approaches on data protection in the biobanking context varied largely. For example, South Africa has enacted its first comprehensive data protection framework that has similar provisions[51] to the General Data Protection Regulation (GDPR),[52] which is the main instrument of EU data protection law. On the other hand, it had been found that Uganda and Kenya should

[37]Eriksson, S., & Helgesson, G. (2005). Potential Harms, Anonymization, And the Right to Withdraw Consent to Biobank Research. European Journal Human Genetics. 13(9), 1071-1076.
[38]Slokenberga, S., Merino Martinez, R., & Reichel, J. (2017). Legal and Ethical Governance of Intercontinental Biobanking: Some Experiences from a H2020 Project. Förvaltningsrättslig Tidskrift. 1, 169-192.
[39]Chassang & Rial-Sebbag, op. cit. note 11, p. 507.
[40]Declaration of Taipei, op. cit. note 25, paragraph 11.
[41]Declaration of Helsinki, op. cit. note 24, paragraph 26.
[42]Declaration of Taipei, op. cit. note 25, paragraph 12.
[43]Halkoaho, A., Pietilä, A.-M., Ebbesen, M., Karki, S., & Kangasniemi, M. (2016). Cultural Aspects Related to Informed Consent in Health Research: A Systematic Review. Nursing Ethics. 23(6), 698-712.
[44]Council of Europe, op. cit. note 20, Article 10(4).
[45]Declaration of Helsinki, op. cit. note 24, paragraph 28.
[46]Gille, F., Vayena, E., & Blasimme, A. (2020). Future-Proofing Biobanks' Governance. European Journal of Human Genetics. 28(8), 989-996.
[47]Bjerregaard, R.B., Gjerris, M., Waldemar, G., & Sandøe. P. (2019). Broad Consent for Biobanks is Best – Provided it is Also Deep. BMC Medical Ethics. 20, 71.
[48]Tzortzatou, O., Slokenberga, S., Reichel, J., da Costa Andrade, A., Barbosa, C., Bekaert, S., et al. (2021). Biobanking Across Europe Post-GDPR: A Deliberately Fragmented Landscape. In O. Tzortzatou, S. Slokenberga, & J. Reichel (Eds), GDPR and Biobanking Individual Rights, Public Interest and Research Regulations across Europe (pp. 397-419). Law, Governance and Technology Series 43. Springer.
[49]Wallace, S.E., Kirby, E. & Knoppers, B.M. (2020). How Can We Not Waste Legacy Genomic Research Data? Frontiers in Genetics. 11, 446.
[50]Whitley, S.N. (2016). Balanced Ethics Review. A Guide for Institutional Review Board Members. Springer International Publishing.
[51]Staunton, C., & De Stadler, E. (2019). Protection of Personal Information Act No. 4 of 2013: Implications for Biobanks. South African Medical Journal. 109(4), 232-234.
[52]European Parliament and Council. (2016). Regulation 2016/679/EU of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC [2016] OJ L119/1 (GDPR). Retrieved May 12, 2023, from https://eur-lex.europa.eu/eli/reg/2016/679/oj.

revise several provisions in their -at the time- draft data protection legislation, to be able to ensure privacy protection.[53] For those protocols specifically dealing with data collected from EU citizens transferred to African countries and vice versa, various sets of EU and national legislations apply; first and foremost, GDPR,[54] which sets the golden standard for data processing activities. In that context, GDPR is used as a case study in order to identify how individuals are protected (see Figure 2). It should be noted that when it comes to data transfers from the EU to third countries, the examined provisions have a general application, being applicable for example also on transfers from the EU to the United States (US)[55] and Canada.[56] Depending on the context, different GDPR provisions will be applicable.

In the biobanking context, biobanks are often the data controller, which under GDPR is defined as the natural or legal person, public authority, agency or other body, that determines the purposes and means of the data processing.[57] Therefore, the biobank must ensure that there is an appropriate legal basis for the processing of personal data (art 6(1) GDPR). Usually, the legal basis is either consent (art 6(1)a) GDPR) or public interest (art 6(1)e GDPR). GDPR also provides a set of legal bases that enable the processing of genetic and health data despite the general prohibition (art 9(2) GDPR). GDPR also sets forth several obligations on data controllers and data processors.[58]

Research participants are equipped with several rights, depending on national derogations legislated by EU Member States.[59] The central derogation avenue is the so-called 'scientific research regime' that enables direct as well as indirect derogations through the respective relevant Member State or EU law.[60] These derogations can be applied on condition that appropriate safeguards, such as pseudonymization, encryption, DPO appointment, filling a record of processing activities, creation of code of conduct and other technical and organizational measures are employed in line with art 89(1) GDPR.[61]

In the context of biobanking, GDPR enables data transfers with third countries under three main avenues, which apply in hierarchical order,[62] in the sense that the latter only applies in the absence of the former. The three mechanisms are 1) the existence of an adequacy decision 2) the provision of appropriate safeguards and 3) derogations for exceptional situations explicitly prescribed under GDPR (art 49 GDPR). One form of appropriate safeguards is the Data Transfer Agreement (DTA) that will be explored in more detail below in Step 2.3.2.

The CoE Convention for the Protection of Individuals with regard to the Processing of Personal Data (Convention 108), which is the first binding international instrument which sought to regulate the cross-border flow of personal data,[63] underwent a modernization process in 2018, leading to the Modernized Convention 108 (Convention 108 +).[64] Accession to the Convention, which is open for signature to non-CoE States, is a criterion to be taken into account in the context of international data transfers.[65]

On a general note, it has been argued that data protection requirements establish a mechanism of controlled access to one's state of separateness,[66] and that is why they are crucial for the prevention of unwarranted interventions. The risk of breaching privacy may be one aspect of 'perceived' harm by the participants.[67]

2.2.3 | Risk of discrimination and stigmatization

The misuse or unintended use of data, especially health and genetic data could result in stigmatization and discrimination and, consequently, could threaten individuals' or groups' equal opportunities and their participation in research benefits or society at large.

Genetic discrimination refers to a person's or their relatives' maltreatment based on the genotype or family history unrelated to symptoms of a disease.[68] Genetic differences may be actual or presumed, while both pose a risk for discrimination at the individual or group level.[69] Harm could, for instance, arise for individuals, when they are categorized or grouped in aggregated data or big datasets based on geographical, ethnic, or cultural characteristics. Hence, research outcomes can pose a real risk for discrimination of these groups and the individuals who share such characteristics.[70] Whether

[53]Slokenberga, S., Reichel, J., Niringiye, R., Croxton, T., Swanepoel, C., & Okal, J. (2019). EU Data Transfer Rules and African Legal Realities: Is Data Exchange for Biobank Research Realistic? International Data Privacy Law. 9(1), 30-48.
[54]Slokenberga, S. (2021). Setting the Foundations: Individual Rights, Public Interest, Scientific Research and Biobanking. In O. Tzortzatou, S. Slokenberga, & J. Reichel (Eds), GDPR and Biobanking Individual Rights, Public Interest and Research Regulations across Europe (pp. 11-30). Law, Governance and Technology Series 43, Springer.
[55]Hallinan, D., Bernier, A., Cambon-Thomsen, A., Crawley, F.P., Dimitrova, D., Bauzer Medeiros, C., et al. (2021). International Transfers of Personal Data for Health Research Following Schrems II: A Problem in Need of a Solution. European Journal of Human Genetics. 29, 1502-1509.
[56]Thorogood, A. (2018). Canada: Will Privacy Rules Continue to Favour Open Science? Human Genetics. 137(8), 595-602.
[57]GDPR, op. cit. note 52, Article 4(7).
[58]Ibid: Article 4(8): 'Processor means a natural or legal person public authority, agency or other body which processes personal data on behalf of the controller'.
[59]Ibid: right to information (Articles 13, 14, 19 and 34), right of access (Article 15), right to rectification (Article 16), right to erasure (Article 17), right to restriction of processing (Article 18), right to data portability (Article 20), right to object (Article 21), right to lodge a complaint with a supervisory authority (Article 77), right to an effective judicial remedy (Articles 78 and 79), right to representation (Article 80), and right to compensation (Article 82).
[60]Ibid: Article 89(2); Slokenberga, op. cit. note 54.
[61]Duguet, A.M., & Herveg, J. (2021). Safeguards and Derogations Relating to Processing for Scientific Purposes: Article 89 Analysis for Biobank Research. In O. Tzortzatou, S. Slokenberga, & J. Reichel (Eds), GDPR and Biobanking Individual Rights, Public Interest and Research Regulations across Europe (pp. 105-120). Law, Governance and Technology Series 43, Springer.
[62]Slokenberga, et al., op. cit. note 38, p. 189.
[63]Council of Europe. (1981). Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data. ETS 108. Retrieved May 12, 2023, from https://rm.coe.int/1680078b37.
[64]Council of Europe. (2018). Amending Protocol to the Convention for the Protection of Individuals with regard to the Processing of Personal Data. CETS 223. Retrieved May 12, 2023, from https://rm.coe.int/16808ac918.
[65]GDPR, op. cit. note 52, Article 45(2)c, Recital 105.
[66]Slokenberga, op. cit. note 54.
[67]Nurmsoo, S., & Hayes, M. (2015). Awareness of Risks of Biobank Research May Affect Public Attitudes Toward Consent. Journal of Community Genetics. 6(2), 181-182.
[68]Rothstein, M.A., & Anderlik, M.R. (2001). What is Genetic Discrimination, and When and how Can it Be Prevented? Genetics in Medicine. 3, 354-358.
[69]Geller, L.N., Alper, J.S., Billings, P.R., Barash, C.I., Beckwith, J., & Natowicz, M.R. (1996). Individual, Family, and Societal Dimensions of Genetic Discrimination: A Case Study Analysis. Science Engineering Ethics. 2(1), 71-78.
[70]Mittelstadt, B.D., & Floridi, L. (2016). The Ethics of Big Data: Current and Foreseeable Issues in Biomedical Contexts. Science Engineering Ethics. 22(2), 303-341.

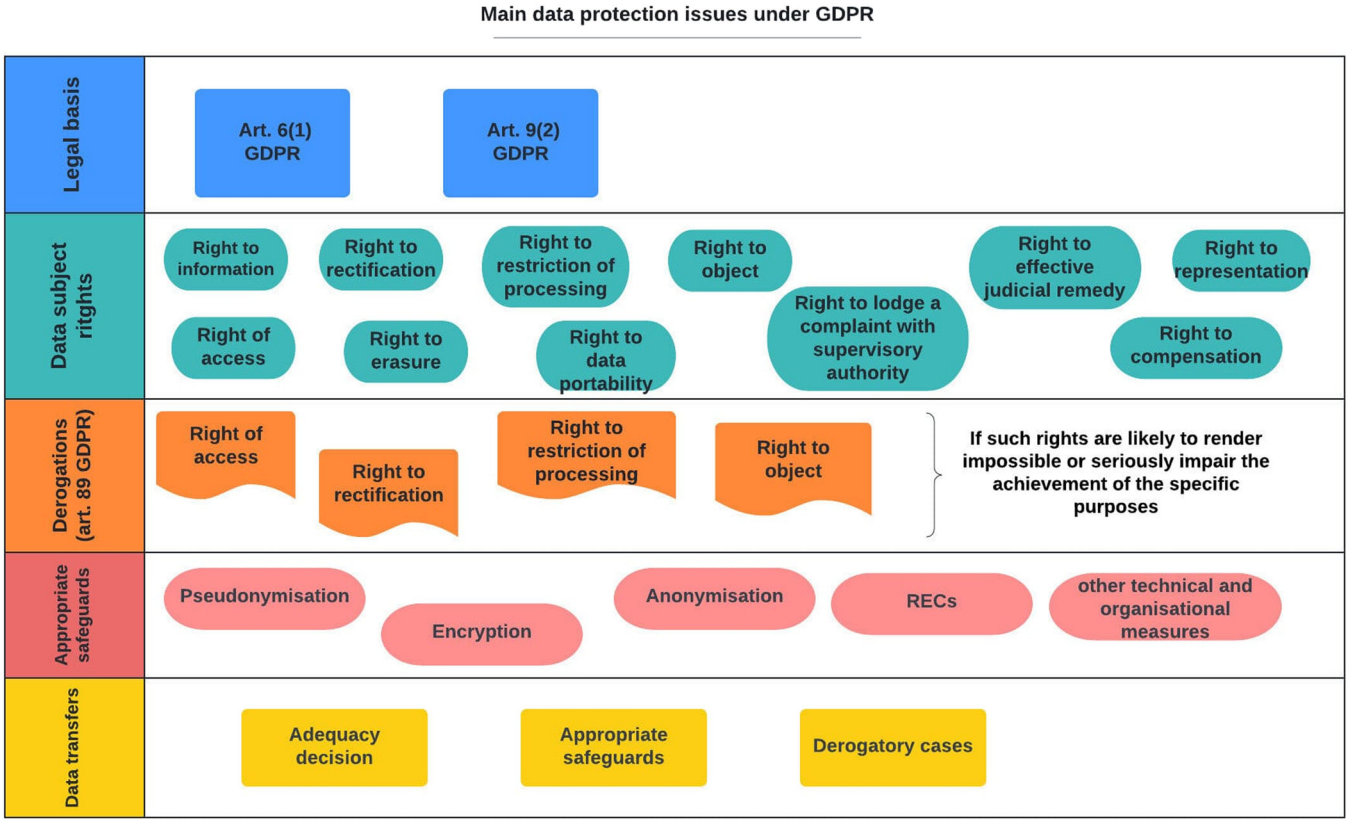

FIGURE 2 Main data protection issues under GDPR.

or not participants might be discriminated against or stigmatized due to their genotype might be influenced by the society's perception over specific characteristics.[71] For example, the case of the Havasupai tribe illustrates how during genetic research on diabetes, findings on ethnic migration and schizophrenia were generated without informing the research participants, opening the possibility of stigmatization of the tribe.[72] Moreover, the operationalization of sexuality, the exclusion of certain groups from the study, and the framing of the question as a health issue bear the risk of stereotyping or stigmatization that have already been overcome.[73] Other studies have shown that genetic discrimination could manifest in different contexts, e.g., in the workplace, when seeking insurance, or it can be related to immigration.[74]

Potential discrimination in the biobank-based research design may include unequal representation of certain groups, which could result in a lack of diversity in genetic information and, hence, biased findings. Bias in research designs, sampling and representation of certain groups, including minors or patients with rare diseases and interpretation of findings could also lead to discriminatory profiling with real life consequences for certain individuals and groups. Discrimination against individual research participants and groups could also take place in terms of denial of benefits and, in the worst case, exploitation of their samples and genetic data.[75] Collaborations with partners from low-income countries must ensure equitable sharing of data and benefits, eg, in terms of credits for the local researchers involved, authorship, funding and training, as well as fair sharing of the research outcomes, knowledge, technologies and other benefits.

Transparency of the research for the benefit of the participants and the community at large are means to ensure social awareness and minimize potential harms mentioned above. A way to avoid discrimination and stigmatization also includes ensuring the confidentiality of research participants during and after the

[71]Phelan, J.C. (2005). Geneticization Of Deviant Behavior and Consequences for Stigma: The Case of Mental Illness. Journal Health and Social Behaviour. 46(4), 307-322.
[72]Garrison, N.A. (2013). Genomic Justice for Native Americans: Impact of the Havasupai Case on Genetic Research. Science, Technology & Human Values. 38(2), 201-223; Helgesson, G. (2012). In Defence of Broad Consent. Cambridge Quarterly of Healthcare Ethics. 21(1), 40-50.
[73]Holm, S., & Ploug, T. (2019). Genome Studies Reveal Flaws in Broad Consent. Science. 366(6472), 1460-1461; Goisauf, M., Akyüz, K., & Martin, G.M. (2020). Moving Back to the Future of Big Data-Driven Research: Reflecting on the Social in Genomics. Humanities & Social Sciences Communications. 7, 55.
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study.[76] Researchers should not make biased assumptions on whether a particular group would perform better or worse than other groups, instead they should base their findings on the data collected and even take special efforts to include members of groups that appear to be under-represented.[77] Researchers could conduct a human rights impact assessment (HRIA) in the context of which they will assess the potential risks to the right to non-discrimination and equality, among other rights.[78] A HRIA allows the identification and assessment of any actual or potential adverse human rights impacts[79] drawing upon internationally recognized human rights standards and principles.[80]

2.2.4 | Community engagement: learning from developments in Africa

Cultural awareness and adaptability of research practices towards cultural and context specificities are crucial for 'improving study participation and retention in a multicultural context'.[81] Community engagement is of great importance for the sustainability of genomic research, as it creates the potential to 'build relationships, increase trust, improve consent processes and empower local communities'.[82] Additionally, it is particularly relevant in the African context due to the communitarian ethos that characterizes many African societies.[83]

Transparency of the research procedures and methods, as well as of the scientific goal, is essential for building the participants' trust and enhancing community engagement. The beliefs of communities regarding their biological samples, such as blood, may be varied and they must be respected, even when they may not be in line with the research practices such as storage in freezers, which for some communities may be considered as 'offensive to their ancestors' or may raise other fears and worries of phenomena as diverse as witchcraft.[84]

Although the local and cultural concerns may vary when establishing and operating a biobank rendering it necessary to adopt context-specific practices, the main processes remain similar and require harmonization to enable cross-national research and collaboration.

2.3 | Step 3: Handling of samples and data

2.3.1 | Collection, quality control, analysis, storage and transfer of data and samples

During the collection of biological samples, the researcher must ensure participants' safety, sample integrity, data security and ensure that the participants' data and samples are uniquely identified.[85] The quality control of samples may typically include visual observation and conducting an assay to determine sample type, integrity or suitability for research area and downstream analytical platform.[86] The data quality control may typically include procedures to identify missing, incomplete, or inappropriate data. In some instances, data may be cleaned or collected eg, to attain missing information during subsequent study visits.

Researchers must ensure that data is kept confidential by state-of-the-art pseudonymization techniques or complete anonymization of samples. Samples and data obtained by a biobank from other institutions may only be stored if permitted by a transfer agreement. When quality control, analysis or storage is performed by a third party, the Principal Investigator (PI) must ensure that the party is informed of and complies with all relevant requirements listed in the existing agreements.

The storage of samples typically requires a secured facility and the adoption of methods to minimize, identify and correct non-conformances of storage conditions, such as temperature. It is also necessary to implement procedures for response to emergencies, such as power failure, flooding, and extra equipment for back-up. Researchers have the option of choosing from a public cloud, private cloud, or a combination of both models for the storage of data.[87] According to GA4GH, data users and organizations need to ensure that the cloud infrastructure they use for uploading the data, complies with local laws and regulations.[88] Also, it is necessary to examine whether the cloud infrastructure has undergone audit against 'comprehensive and internationally recognized and respected information security standards', such as those produced by the Organization for Standardization (ISO) and Statement on Standards for Attestation Engagements (SSAE).[89]

[76]CIOMS, op. cit. note 26, Commentary on Guideline 4.
[77]CIOMS, op. cit. note 26, Guideline 3.
[78]MacNaughton, G. (2015). Human Rights Impact Assessment: A Method for Healthy Policymaking. Health and Human Rights Journal.17(1), 63-75.
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[81]Gille & Brall, op. cit. note 29.
[82]Staunton, C., Tindana, P., Hendricks, M., & Moodley, K. (2018). Rules of Engagement: Perspectives on Stakeholder Engagement for Genomic Biobanking Research in South Africa. BMC Medical Ethics. 19, 13.
[83]Staunton, C., & de Vries, J. (2020). The governance of genomic biobank research in Africa: reframing the regulatory tilt. Journal of Law and the Biosciences. 7(1), lsz018.
[84]Ibid.
[85]ISBER, op. cit. note 2.
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[87]Aryotejo, G., Kristiyanto, D.Y., & Mufadhol (2018). Hybrid Cloud: Bridging of Private and Public Cloud Computing. Journal of Physics: Conference Series. 1025, 01209.
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[89]Ibid.

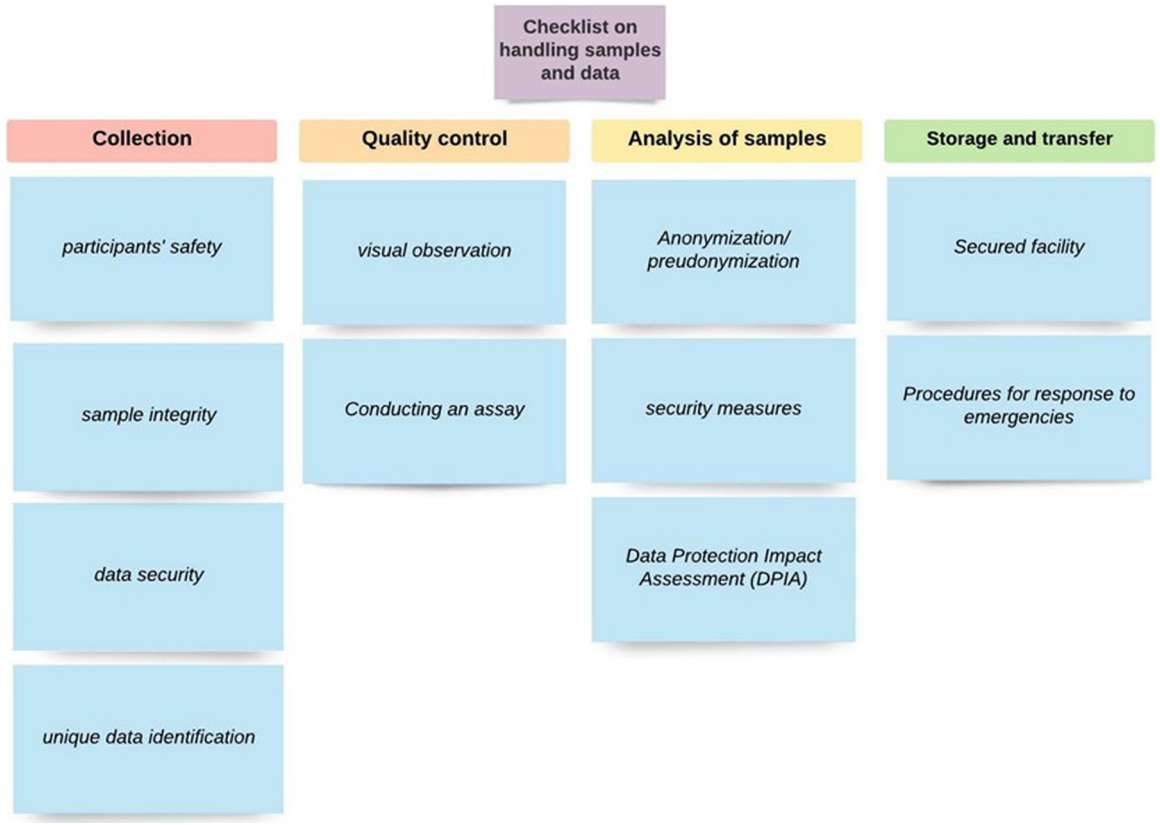

FIGURE 3 Checklist on handling samples and data.

Most institutions rightfully restrict specific storage private cloud methods (e.g., Dropbox, Google Cloud) for security reasons due to potentially elevated risk of data breach or intellectual property concerns. Certainly, encryption methodologies for end-to-end secure communications arguably minimize such risks.[90] Typically, the requirements for sample and data storage are defined by the duration of the study, the study protocol, the contract, institutional policy requirements or a combination of these. Figure 3 describes the checklist on handling samples and data for collection, quality control, analysis, storage and transfer of data and samples.

2.3.2 | Material and data transfer agreements

The transfer of data and samples must be carried out in compliance with applicable law, practices, REC's approval and decisions and practices established by other relevant parties, such as national Data Protection Authorities (DPAs) and DACs, if applicable. If data is being transferred from the EU, GDPR and local and institutional requirements must be met,[91] as explained in Step 2. International shipments can require export and import permits, according to the country's requirements. Also, the transport of samples must be conducted according to the International Air Transport Association (IATA) guidelines.

Whenever samples or data are transferred to another research entity, wherever located, parties enter into agreements commonly known as Material Transfer Agreements (MTAs), DTAs and Data Collaboration Agreements (DCAs), henceforth called 'transfer agreements'.[92] A transfer agreement can either follow a Confidentiality Disclosure Agreement (CDA) between the involved parties or it may be implemented prior to when the transfer takes place.

The procedures for publishing research results related to samples and data should be strictly described within the transfer agreements, setting out a framework for publications and inventions or other intellectual property issues. Transfer agreements are also a relevant platform for addressing industrial property issues relating to material transfer, such as inventions that may occur, including whether and under which conditions commercialization is permissible (see Figure 4 for more details on Transfer Agreements).

[90]Mettu, G.R., & Patil, A. (2018). Data Breaches as Top Security Concern in Cloud Computing. International Journal of Pure and Applied Mathematics. 119(14), 19-28, 20-21.
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[92]Mascalzoni, D., Dove, E.S., Rubinstein, Y., Dawkins, H.J.S., Kole, A., McCormack, P., et al. (2015). International Charter of Principles for Sharing Bio-Specimens and Data. European Journal of Human Genetics. 23, 721-728.

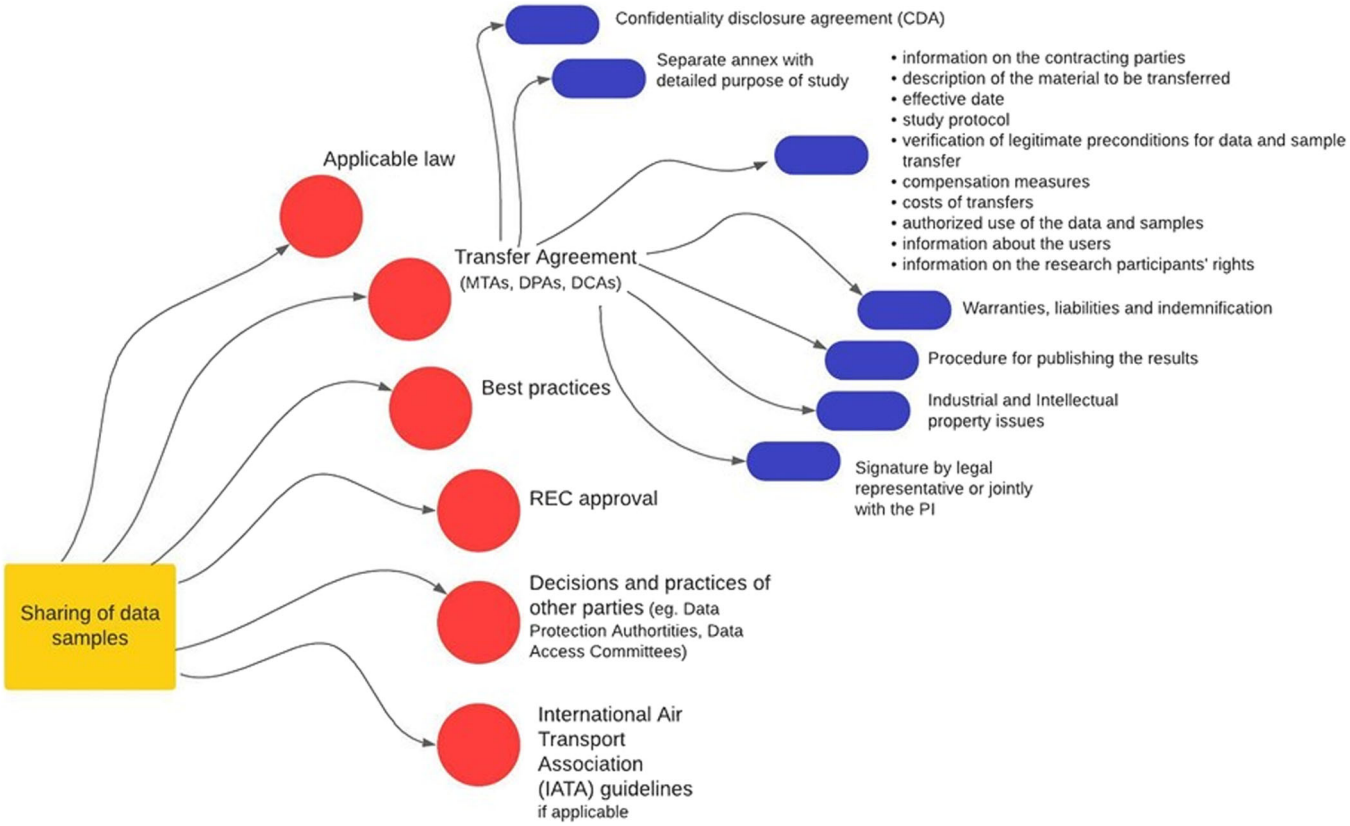

FIGURE 4 Steps for handling of data samples for material and data agreements.

2.4 | Step 4: Research results and incidental findings

Researchers and biobanks must address the interest and right of society to benefit from the research results.[93] However, although it is advised that research participants are informed about the benefits that will result from the research studies, due regard should be given to the risks of discrimination, stigmatization, and possible harm to vulnerable groups.

Research participants should be given the option to be informed regarding IRRs and IFs that might result from the research.[94] IRRs are results from the research providing information about the health of the research participant, e.g., test results or health prognosis. IFs have been defined as 'findings concerning an individual research participant that has a potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study'.[95]

Key arguments in support of disclosing IFs are the benefit for individuals, the promotion of their autonomy, the reciprocity duty towards the research participant, the trust of the individual that any existing important abnormality will be identified by the research team.[96] There are nevertheless numerous arguments against, including the practical challenges which render the disclosure unfeasible, research results may not be clinically validated and the fact that the researcher-participant relationship does not create a disclosure duty contrary to the physician-patient relationship.

In the absence of a consensus among the scientific community and specific legal norms governing the handling of IFs, it is the responsibility of biobanks and researchers to design appropriate policies and adequately informing the participants. As argued, 'the researchers should plan for IFs in the protocol development, discuss the possibility of IFs with research participants during the informed consent process, responsibly address IFs that arise, evaluate IFs (with a consultant if needed), and in some cases offer to disclose IFs directly to research participants'.[97]

Considerations such as the return of IRRs to the participants or their family members during the research participant's lifetime or

[93]Knoppers, B.M., Joly, Y., Simard, J., & Durocher, F. (2006). The Emergence of An Ethical Duty to Disclose Genetic Research Results: International Perspectives. European Journal of Human Genetics. 14(12), 1170-1178.
[94]Helgesson, G. (2014). Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights Are There, and Who Should Decide about Exceptions? Journal of Law, Medicine & Ethics. 42(1), 28-37.
[95]Wolf, S.M., Lawrenz, F.P., Nelson, C.A., Kahn, J.P., Cho, M.K., Wright Clayton, E., et al. (2008). Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations. Journal of Law, Medicine & Ethics. 36(2), 219-248.
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[97]Wolf, et al., op. cit. note 95.

after death should also be tackled.[98] Furthermore, issues that relate to different groups, for example, whether and how research results of minors should be returned to the parents or legal guardians, are highly divergent and discussed.[99] Guidelines generally recommend communicating research results to participants, but it seems that opinions differ on details.[100] To make the return of IRRs practically possible, several issues need to be considered. For example, it might appear financially unfeasible, or operationally impossible to return IRRs.[101] As of now, there are diverse regulations and practices regarding how IRRs are handled.[102] As a final note, it has been observed that research participants have strong expectations to receive research results after the conducted research, therefore it is recommended that researchers seeking consent, should be careful not to give assurances that they may not be able to meet at the end of the research.[103]

Furthermore, it has been recently contested whether there is an appropriate means to acknowledge the contribution of biobanks to research. For instance, the Bioresource Research Impact Factor (BRIF)[104] initiative consists of several steps, a) citation of BioResources in journal Articles (CoBRA) guidelines, b) open journal of bioresources, c) other tools in development. This approach allows recognition, without assigning authorship.[105] Most recently, a systematic review of current and proposed incentives for researchers for data sharing in biomedical sciences, including BRIF and co-authorship was conducted with important findings on this aspect.[106] Concerning the latter, it is questioned whether the quantitative measurement of publications and citations is an adequate mechanism, as co-authorship may conflict with authorship guidelines, or does not allow to resolve potential disagreement on the interpretation of results between the researchers involved. The authors conclude that alternative mechanisms need to be established, such as alternative crediting systems promoted by Open Science.

3 | CONCLUSION

In this paper we presented a procedural model for assisting compliance with ethical and legal requirements that researchers need to consider when planning and implementing biobank-based research. In the four steps that we identified, namely 1) designing the study protocol, 2) recruiting participants, 3) handling samples and data and 4) handling the research results, we touched upon numerous aspects that relate to the existing international legal instruments and ethical requirements and highlighted potentially overlapping or contradictory provisions. We considered numerous regulations, guidance documents and tools developed by ELSI scholars and international organizations. With this paper, we aim to provide a practice-oriented guidance that facilitates a simpler navigation of the diverse sets of legal frameworks, ethical guidelines, and an overview on current responsible research practices for the biobanking and life sciences community.

ETHICS

Not applicable.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interests.

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[105]Ibid.
[106]Devriendt, T., Shabani, M., & Borry, P. (2021). Data Sharing in Biomedical Sciences: A Systematic Review of Incentives. Biopreservation and Biobanking. 19(3), 219-227.

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