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Principles for the donation and management of medical products of human origin

The purpose of this document is to build a global consensus on a framework of principles that apply to the donation and use of all Medical Products of Human Origin (MPHO). Considering the rapid increase of medical interventions using MPHO including organs, tissues, cells, blood and blood components, as well as the numerous innovative strategies that should be developed in a near future, there is a need to work towards the harmonization of procedures in this field. A number of international documents were adopted over the past years, in order to protect potential donors of MPHO and to improve safety and quality of procedures; however in 2015 the Executive Board of the World Health Assembly requested the World Health Organization to work with its Member States on a common framework of principles. This draft was developed with the contribution of a large group of experts and is now submitted to an open consultation with an aim to capture a large scope of inputs from all relevant stakeholders active in the field.

BACKGROUND

1. During its 136th session held in February 2015, the Executive Board of the World Health Assembly "requested that the Director-General convene consultations with Member States and international partners, to support the development of global consensus on guiding ethical principles for the donation and management of medical products of human origin; good governance mechanisms; and common tools to ensure quality, safety and traceability, as well as equitable access and availability, as applicable, to result in a document to be submitted to the Seventieth World Health Assembly for its consideration."[1]
2. MPHOs are "substances that are derived wholly or in part from the human body and intended for clinical application."[2] Components of the human body used to create MPHOs range from organs, tissues, blood, cells, and gametes to breast milk, hair, nails, urine and feces. MPHOs often represent the most beneficial and cost effective therapies for several life-threatening or debilitating conditions. They have also enabled the birth of many much-wanted children.
3. MPHOs are fundamentally different from other medical products because they depend on the donation of biological materials from living or deceased persons. Concern for the dignity and human rights of donors, in particular their own rights to health and security of their persons, requires high ethical standards in the procurement of biological materials for use in MPHOs. Particular care must be taken to ensure that donors are not subject to exploitation, coercion, or abuse.

[1] WHO Executive Board. 2015. EB136/.DIV/3. Decisions and list of resolutions. Available at: <http://apps.who.int/gb/ebwha/pdf_files/EB136/B136_DIV3-en.pdf>.

[2] Noël, L. and Martin, D. E. 2015. "The Exception of Medical Products of Human Origin: Towards Global Governance Tools". In Rainhorn and El Boudamoussi (Ed.s). *New Cannibal Markets: Globalisation and Commodification of the Human Body*. Editions de la Maison des sciences de l'homme, p.383.

4. The human origin of MPHOs also entails risks to public health. The recurrent emergence of diseases, such as the recent Zika virus outbreak, requires systems of MPHO production that can predict and mitigate transmission of known or unknown pathogens and swiftly adapt to new threats. Essential safety mechanisms include appropriate donor screening and testing, pathogen reduction or inactivation techniques, and adequate traceability of MPHOs, such that sentinel events of disease transmission can be promptly investigated and linked to specific MPHOs, source individuals and recipients, enabling development of new risk containment and mitigation strategies such as timely product recalls.
5. Considerable inequalities remain in access to MPHOs, even for blood and blood components, between and within countries and regions. For instance, "of the 112.5 million [whole] blood donations collected globally, approximately half of these are collected in the high-income countries, home to 19% of the world's population."[3] Lack of universal health coverage is a critical factor contributing to inequalities of access to MPHOs. Regrettably, individuals that lack access to the benefits of MPHOs are sometimes those most likely to be exploited as sources of biological materials used in MPHOs, where protective measures against trafficking of products or donors are inadequate.
6. The demand for MPHOs is growing with the emergence of new therapeutic applications; improved access to health care in some regions; and changing demographics of potential donor and recipient populations, such as ageing and increased burdens of chronic diseases. Failure to prevent progression of many of the diseases which lead to needs for MPHOs, such as trachoma causing corneal blindness and diabetes resulting in kidney failure, mean that growth in demand for these products continues to outpace the increase in their availability for supply.

ETHICAL PRINCIPLES, STRATEGIES, AND POLICY OPTIONS AND INTERVENTIONS

7. Guidance for Member States concerning ethical principles and governance mechanisms, as well as global tools to facilitate their implementation, are already available from WHO,[4] WHO Collaborating Centers, or Nongovernmental Organizations (NGOs) in official relations with WHO.[5] This document builds on previous guidance by identifying ethical principles and governance mechanisms valid for all types of MPHOs, and proposing a globally harmonized approach to governance using shared tools. The goal is to foster consistency of ethical practices to strengthen the overall safety, quality and availability of MPHOs.
8. The following table sets forth ten key principles, each of which is elaborated with strategic approaches and potential policy options and interventions for the attainment of each strategy. This non-exhaustive list has been developed on the basis of literature reviews, input from technical consultations, and expert opinion. The appropriate mix of policies and interventions to be used at the country level will need to be designed and developed according to the local context, values, and priorities.

[3] WHO Fact sheets: Key facts on blood safety and availability (as of July 2016). Available at <http://www.who.int/mediacentre/factsheets/fs279/en/>

[4] Resolutions WHA28.72,(20) WHA58.13,(21) and WHA63.12,(22) as well as the WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation endorsed in resolution WHA63.22.

[5] For instance, in 2008 The Transplantation Society and the International Society of Nephrology developed the Declaration of Istanbul to address organ trafficking.

Table. Principles, strategies policy options and interventions for promoting ethical practices in the donation and management of medical products of human origin

Principle 1: Governments are responsible for assuring the ethical and effective procurement, distribution and use of MPHOs. This responsibility includes the obligation to develop and enforce regulations to assure the maximum level of safety, quality and efficacy within and across national borders.

Governmental authorities, as representatives of the public, are responsible for assuring the ethical and effective procurement, distribution, and use of MPHOs. This responsibility stems not only from the governments' core duty to protect and promote the public health but also from its role in protecting the fundamental rights and freedoms of individuals, which may be endangered in the context of unethical procurement or distribution practices. Fulfilling this responsibility depends on the effective operation of healthcare services and systems, as well as the creation and enforcement of regulations to assure a high level of safety, quality, and efficacy within and across national borders.	
Strategic Approach	**Policy options and interventions**
1.1 Promoting governmental efforts to assure a sufficient supply of MPHOs through encouragement and facilitation of donation	• Establishing and enforcing legislation to facilitate individuals' ability to consent to donation, such as by enabling individuals to indicate their consent to donation on driver's licenses; • Engaging the public through campaigns to encourage the donation of biological materials for use in MPHOs; • Developing school curricula that present the donation of biological materials for use in MPHOs as a civic behaviour;
1.2 Promoting governmental efforts to protect the health and interests of potential and actual donors	• Establishing and enforcing legal and regulatory frameworks that define essential requirements for protecting donors' safety; • Placing responsibility for ensuring donors' safety under the oversight of regulators with the authority to enforce laws and policy; • Ensuring that establishments that procure biological materials for use in MPHOs are licensed, registered, permitted, or otherwise formally approved as such by competent authorities; • Establishing and enforcing legislation related to consent to donation, as detailed further in Principle 3;

1.3 Promoting governmental efforts to ensure the transparency of information related to MPHO processes	• Empowering governmental agencies to oversee the collection and dissemination of comprehensive data related to MPHOs process, as detailed further in Principle 9; • Publishing national data on MPHO activities and practices on at least an annual basis;
1.4 Promoting governmental efforts to respond to crises that impact MPHO service delivery, such as an insufficient supply of eligible donors, lack of trained professionals able to provide MPHO services, increased demand for MPHOs, violation of ethical norms governing MPHO services, or contamination of MPHO supplies	• Developing crisis management plans and policies; • Establishing agreements for collaboration between national authorities to assist in sharing resources and expertise in the event of a crisis;

Principle 2: Equity in donation should be promoted by engaging all members of society in efforts to meet needs for MPHOs.

In principle, if all members of society have an equitable share in the benefits of MPHOs supply, they have a shared responsibility to help meet needs for MPHOs through donation when possible. Health authorities have responsibilities to establish systems and organizations that reduce or eliminate barriers to donation and to access to MPHO, thereby promoting equity. Individuals and groups should be neither denied the opportunity to donate biological materials for use in MPHOs where this exists, nor encouraged to donate where others are not, except where clearly justifiable reasons apply. Where a prospective donation may be unnecessary, for example if there is surplus of a particular MPHO, or unduly harmful for the prospective donor or intended recipients, healthcare providers must not be obliged to proceed with donation.	
Strategic Approach	**Policy options and interventions**
2.1 Removing barriers to donation of biological materials for MPHOs	• Providing broad opportunities for individuals to express their desire to donate biological materials; • Initiating discussions about donation of biological materials as soon as the possibility of donation becomes a foreseeable option; for example, when deciding to introduce or maintain life-sustaining interventions, or when deciding to store "surplus" gametes procured for autologous use; • Covering living donor travel expenses and lost wages (not to exceed the actual costs incurred by the donor); • Preventing discrimination against living donors by health insurers;

2.2 Eliminating policies or practices that unfairly impose an increased burden of donation upon individuals or groups on the basis of factors such as financial status, ethnicity, religion, nationality, or gender	• Avoiding donor recruitment strategies that unfairly result in an inequitable distribution of the burden of donation, such as the use of financial or other incentives for donation; • Providing public education about MPHOs that is inclusive of all members of society; • Basing exclusion from or deferral of donation strictly on medical criteria to reduce risks of harm to donors or recipients; such criteria may differ according to the urgency of the need, the existence of alternative treatment and the type of MPHO; • Establishing a globally equitable and sustainable supply of plasma for medicinal product manufacture that reduces the disproportionate dependence on countries that provide financial incentives for plasma donation; • Developing and implementing infrastructure necessary for achievement of Good Manufacturing Practice (GMP) standards in blood collection, to reduce discards of plasma derived from whole blood donation;
2.3 Developing targeted recruitment strategies when needed to address potential barriers to donation among particular groups, taking care to ensure that the outcomes of any such measures achieve the intended results and do not undermine equity in MPHO donation and allocation	• Establishing tailored programs to address specific cultural or religious concerns about donation; • Encouraging voluntary donation by members of ethnic groups who are less likely to receive a suitably matched MPHO;

Principle 3: MPHOs should be used only when of proven efficacy and in the absence of alternative therapies of comparable or superior efficacy.

Responsible stewardship of MPHOs requires using these exceptional health resources as efficiently as possible, thereby minimizing the burdens of donation on individuals and maximizing access to necessary products. The efficient use of MPHOs requires good clinical practice and management within the broader healthcare system. Human biological materials should only be procured when necessary to meet the anticipated needs of recipients or, with the consent of donors, for other purposes such as research or training, which may serve to accomplish donors' overarching goals of contributing to human health.

Strategic Approach	Policy options and interventions
3.1 Developing and applying evidence-based clinical policies and practices to achieve efficiency in MPHO supply and use	• Incorporating Health Technology Assessments to inform policy and practice on the use of MPHOs; • Developing innovative therapies using MPHOs based on strict and well-designed pre-clinical and clinical trials that adhere to good clinical practices;
3.2 Minimizing needs for MPHOs	• Educating the public on preventive health care; • Improving the clinical management of chronic diseases, such as diabetes and hypertension, to prevent the need for organ transplantation; • Preventing the development of anaemia during pregnancy, in order to reduce the need for peri-partum blood transfusions;

Principle 4: Donation of components of the human body for use in medical products should be conditional upon informed and voluntary decision-making by donors or their relatives.

Whether deciding to receive an MPHO or to donate biological material for use in MPHOs, individuals should be enabled to make a voluntary and informed decision. The requirement for consent protects potential donors against violation of their bodily integrity and respects their interests in making important life choices in accordance with their values and personal goals. The requirement also protects the interests of potential donors' families in cases of deceased donation where the donor's preferences are unknown. In the absence of effective processes for informing potential donors and obtaining consent, individuals and families may be vulnerable to coercion or exploitation, such that they are forced to donate or agree to donate against their personal preferences and values. Or, potential donors may choose not to donate when they would otherwise have done so if they were sufficiently informed.

Strategic Approach	Policy options and interventions
4.1 Enabling individuals to make voluntary and informed decisions about the receipt of MPHOs or the use of their biological materials in MPHOs	• Establishing and enforcing legislation requiring that, before biological materials are procured from living persons for use in MPHOs, the person has made an informed and voluntary decision to donate such material for that purpose; • Establishing and enforcing legislation requiring that, before biological materials are removed from the bodies of deceased persons for use in MPHOs, the person has previously made an informed and voluntary decision to donate, or the

	person's family believes that donation would be consistent with the person's values and preferences; • Promoting the use of professional psychosocial counselling and professional independent donor advocates to assist donation decision-makers in understanding the potential implications of donation and to minimize the risk of distress; • Establishing and enforcing professional and institutional policies that prohibit the procurement, processing, distribution or use of MPHOs by anyone who knows or has reason to suspect that the underlying human biological materials have been obtained through coercion, exploitation, or in violation of the law, policies, or guidelines governing practices related to MPHOs;
4.2 Protecting the interests of potentially vulnerable populations, such as minors and legally incompetent adults, migrants, and the poor	• Establishing and enforcing legislation that narrowly limits the circumstances under which minors or legally incompetent adults may serve as living organ donors; • Ensuring that, when minors or legally incompetent adults serve as living organ donors, dedicated efforts are made to obtain the donor's assent as well as the permission of the parents or legal guardians; • Ensuring that an objection to donation by a minor or incompetent adult is respected, regardless of whether permission has been provided by any other party; • Establishing procedures for the independent assessment and approval of living organ donation when a potential conflict of interest may be present, for example if the intended recipient is a family member; • Establishing and enforcing legislation establishing minimum age requirements for blood donation;

Principle 5: Financial neutrality: In order to guard against the exploitation of vulnerable individuals and promote equity in donation, persons who provide their biological materials for use in MPHOs should not benefit or lose financially as a result of the donation.

When payment is provided in exchange for consent to procure biological materials from a living person or deceased body, or to obtain materials that have been previously procured, and such payment is intended to leave the person authorizing procurement or providing these materials financially advantaged, the human body and its parts, as such, becomes a source of financial gain. Financial gain in the human body as such is ethically problematic for a number of reasons. It increases the risk of coercion and exploitation of potential living donors; it results in the inequitable distribution of burdens of donation which in turn may result in stigmatization of donation; it may encourage potential living donors to assume a higher level of risk; it may result in recruitment of donors who are at a higher risk of harm or whose materials may present higher risks for recipients; it may impair trust in the integrity of death determination and deceased donation; it may negatively impact voluntary and unpaid donation; it may represent a perverse incentive for the production of more 'lucrative' MPHOs to the detriment of those for which there is greater clinical need; and it may promote inequities in distribution of MPHOs. The notion that the human body or its parts as such may be a source of financial gain further threatens respect for the fundamental dignity of human beings: recognition of the inherent, unique, and non-transferable value of persons.

The principle of financial neutrality is consistent with payments, reimbursement or coverage of reasonable costs associated with donation, such as transportation expenses, documented lost wages etc.. Just as donors should not benefit financially as a result of donation, neither should they suffer financial injury as consequence of donation.

Despite the ethical concerns discussed previously, in exceptional circumstances, some procurement systems go beyond the principle of financial neutrality and permit payments to donors of certain biological materials that exceed direct coverage of the costs associated with donation. Governments in countries that authorize such payments should ensure that systems are in place to minimize the risk of harm to vulnerable individuals, such as tracking systems to limit how frequently an individual can serve as a donor, and adequate insurance/protections for donors irrespective of payments made to them.

Strategic Approach	**Policy options and interventions**
5.1 Ensuring that financial remuneration is not provided in exchange for the donation of biological material for use in MPHOs	• Establishing and enforcing regulations prohibiting any form of financial remuneration in exchange for the donation of biological materials for use in MPHOs, including non-cash benefits such as educational scholarships or fungible commodities such as gold medals;
5.2 Enabling legitimate payments to donors to cover their actual costs of donation, as well as legitimate payments to others involved in the procurement, processing, preservation, distribution or clinical application of MPHOs to compensate for their work, intellectual	• Requiring that any payments to donors or others involved in the procurement, processing, preservation, distribution or clinical application of MPHOs be transparent and clearly justified by well-documented costs; • Prohibiting any payments to donors or

property, or investments in necessary technology	others involved in the procurement, processing, preservation, distribution or clinical application of MPHOs that varies according to the quality of the biological materials or the purpose of the donation; • Requiring that costs or fees for services associated with MPHO procurement, manufacture, storage, distribution or use are comparable to those related to similar products of non-human origin;
5.3 Establishing effective oversight of payments related to the procurement, processing, preservation, distribution or clinical application of MPHOs	• Establishing and enforcing professional regulations and institutional policies to ensure that any financial incentives provided to donors or others involved in the procurement, processing, preservation, distribution or clinical application of MPHOs are transparent and disclosed to all stakeholders, especially donors and recipients; • Creating oversight systems to ensure the monitoring and evaluation of systems, processes, and outcomes in systems where payments are provided in exchange for consent to authorization of procurement of human biological materials for use in MPHOs; • Promoting the use of independent donor advocates in systems that provide financial incentives to living donors of biological materials, in order to protect donors' ability to make informed decisions about donation;

Principle 6: Prospective and actual donors of human biological materials for use in medical products should be protected against physical and psychosocial risks to the fullest extent possible.

Prospective and actual donors of various human biological materials face a range of physical and psychosocial risks. These may be associated with the evaluation process, procurement, or long term sequelae of donation. Risks will vary according to the type of donation, the individual, and to the context in which donation occurs. Improvements in donor health care and advanced procurement procedures have almost eliminated or significantly reduced some risks, while new risks have emerged for some practices as a result of research or new procurement practices. Thus risks cannot always be accurately predicted, and may evolve during the lifetime of a donor.

Strategic Approach	Policy options and interventions
6.1 Protecting donors of biological materials from potential harms that may occur during or after donation	• Establishing healthcare programs dedicated to donors of biological materials for use in MPHOs; • Ensuring that those involved in the procurement of biological materials for use in MPHOs carefully evaluate and select prospective donors to screen out those for whom donation would pose undue risk; • Establishing and enforcing best clinical practices for the care of donors, both during and after donation; • Vigilantly monitoring adverse occurrences in donors to identify and address emerging risks or complications and to inform measures to further reduce risks for future donors; • Incorporating follow-up research to monitor long-term outcomes in living donors; • Assuring the integrity of the death determination process for prospective deceased donors and ensuring that donation occurs within the context of appropriate end-of-life care;
6.2 Protecting prospective donors of biological materials against potential harms associated with undergoing evaluation for donation, whether or not these persons actually proceed to become donors	• Protecting the confidentiality of information acquired during the donor evaluation process; • Ensuring appropriate referrals to follow-up care for prospective donors determined to have diseases or conditions that preclude donation; • Providing care to attenuate the psychosocial harm that can result from the deferral of a volunteer donor;

Principle 7: Information about the relevant product, including its human origin, should be routinely provided when offering MPHOs to prospective recipients.

In addition to information about the potential risks and benefits of using specific MPHOs, which should be provided to prospective recipients as part of routine consent procedures, prospective recipients should also be explicitly informed that the clinical product they are to receive is derived wholly or in part from human biological materials. Recipients of MPHOs should also be informed about the policy for donation in their country or local

healthcare jurisdiction. This constitutes an acknowledgement of the donors and promotes societal awareness of the necessity of donation.	
Strategic Approach	**Policy options and interventions**
7.1 Ensuring that prospective recipients of MPHOs are explicitly informed that the clinical product they are to receive is derived wholly or in part from human biological materials, as well as about the policy for donation of MPHOs in their country or local healthcare jurisdiction.	• Establishing and enforcing legislation requiring that, before MPHOs are used in medical procedures, the recipient is explicitly informed that the clinical product they are to receive is derived wholly or in part from human biological materials, as well as about the policy for donation of MPHOs in their country or local healthcare jurisdiction; • Establishing and enforcing professional and institutional policies designed to ensure that recipients of MPHOs understand that the clinical product they are to receive is derived wholly or in part from human biological materials, as well as about the policy for donation of MPHOs in their country or local healthcare jurisdiction;

Principle 8: Equity in access to the benefits of MPHOs should be promoted by sustained efforts to remove barriers to access, and to establish and implement waiting lists and allocation systems for MPHOs that are based on clinical criteria and ethical norms, not considerations of financial or social status.

Where there is an insufficiency of particular MPHO to meet clinical need within society, systems should be implemented to ensure equity in allocation of available products, such that unavoidable inequalities of distribution are fair and necessary. Achieving equity in the allocation of MPHOs requires attention to the criteria used in establishing waiting lists and allocation protocols, as well as to barriers in access healthcare services more generally. Although directed donation of biological materials has the potential to undermine equity in access to the benefits of donation, some directed donation programs may actually reduce the societal burdens of unmet needs for MPHOs.	
Strategic Approach	**Policy options and interventions**
8.1 Ensuring fairness in the determination of eligibility criteria for waiting lists, as well as in the development of allocation protocols and guidelines	• Embedding allocation criteria for MPHOs, including procedures for establishing waiting lists, in legislation or regulation; • Ensuring that allocation criteria and rules are externally justifiable, transparent and open to scrutiny; • Ensuring that allocation criteria and rules are based on clinical criteria, not the financial or social status of potential

	recipients, and that they adhere to ethical norms such as non-discrimination;
8.2 Addressing barriers to accessing healthcare services that can preclude timely assessment of patients and addition to waiting lists for MPHOs	• Coordinating efforts to promote equity in the allocation with MPHOs with broader efforts to improve equity of access to healthcare services at all levels;
8.3 Ensuring that directed donation of MPHOs does not undermine the goal of promoting equity in access to the benefits of MPHOs	• Facilitating programs for directed organ donation with paired exchange programs, which reduce demand for deceased donor kidneys and may increase opportunities for living donor transplants; • Giving weight to the preferences of donors of haematopoietic stem cells, organs or gametes when the primary motivation for donation is the desire to benefit a relative or friend;

Principle 9: In order to minimize the risk of harm to donors and recipients and to protect the stability and sustainability of MPHO services, all steps in the development and use of MPHOs should be fully traceable and subject to rigorous quality management systems and vigilance and surveillance programs.

Routine monitoring and evaluation of systems and processes pertaining to MPHOs provides information that guides ethical practice and policy, informs decision-making by the public, professionals and policy makers, and fosters continuous clinical and scientific improvement. Likewise, quality management systems and vigilance and surveillance programs promote timely responses to new or recurrent threats and enable the application of new knowledge to improve the safety and quality of products, thereby protecting donors, recipients, and public health.	
Strategic Approach	**Policy options and interventions**
9.1 Ensuring the strict traceability of all steps from procurement to use of products and follow-up of recipients and donors.	• Establishing and enforcing regulatory requirements to ensure the full traceability of MPHOs; • Using unique national identifiers for all MPHOs that are translatable at the international level; • Adhering to international standards for product terminology and nomenclatures;
9.2 Ensuring the effectiveness of quality management systems and vigilance and surveillance programs to minimize the risk of harm to donors and recipients and to protect the stability and sustainability of MPHO services	• Ensuring that a national vigilance and surveillance program is in place for all MPHO that is capable of identifying and anticipating adverse occurrences, including potential long-term sequelae identified during follow-up of donors and recipients;

	• Establishing routine monitoring and evaluation of all systems and processes pertaining to MPHOs; • Establishing quality management systems and vigilance and surveillance programs under the oversight of health authorities; • Ensuring that establishments providing MPHO services report at least on an annual basis on activities and practices through regional and/or national coordination; • Ensuring that establishments providing MPHO services are regularly evaluated using established national or international standards;

Principle 10: The organization and delivery of MPHO-related activities, as well as their clinical results, must be transparent and open to scrutiny, while ensuring that the personal anonymity and privacy of donors and recipients are always protected.

Establishing and maintaining public trust in the systems managing procurement, distribution and use of MPHOs encourages participation in donation opportunities and is best achieved by transparent presentation of policies and practices and reporting of outcomes. The provision of adequate information and data enable the public to make informed choices about donation and use of MPHO. Such transparency and mechanisms to ensure the traceability of MPHO are not incompatible with the protection of private and confidential information concerning individual donors and recipients of MPHO.	
10.1 Ensuring that all systems and processes and the results of evaluations related to the procurement, processing, preservation, distribution and clinical application of MPHOs are transparently communicated to all stakeholders	• Instituting ongoing mechanisms to regularly gather current data on the procurement, processing, preservation, distribution and clinical application of MPHOs; • Maintaining public access to regularly updated comprehensive data on MPHO processes, in particular information regarding types of donors recruited and MPHO produced, allocation systems, clinical application activities, and outcomes for both recipients and living donors, as well as data on organization, budgets and funding of MPHO services;
10.2 Protecting the privacy and confidentially of personal data related to donors and recipients of human biological materials	• Establishing effective data protection and robust data management programs;

IMPLEMENTATION APPROACH

9. Although various types of MPHO may require different operational systems and regulatory oversight adapted to their specificities, some governance mechanisms are generally valid for all MPHOs, including: policy and plan legislation and regulation; financial sustainability; traceability; vigilance and surveillance; transparency; public engagement; and crisis response plans. Consolidation of regulatory oversight and national coordination of services providing different types of MPHOs, e.g. blood, tissues, organs and gametes, may be beneficial through economy of scale, optimal use of professional expertise or consistent communication with the public. Services related to the procurement, manufacture, and provision of MPHOs, their coordination, and their regulatory oversight should be integrated in the health system to ensure smooth and efficient communication with users of MPHOs and regulators of other types of health products.
10. Some MPHOs, specifically those that undergo an extensive manufacturing process such as plasma derived medicinal products, may be regulated as pharmaceuticals, while others, such as tissue-derived products used in orthopaedics, may be regulated independently or as medical devices. Regardless of how particular MPHOs are classified, all forms of regulation should explicitly address MPHO-specific requirements such as donor protections. In practice, close collaboration among regulators internationally and among regulatory bodies within countries, and oversight of the various steps from procurement of the human biological material through to clinical application of the final product will be necessary to ensure efficiency and maintenance of standards across the whole MPHO process.
11. Global common tools can facilitate governance of MPHOs, supporting ethical practice and policy and efforts to establish and maintain sufficient supply of safe, high quality MPHOs to meet patient needs. Potential tools include communication tools, e.g. global nomenclature or glossaries of MPHOs; transparency tools, e.g. global databases of national activities and practices with regards to MPHO services; public engagement tools, e.g. world donor days; tools for vigilance and surveillance, e.g. global vigilance and surveillance systems for MPHOs and for donors; traceability tools, e.g., globally integrable coding systems for all MPHOS. The not-for-profit status of many MPHO services and the exceptional nature of MPHOs as health resources derived from societal members place responsibility on governing authorities to support development and maintenance of global governance tools.

Appendix 1: Substances used as MPHO

TISSUE PRODUCTS (INCLUDING CORNEAL TISSUE)

	Donor type	Benefits/use	Volume of activity annually (estimated)	Challenges
Skin	Predominantly deceased	Treatment of burns	>321 patients transplanted in Europe[1]	• Traceability[4] • Disease transmission[7] • Insufficiency of supply, e.g. Estimated demand for corneal transplants is 70x current activity[2] • **Transnational activities:** 11% of corneal transplants performed worldwide use imported tissue, with 27 countries wholly dependent and 43 countries partially dependent on imported tissue.[2] 8% of corneal tissue procured annually is exported, primarily from the United States, which accounts for 85% of corneal exports, Sri Lanka (9%), and Italy (3%).[2] • Reliance on foreign skin banks in major emergencies • Regular export of tissue products from Europe and the US
Cardiac valves	Deceased	Treatment of heart valve disease	>13,257 transplants worldwide[3] >4,966 donors worldwide[3]	
Bone, muscle, tendons, ligaments	Predominantly deceased	Treatment of orthopaedic injury or disease	>43392 patients transplanted in Europe[1] Possibly 1 million tissue *products* used in the US	
Blood vessels, other tissues			>1919 patients transplanted in Europe[1]	
Corneas	Deceased	Treatment of corneal blindness	184,576 transplants worldwide[2] >142,000 donors worldwide[2]	
Placental tissues including amnion	Living	Treatment of corneal deficits,[5] chronic wounds[6]	>715 placental donations in Europe[1] 4097 patients transplanted with amnion tissue grafts in Europe[1]	

Blood and plasma products

	Donor type	Benefits/use	Volume of activity (annual)	Challenges
Whole blood	Living	Treatment of anaemia; acute blood loss	103 million whole blood donations and >9million patients transfused worldwide[8]	
Plasma derived products		Coagulation disorders; autoimmune diseases; Alzheimer's disease	>23million plasma donations in the United States[9]	**Transnational activity:** US supplies 70% of global plasma products

Haematopoetic stem cells

Sources of HPSC	Donor type	Benefits/use	Volume of activity (annual)	Challenges
Umbilical cord blood	Living	Treatment of haematological malignancies; immunodeficiencies	61,000 cord blood units added to BMDW registries[11] >23,500 allogeneic HPSC transplants worldwide[10]	Private banking for potential future personal use
Bone marrow				**Transnational activity:** dependency on global exchange of HPC for matching
Peripheral blood stem cells				

Secretions and excretions

	Donor type	Benefits/use	Volume of activity (annual)	Challenges
Breast milk	Living	Nutrition for premature and low birth weight infants; "compared with formula, donor human milk is associated with lower incidence of necrotizing enterocolitis, and other infections[16]"	170, 434 donors and 161, 304 recipients in Brazil[12] >6,800 donors in US[13] >975 donors in Italy[14]	• Lack of banks in some countries[15] • Variation in standards and operational procedures[18] • Cultural concerns[17] • Unregulated personal arrangements for breast milk donation "sharing" and disease risks
Faecal microbiota (FM)		Treatment of recurrent *Clostridium difficile* intestinal infection[20]	>516 patients reported to have received FM transplant[19] in last few years…	• Barriers to establishing programs including costs[21] • Uncertainty concerning long term risks for recipients[22]

Organs

	Donor type	Benefits/use	Volume of activity (annual)	Challenges
Organs	Living Deceased	Treatment of organ failure; replacement of missing organs	>119,873 solid organ transplants performed worldwide[23] 27,397 deceased donors of organs worldwide[23] >33,055 living kidney donors worldwide[23] >5,515 living liver donors worldwide[23]	Estimated that <10% of global needs are currently met[23] **Transnational activities:** regional sharing programs, travel for transplantation

Reproductive cells

	Donor type	Benefits/use	Volume of activity (annual)	Challenges
Oocytes	Living	Treatment of infertility with creation of children using assisted reproductive technologies	>30 298 egg donation cycles in Europe[24] >7213 deliveries from use of donor eggs (fresh or in frozen embryos)[24] >19,320 ART cycles used donor eggs or embryos created using donor eggs in the US resulting in >9363 live births25	• Donor anonymity • Traceability e.g., in the event of genetic disease transmission[28] • Limited follow up of donors
Sperm			>14 117 ART treatment cycles performed in Europe using donor sperm[24] >30,000 births in the US using donor sperm estimated in 1987	• Donor anonymity • Lack of registries • Unregulated personal arrangements for sperm donation and disease risks • Traceability in the event of genetic disease transmission[26] • Variability of sperm quality[27]

Other

Hair	Living	Alopecia following chemotherapy, radiation, trichotillomania, alopecia areata in children etc.	>105000 donations /year just to one organization (locks of love)	

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