Ethical principles guiding the donation and procurement of Medical Products of Human Origin

a document developed by NGO in official relations with the WHO

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Medical Products of Human Origin (MPHO) include all substances derived wholly or in part from the human body and intended for human application (see Noel and Martin). They include cells, organs and fluids irrespective of their fate in the recipient. Some MPHO may engraft and proliferate, whilst others may persist or be present only transiently.

MPHO encompass, but are not limited to,

- organs
- tissues, including cornea, skin, heart valves, bones, dura mater, joints, tendons, nerves, veins
- cells, including
    - clusters of cell types, either anatomically defined such as pancreatic islet cells or artificially derived *in vitro*
    - manipulated or *ex vivo* cultured cells like mesenchymal stromal cells (MSC) and dendritic cells
    - haemopoietic stem cells (HSC)
    - multipotent stem cells including induced pluripotent stem cells.
    - reproductive cells*
- blood and blood derived products including plasma
- cord blood
- liquids, including milk

MPHO comprise a broad range of products, some of which are highly manipulated and some which are under development. There is a wide range in the level of risk both for the recipient and for the donor of different types of MPHO. MPHO have constituted one of the major advances in modern medicine, providing life-saving therapy for millions of people from formerly incurable

* *Most of the principles outlined in the document apply to donor reproductive cells but there are additional complexities that require further consideration and are outside the scope of this document*

diseases. Many MPHO are the treatment of choice for a wide variety of diseases, ranging from haematological malignancies through to end-stage organ failure. Blood transfusion remains essential supportive care in many clinical situations. The World Health Organization (WHO) global database on blood safety estimated that 108 million units of blood were collected for transfusion in 2012

National health authorities are responsible for defining clear strategies and policies to ensure that safe and effective MPHO are available to meet clinical needs within the framework of their national health system. This includes the responsibility to promote donation, equitable allocation and avoidance of inappropriate or unnecessary application.

However it must be remembered that the source of these products is a human donor. Usually, MPHO are donated voluntarily by individual donors with no knowledge of the identity of the possible recipient(s). Such donation should be underpinned by beneficent intent i.e. the donation is given for the benefit of others with no direct personal gain to the donor. This strengthens the universal principle of social solidarity and the fact that we belong to one common humanity.

Given the scale and importance of MPHO in the practice of modern medicine and the nature of donation, it is essential that MPHO are collected safely and the welfare of the donor is protected. The principles guiding the welfare of human donors have been derived by the relevant professional organizations associated with a given process e.g. blood transfusion, solid organ transplantation, HSC transplantation, cell and tissue transplantation and corneal transplantation[1-5]. However the simplistic divides between sectors of MPHO are becoming blurred with considerable cross-over between technologies and therapies. For these reasons the Transplantation Society, the International Society of Blood Transfusion, the Worldwide Network for Blood and Marrow Transplantation and the International Council for Commonality in Blood Banking Automation have come together to develop an overarching set of ethical principles that provide the basis for appropriate and safe practices in the care of human donors of source material for MPHO.

Examples of the added complexity of MPHO and their impact on donors include organ transplant recipients who may receive concomitant HSC transplantation to induce tolerance, as well as the transplanted organ from the same donor, and who may in the future receive manipulated T cell therapy to modify their immune system. HSC transplant recipients may receive a stem cell transplant in addition to undergoing adoptive T cell therapy to restore immune competence and treatment of opportunistic infections. Other new therapies are being developed such as embryonic, pluripotent or MSC therapies for a variety of known and as-yet unknown clinical indications. This means that the potential use of MPHO is likely to expand rapidly and will do so in a heterogeneous regulatory environment. Expansion in the use and indications for MPHO has important implications for the field in general:

- Continued donation of MPHO relies on community trust that products are collected and produced in a safe manner for donors and for recipients, to consistent standards, allocated equitably for the common good of society.
- The development of new technologies means that more donors will be sought to provide potentially more complex MPHO. A lack of adequate numbers of donors in developed countries risks the potential exploitation of donors from poorer regions with consequent risks to safety and well-being. This is especially the case in settings with little or no access to appropriate health care.
- In many instances a recipient may receive multiple types of MPHO in a single treatment often sought from the same donor. This poses potentially greater demands and risks for donors.
- The traditional definitions of what constitutes organ, tissue, cell or blood donors are becoming blurred.
- Uniform ethical standards across disciplines are an essential component to avoid providers indulging in "regulation shopping" or avoidance of oversight.
- Because of their well -developed networks and processes, blood transfusion and HPC transplant services are likely to become more involved in procuring other cells for therapeutic applications.
- Improvement in cryopreservation and perfusion technology means that cells tissues or organs collected and processed in one jurisdiction can be transplanted in another. Collecting products from donors in a less regulated region could result in potential avoidance of regulation, which is designed to protect donors and recipients. Unethical practice risks compromising safety, both for the donor and the recipient. Additional manipulation and/or cell expansion means these risks may be amplified.
- Regulation inevitably lags behind scientific innovation. The development and implementation of a set of overarching ethical principles aimed at protecting the donor will likely be more effective in ensuring that all MPHO will be regulated regardless of current or future technology and definitions.

The four international societies that have developed this document are non-governmental organisations in official relations with the WHO and involved in the development, use and safety of MPHO. The ethical principles outlined in this document are considered to be applicable to all donors of MPHO source materials. It is anticipated that the principles will guide development of ethical and safe practices for donors and will underpin future regulation of MPHO.

The ethical principles that underpin this document are those derived by the WHO and endorsed at the 2010 World Health Assembly that relate to the issues of blood, cell, organ and tissue transplantation and blood transfusion [EB126.R14][6].

1. Ethical principles for the recruitment of donors and the procurement of MPHO

MPHO may be sourced from living and/or deceased donors, depending on the type of MPHO. Recruitment of donors and subsequent procurement of MPHO

should be ethically based and ensure the safety of both the donor and the recipient. In the case of organ and tissue donors the use of MPHO from deceased donors will normally be preferred since this will eliminate the risks that accompany living donation.

Whilst donation of (and access to) MPHO is an expression of community cohesion and solidarity, there is no 'right to donate'. Eligibility criteria for selection and exclusion of donors should be evidence-based and allow maximum community participation whilst being restrictive to those who might pose a risk to either themselves or to the recipient.

Prospective living donors must be able to give informed consent for the donation, which will require the provision of complete and understandable information on:

- Any foreseeable risks that the donation might have for the donor. This should include information on any medicines or related substances that will be administered to the donor as part of the donation process. The donor must be made aware of possible adverse events associated with the procedure including information on possible early, medium and long term complications and the need, where necessary, for regular post-donation check-ups.
- The intended use of the MPHO that will be produced from their donation. This should include information on possible commercialisation of the MPHO and, where appropriate, on whether the donation might be used for research and quality control.
- The responsibilities of the donor to the recipient of the MPHO. This should include information on risks associated with the transmission of diseases.

Donation should not occur until after informed consent has been obtained. The process should ensure that the donor understands the nature of the procedure and the risks involved.

The donation must in all instances be voluntary and no undue pressure or coercion should be placed on a living individual to donate. The donor should be informed of the right to opt-out and, if appropriate, the point at which this will result in damage or death of the recipient (e.g. when the recipient has received myeloablative conditioning for HSC transplant). Donors should be provided sufficient time to make a final decision on whether to donate and for more complex MPHO should be provided access to a 'donor advocate' or support person.

Only adults capable of giving a valid consent should be allowed to donate non-regenerative tissues, including liver. In case of regenerative tissue appropriate policies must be in place to safeguard children and legally incompetent adults.

Decisions about deceased donation should be based on the known wishes of the donor, so far as these are documented. The views of the family will be important

as their co-operation will be required to elicit the donor's medical history and identify risks to the recipient. Clear policies should be available on the issue of consent.

Donors of MPHO should donate for the benefits of others (beneficence). Payment for donation and non-financial incentives that might influence the underlying reason to donate should be actively discouraged and must be prohibited if this will either impact on the safety of the MPHO, result in exploitation of the donor or lead to inequity of access for recipients. A prohibition on payment is included in the guidelines developed by many professional societies involved in the field. The use of incentives to improve the rate of recruitment should be minimized and caution should be adopted where the incentive might act as an inducement with consequent reduction in the commitment to beneficence. This shall not preclude the reimbursement of direct costs incurred by the donor and loss of income related to the donation process

2. The principle emphasis on safeguarding the donor

With the increasing complexity of MPHO, there is the potential for increased physical and psychological demand on donors. In some procedures donors are requested to donate more than one product e.g. kidney donors may also be asked to donate HSCs.

The health, safety and well-being of the donor are of paramount importance and should not be compromised.

The evaluation of the medical and psychosocial suitability of the donor should be undertaken by a medical professional who is independent of the care of the potential recipient. The professional should be free of conflicts of interest and should be neither incentivised nor under any undue pressure or coercion – financial or otherwise. The suitability of potential donors of MPHO should be assessed according to documented selection criteria. These should, where available, be consistent with requirements established by national regulatory authorities and the recommendations of the relevant specialist societies e.g. Vancouver and Amsterdam Forums for organ donation[1-5].

Appropriate medical care must be provided to donors of MPHO at the time of donation. Post-procedure medical and psychosocial care should be provided to cover possible short– and long–term consequences of donation. Any finding from the evaluation relevant to donor health must be communicated to the donor and appropriate medical advice provided.

All jurisdictions should ensure that donors have access to appropriate medical care related to the donation event, regardless of whether there is universal health coverage or not.

Health and/or life insurance coverage and employment opportunities of persons who donate MPHO should not be compromised.

Registration of donor outcomes and reporting of any harm to the donor are an important aspect of donor safety and should be implemented as a component of donation.

3. Ethical principles for the use and development of MPHO Clinical trials and registries

The WHO Guiding Principle # 10[6] highlights the critical need inherent in MPHO for both clinical trials and registries of both donor and recipient outcomes. The principles underlying the requirement for donor registries and clinical trials (where indications for MPHO are not proven) include:

- Under the oversight of national health authorities, transplant, transfusion and cell therapy programs should monitor both donors and recipients to ensure that they receive appropriate care. Evaluation of information regarding the long-term risks and benefits is essential to the consent process and for adequately balancing the interests of donors as well as recipients.
- Donors should not be permitted to donate in clinically hopeless situations.
- Donation and transplant programs are encouraged to participate in national and/or international transplant registries.
- Traceability should be ensured for the lifetime of the donor and the recipient.

Clinical trials provide the evidence base for clinical use of all MPHO because they compare 'standard of care without the use of MPHO', direct comparison of different types of MPHO and the outcomes from use of MPHO. All clinical trials must be conducted in conformance with the Declaration of Helsinki and approved by institutional review boards[1].

Registries are critical to the recording of activities that relate to both donation and utilization of MPHO. Recipient registries are the most effective and comprehensive way of evaluating medium and long term outcomes and should be developed, as are donor outcome registries, especially where there is an increased likelihood of long term donor risks or where long-term risks are unknown e.g. for HSC or living organ donors.

In many of the new and highly manipulated MPHO their intended use is different from that of the original function of the cell or tissue involved. These novel products have important implications for both the donor and the recipient. In

[1] The requirement for lodging clinical trials in public databases was instituted to avoid the problem of publication bias, and ensure that trials that provide either negative answers or inconvenient answers to the investigators are visible to the international community. Clinicaltrials.gov provides one such database. All clinical trials of MPHO should be subjected to the same standard if they are to be considered by regulatory authorities for approval of the indication for use of an MPHO. Whether the donor is considered to be a research subject a clinical trial using MPHO is complex and depends on the degree of involvement of the donor. Careful thought must be given in each clinical trial of an MPHO as to whether or not the donor is a subject of the study and must thus provide informed consent.

these circumstances the MPHO should lead to an improvement in human health status of the recipients.

4. **The principle of the non-commercial nature of MPHO based on the concept of a common humanity where human beings are not to be viewed as a product.**

Non-commercialization of the human body and its parts has been enshrined as a fundamental principle in a number of international legal (binding and non-binding) instruments as well as professional statements and declarations[7-17]. However, commercialization of MPHO does exist to varying extents depending on the substance (some of the newer investigational MPHO and advanced therapeutic medical products (ATMP) like MSC are already commercialized) and the jurisdiction but this should not compromise any of the other principles stated in this document as well as the paramount importance of safeguarding the donor

Commercialization of MPHO is defined as a policy or practice in which the original human body material utilized in a MPHO is treated as a commodity subject to financial transactions. Commercialization implies that the donor themselves, or a third party, who provides such human material receives a tangible return. Commercialization of MPHO does not include:

- The reimbursement of living donors for justifiable and verifiable expenses incurred in the context of donation and the resultant loss of income related to the donation procedure that impacts the donor´s ability to work (consistent with removal of disincentives to living organ donation).
- The payment of justifiable fees for the medical and technical services required (e.g. evaluation and selection of donors, procurement, preservation, processing, storage, and clinical use of MPHO) for the provision of treatment with MPHO.
- Paired exchange programs that are designed to expand the donor pool and avoid donor/recipient incompatibilities.

Whilst marketing for profit of ATMP is permissible, it should be limited to the modification and complexity of production and should not be applied to the cells of origin. It should also require oversight by health authorities that this meets the medical needs of patients

Any other action that leaves the living donor (or a third party) better off financially than they would have been without donating is considered commercialization of MPHO. From an ethical perspective, financial incentives or other benefits which constitute encouragements to those altruistically disposed to donate, and incentives that would make those not contemplating donation to consider doing so, should be actively discouraged or prohibited.

The principle of non-commercialization of MPHO arises from the respect for fundamental human values, in particular that of human dignity and recognition of MPHO as of unique origin of an exceptional nature - humanity. Commercialization tends to target vulnerable people of a population and jeopardizes them as victims of exploitative actions. On the contrary, the spirit of non-commercialization builds on donation as a beneficent act that serves to help others, an act of societal contribution. In response and respectful of the principle of autonomy, society should ensure that the option of donation is presented to the individual when the opportunity arises and that ensuing benefits of donated MPHO are distributed equitably.

Since payments for fees are routine mechanisms in health care, protection of the donor, the recipient and society at large can only be guaranteed by transparency and traceability, implemented through rigorous oversight and scrutiny by the relevant national and international competent authorities. **Noting that the prohibition of financial gain on MPHO does not currently apply in all areas, there is a need to ensure transparency such that the commercial status of MPHO is clearly and openly documented and available to society, and hence to prospective donors and recipients.**

In addition, it is essential to ensure that the donor is protected from exploitation for commercial gain. Because of the commercial nature of the donation, additional safeguards need to be in place. These include oversight or regulations that are independent of the product provider. These are required to ensure that commercial pressures do not impact on the decision to donate, the decision to accept a donor as medically suitable, or the level of safety and care afforded to the donor. These safeguards should be developed by an independent person or body who is not involved in the donor product procurement and where there is no conflict of interest.

Protection of the privacy and confidentiality of donors and recipients is critical. Transparency establishes and maintains public trust, and facilitates traceability, evaluation of outcomes, vigilance and surveillance such that quality, safety and efficiency of MPHO use are optimised. Transparency can only be assured by the adoption of a globally harmonized system of coding for all MPHO, and regulation to ensure the appropriate use of codes and standard terminology to indicate the commercial status of the MPHO on product labels.

5. Development of sufficiency by jurisdictions as an essential component of donor and recipient protection

Development of MPHO is a global phenomenon and patients generally seek medical care with access to MPHO in their local environment. An expectation of any given community is that its recipient pool would receive safe, ethically derived MPHO. However, where community sufficiency is not achieved, there may be movement of patients to other jurisdictions in an attempt to gain access to relevant treatment. For example in the case of organs, insufficiency has led to transplant tourism and exploitation of vulnerable populations. Alternately, in the

case of some MPHO, sufficiency is a goal that will not be achieved in many jurisdictions. For example in the case of HSC donation by matched unrelated donors, maximizing outcome benefits can only be achieved by global cooperation across borders rather than simply through self-sufficiency.

Within this context and in general, to achieve their goal a national authority must commit to developing standards and laws ensuring the health of their donors, and safe practices to minimize risks associated with the retrieval of MPHO.

National authorities are responsible for defining national policies of the procurement and utilization of MPHO taking into account the state of development of the overall health framework in the country. Key components of effective programs include public education and awareness, health professional education and training, and defined responsibilities and accountabilities for all stakeholders involved in the collection, manipulation, storage and delivery of MPHO

Jurisdictions, countries and regions should strive to maximize the supply of MPHO from within the country or through regional cooperation. Where feasible, efforts should be made to procure sufficient MPHO from within the country to meet local needs (self-sufficiency). Participation in reputable regional and international networks for sharing of MPHO should also be supported for HSC donations by highly matched donors for given HSC recipients or donations of organs for highly immunized recipients. Collaboration between countries is not inconsistent with national sufficiency as long as the collaboration protects the vulnerable, promotes equality between donor and recipient populations, and does not violate these principles.

Self-sufficiency should not prejudice cooperation between jurisdictions in exceptional circumstances of mass incidents

Both intra and inter-jurisdiction supply of MPHOs must be in the context of full traceability using unique identification and with reporting of adverse events and reactions during and after donations.

6. Highlight the need for jurisdictions to develop laws and regulations that will protect donors of MPHO

Governments have a responsibility to develop legislative and regulatory frameworks which can protect donors and recipients of MPHO. The framework of legislation and regulation should be based upon the 'WHO Guiding Principles' that address:

- standards for determining and declaring death;
- procurement of the MPHO from deceased and living persons;
- fair and transparent allocation of MPHO to patients (waitlisted for organs and tissues) based upon medical criteria and not upon social status, nor gender or ethnicity;

- establishing competent authorities that are accountable and responsible for the organization, authorization and certification of programs pertaining to MPHO;
- the prohibition of trafficking and exploitation of donors of MPHO.

Governments have this responsibility because MPHO are a matter of societal oversight beyond medical practice and because it involves donors both living and deceased. MPHO are a resource of the national society.

Governments should also legislate for a mandate for the collection of data as a criterion of authorization. Such data enable the development and revision of policy and the assessment of performance. They are vital to the protection of donors and recipients by ensuring quality and safety of MPHO.

To date there have not been uniform regulations regarding the safe and ethical treatment of donors; in some jurisdictions, the governments may be unaware of the occurrence and the details of donor treatment.

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