ILLICIT AND UNETHICAL ACTIVITIES WITH HUMAN TISSUES AND CELLS:

ADDRESSING THE NEED FOR THE ELABORATION OF AN INTERNATIONAL LEGAL INSTRUMENT TO PROTECT DONORS AND RECIPIENTS

as adopted following the 22nd meeting of the European Committee on Organ Transplantation (CD-P-TO) on 12 October 2018

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1 Introduction

Biomedical innovation has led in recent years to an increase in the use of human cells, tissues and cell- or tissue-based products. Today these human substances, including musculoskeletal, cardiovascular and ocular tissues, haematopoietic progenitor cells, gametes and embryos, are routinely used for medical purposes, therapy and research. A consequence of this growth is that the processing and distribution of tissues and cells of human origin has progressively become an "industry" in some settings and donated human material treated as a commodity [1].

Despite considerable efforts by the European Commission, the number of human tissues and cells that are used for human application in the European Union (EU) healthcare setting can only be estimated. In a survey of EU competent authorities, more than 2.1 million human tissue and cell products were reported to have been distributed for medical use in 2015 [2]. It is unclear from these data whether these are only allogeneic products, or if tissues and cells for autologous use are also included in the reports from the member states (MS). Furthermore, information on the volume of tissue products imported into the EU from third countries or exported outside of the EU is not systematically collected.

From surveys of relevant professional societies in the field and estimates by the European Commission, the total number of tissues and cells used for human application can be broken down into the rough annual figures described in **Table 1**.

Table 1. Estimated annual volume of clinical use of human tissues in the European Union[2]

Human substance	**Estimated volume***
Corneas	35,000
Heart valves/cardiovascular tissue	5,000
Hematopoietic stem cells (including cord blood)	57,000
Musculoskeletal tissue	190,000–250,000
Skin	14,000
MAR **	700,000–800,000

** In products/transplants/implants; ** Medically Assisted Reproduction (MAR), including partner donation*

This burgeoning field is in some cases highly profitable. In some countries, a progressive transformation of initially not-for-profit activities into for-profit activities in the tissues and cells field (e.g. cornea [3], bone, gametes [4]) has been described, with the potential risk of not complying with the essential principle that *"the human body and its parts shall not give rise, as such, to financial gain"*. Thus, profit rather than medical need may be the motivating factor for

the procurement of tissues and cells. Furthermore, the availability of donors (both living and deceased) is often a limiting factor for the procurement of tissue and cells, thus source materials are often scarce. Due to this scarcity and the potential financial profits, the risk of illicit and unethical activities involving human tissues and cells can be considered a realistic threat.
Much has been written about trafficking in human organs and human trafficking for the purpose of organ removal [5]. Reports of human exploitation for organ removal and its consequences have been widely reported in the literature [6]. Resolutions, Conventions and professional declarations and statements against these crimes have been adopted by the international community and national laws have been enacted or reinforced in many countries to not only prohibit, but also criminalise the trade in human organs. In contrast, limited attention has been paid to illicit and unethical activities associated with the procurement and clinical use of other substances of human origin, such as tissues and cells. This is perhaps because society is less familiar with tissue and cell transplantation compared with organ transplantation, although the latter happens far less frequently. Moreover, there is no international agreement on what represents illicit and unethical activities with human tissues and cells, and there is no consensus on which of these practices should be criminalised.

Various ethical and safety-related scandals have been reported, such as procurement without consent or authorisation, inadequate testing, inaccurate or false donor files, irresponsible allocation and illegal trade. Hearings, lawsuits, convictions, resignations and closures of tissue establishments have followed. Mediatised cases such as the “France Hypophyse scandal” [7], the “New York body-snatching ring” [8] and the “Alder Hey organ retention scandal” [9] drew public attention and called into question the adequacy of the regulatory framework that governed the human cell, tissue and cellular- and tissue-based product industry [10].

Furthermore, there are activities that, in addition to their illicit and unethical component, could seriously jeopardise the quality and safety of tissues and cells and thus the recipient’s safety. This is the case when excessive reimbursement for donation is given (e.g. in a third country) that could be an incentive for the donor not to disclose relevant information related to certain health risks, or when cell-based experimental treatments are promoted or performed without any clinically demonstrated safety and efficacy.

Regrettably, knowledge about the true extent of these illicit and unethical activities with tissues and cells remains limited [11]. Little information is available from official sources, with figures and trends mostly the result of estimates and rumours. Unsubstantiated reports often appear in the media, such as those describing the existence of undercover networks of brokers, technicians and physicians in various countries. There are probably more cases, but many may go unreported due to fear on the part of the victims/donors and silence on the part of those directly involved in these illicit but lucrative activities. Furthermore, when detected, there are significant disparities from country to country in the management of suspected activities in this context. Inspectors and

enforcement officers lack specific training on how to deal with, identify and handle cases of suspected or confirmed illicit activities related to tissues and cells [12].

In view of this evidence, it becomes clear that a definition of "Trafficking in Human Tissues and Cells" should be agreed upon at international level with the involvement of all the relevant stakeholders. Furthermore, the Council of Europe could play a leading role in elaborating an international legal instrument setting out this definition and the measures to prevent such trafficking and protect the victims, as well as the criminal-law measures to punish the crime. Such initiative would follow the elaboration of the *Convention against trafficking in human organs*, which was adopted by the Committee of Ministers of the Council of Europe in July 2014, and represented the first legal document providing an internationally agreed upon definition of trafficking in human organs, and identifying activities that ratifying states must criminalise [11, 13]. During the preparation of the Convention, ad-hoc Committee of Experts on Trafficking in Human Organs, Tissues and Cells (PC-TO) acknowledged the need to develop an *Additional Protocol on Tissues and Cells* in the future. This need was further stressed by the Committee on Organ Transplantation of the Council of Europe (CD-P-TO) and the Council of Europe Committee on Social Affairs, Health and Sustainable Development of the Parliamentary Assembly [14].

2 Objectives

With this paper, the CD-P-TO aims to raise awareness among Council of Europe decision-making bodies of the necessity to explore the need for an additional protocol to define, prevent and combat illicit activities in the chain of donation to clinical application of human tissue and cells, and to protect donors and recipients.

The present document outlines the issues related to illicit and unethical activities with tissues and cells. In particular, it is intended to provide: i) a review of the existing international legal framework that regulates practices in the field of tissues and cells; ii) a compilation of the available evidence with regard to the dimension and features of illicit and unethical activities involving tissues and cells; iii) a description of the consequences of such practices from the public health and other perspectives; iv) based on the above, a discussion on the need to develop additional international legal tools against unethical practices in the field of human tissues and cells.

In summary, our intention is to use the conclusions and recommendations reached by the CD-P-TO and summarised in this project as food for thought for the Council of Europe decision-making bodies. We are convinced that this study will make us stronger in our fight against illicit activities involving tissues and cells of human origin.

3 International standards in the field of tissues and cells

3.1 World Health Organization

The World Health Organization (WHO), through its 2010 *Guiding Principles on Human Cell, Tissue and Organ Transplantation*, sets out standards for the donation, procurement, clinical use and equitable distribution of human tissues and cells [15]. Although not legally binding, the WHO Guiding Principles have profoundly impacted upon national legislation and professional codes of practice. The fundamental principles laid down include:

- Consent requirements: the living donor must provide duly informed, specific and free consent to the removal of tissues and cells. The Guiding Principles also call for the prohibition of the removal of tissues and cells from living minors, although exceptions may be permissible under national law in the case of regenerative tissues, provided that the minor is duly protected. In the case of the deceased donor, consent for the removal of tissues and cells must be obtained as required by national law, only where there is no reason to believe that the deceased person objected to such removal. Consent may be explicit (”opt in”) or presumed (”opt out”) depending on the existing legal requirements within a given jurisdiction. Where explicit consent has been given and recorded, for example in a donor registry, such consent may be withdrawn at any time before the procurement. Procurement on the basis of presumed consent cannot proceed where the donor has recorded or otherwise made known an objection to deceased donation.
- Prohibition of financial gain: the principle of unpaid donation and the prohibition of financial gain from the human body and its parts is established in the WHO principles. Living donors may be reimbursed for reasonable and verifiable expenses and loss of earnings directly related to the donation, but countries should define the conditions under which such compensation is justified, always avoiding financial incentives or benefits in kind to living donors or deceased donor families. Procurement must be carried out on a non-profit basis. Similarly, WHO allows the payment of professional fees for the services rendered in connection with the donation, procurement and clinical use of human tissues and cells. The prohibition of advertising the need for, or the availability of, human tissues and cells with a view to offering or seeking financial gain or comparable advantage is also set down.
- Allocation: the allocation of tissues and cells should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified and transparent.
- Self-sufficiency: countries should strive to achieve self-sufficiency in human tissues for patient treatment by endorsing donation of tissues and cells and thus removing the incentive for unethical practices involving tissue and cells of human origin.

- Altruistic donation: solidarity between donors and recipients should be advocated without financial gain.
- Equal access to grafts: allocation of human tissues and access to treatment should be based on clinical need only.
- Efficacy, safety and quality: WHO sets out the need to ensure traceability and vigilance systems and to assess the outcomes of recipients of these substances of human origin and of living donors.

3.2 Council of Europe

The Council of Europe *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* (Oviedo convention) and its *Additional Protocol concerning Transplantation of Organs and Tissues of Human Origin* detail some of the essential principles related to the donation of organs and tissue that have been agreed upon [16, 17]. This Convention has been ratified by 29 Council of Europe MS that are hence bound by this treaty.

The fundamental principles laid down by the Oviedo Convention include:

- Organ and tissue removal from living donors: removal of organs or tissue from living persons for clinical use may only by carried out when there is no other therapeutic alternative or organ/tissue available from deceased persons. The necessary consent as provided for under Article 5 must have been given expressly and specifically either in written form or before an official body (Article 19).
- Protection of persons not able to consent: the Convention prohibits the removal of organs or tissues from persons not able to provide valid consent (Article 20).
- Prohibition of financial gain: the human body and its parts shall not, as such, give rise to financial gain (Article 21).
- Disposal of a removed part of the human body: the use of parts of the human body must be restricted to that for which specific information and consent was given (Article 22).

The above principles are complemented by those in *the Additional Protocol concerning Transplantation of Organs and Tissues of Human Origin* as follows [17]:

- Professional standards and safety: the Protocol stresses the need to conform to professional obligations and standards (Article 4) and further expands on the need to minimise disease transmission or other harm to recipients (Article 6).
- Consent requirements: an organ or tissue may be removed from a living donor only after the person concerned has given free, informed and specific consent to it either in written form or before an official body (Article 13). As regards deceased donation, it is stipulated that organs or tissues shall not be removed from the body of a deceased person unless consent or authorisation required by law has been obtained. The removal shall not be carried out if the deceased person had objected to it (Article 17).
- Prohibition of financial gain: it is stated that *"the human body and its parts shall not, as such, give rise to financial gain or comparable advantage"*. The text goes on to say that the prohibition of financial gain does not prevent: (i) compensation of living donors for loss of earnings and reimbursement of any other justifiable expenses caused by the removal or by the related medical examinations; (ii) compensation in the case of undue damage resulting from the removal of organs, tissues or cells; (iii) the payment of a justifiable fee for medical or related technical services rendered in connection with the donation (Article 21).
- Organ and tissue trafficking: organ and tissue trafficking are expressly prohibited (Article 22). It must be noted that, while the Council of Europe has developed an international definition of practices that are consistent with trafficking in human organs [13], it has not performed the same exercise in the field of human tissues and cells.

To provide guidance to MS on the implementation of the principle of the prohibition of financial gain as laid down in Article 21 of the Oviedo Convention, a guide was adopted in 2017 – *Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts, as such, from living or deceased donors* – which provides clarification on key notions relevant to the above-mentioned principles and examples of what are considered as "altruistic focused measures" [18].

3.3 European Union

The *Charter of Fundamental Rights* of the EU should be highlighted, notably the principle set out in Article 3(2)(c), which states that the prohibition on making the human body and its parts as such a source of financial gain must be respected [19]. As mentioned above, this principle is also enshrined in Article 21 of the *Convention on Human Rights and Biomedicine* [16], and in the *WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation* [16].

The European Commission has issued the following EU Cell and Tissue Directives: *2004/23/EC* [20]; *2006/17/EC* [21]; *2006/86/EC* [22] and *2015/565/566/EC* [23]. These directives

were designed to ensure harmonised and high standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human cells and tissues, to facilitate their cross-border movements and to ensure availability in the EU. If MS cannot achieve self-sufficiency, for example because of the scale of the issue or the effects of the potential measures, this can be done at Union level. This means that the Union is allowed to adopt measures in accordance with the principle of subsidiary as set out in Article 5 of the *Lisbon Treaty*[1].

These Directives apply to tissues and cells, including hematopoietic peripheral blood, umbilical-cord blood and bone marrow stem cells, reproductive cells (oocytes, sperm), foetal tissues and cells and adult and embryonic stem cells.

Under *Directive 2004/23/EC* [20], MS must establish an accreditation system for tissue establishments and ensure that appropriate control measures are in place for the procurement of human tissues and cells. Furthermore, MS must organise inspections and control measures, which have to be carried out by officials representing the competent authority, to ensure that tissue establishments comply with the provisions under the EU Directives. The officials involved in inspections and control measures must be appropriately qualified and receive adequate training.

The EU Directives do not, however, describe the penalties that can be imposed in cases of infringement of the national provisions adopted under the EU Directives. MS are obliged to lay down national rules on penalties with regard to breaches of compliance with the EU Directives, penalties that must be effective, proportionate and dissuasive. There is no general overview available of the penalties that the different MS have adopted to ensure compliance with the EU Directives, because of the freedom given to the MS in choosing a legal framework. However, it is known that not all MS have implemented criminal legislation for cases of infringement of the relevant legislation on the quality and safety of tissues and the protection of donors' rights.

To support MS implement a legal framework to combat illicit activities involving tissues and cells, an Inspection guide for Competent Authorities was published in 2011– *Guidance on the detection and investigation of suspected illegal and/or fraudulent activity (IFA) related to tissues and cells* [24] to provide guidance to European Union (EU) Competent Authorities for detecting / identifying, investigating, managing and communicating such activities.

[1] Under the principle of subsidiarity, in areas which do not fall within its exclusive competence, the Union shall act only if and insofar as the objectives of the proposed action cannot be sufficiently achieved by the Member States, either at central level or at regional and local level, but can rather, by reason of the scale or effects of the proposed action, be better achieved at Union level.

3.4 Professional societies

The *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, originally adopted in June 1964, is a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA). [25] It is widely regarded as the cornerstone document on human research ethics. The Declaration developed the ten principles first stated in the *Nuremberg Code* [26], and tied them to the *Declaration of Geneva* (1948), a statement of physicians' ethical duties [27]. Subsequently, in 2012, the WMA also adopted a *Statement On Organ And Tissue Donation* [28].

The *Barcelona Principles: An Agreement on the use of human donated tissue for ocular transplantation, research, and future technologies* is an international consensus document, developed by the eye bank and ophthalmic communities under the leadership of the Global Alliance of Eye Bank Associations (GAEBA), to inform on the management of altruistic and voluntary ocular tissue donations, their subsequent utility within ophthalmology and research, their retention as a public resource for the shared benefit of all, and their accessibility by waiting recipients [29]. This document is the result of global sector engagement over a 12-month period that aims at providing leadership, guidance and recommendations that inform and support sound policy, sector wide strategic planning and implementation at local, national, regional, and international levels.

4 Dimension and characteristics of unethical activities involving human tissues and cells

Little research has been performed to investigate the extent of illicit and unethical activities with human cells and tissues in Europe and worldwide. Most of the information comes from case reports, investigating authorities such as the police or health departments and from articles published in the press.

When illicit and unethical activities involve donors, they frequently relate to recently deceased persons. Tissues may have been sold for the purpose of research or clinical use without the authorisation required in the corresponding jurisdiction, or with falsified papers. Illicitly obtained tissues from one deceased person can reach up to 90 tissue recipients.

When recipients are victims of such practices, cases involve the use of illicitly and/or unsafely procured grafts, but also unethical medical practices such as unauthorised indications or medical treatments without any evidence of efficacy that may cause harm to patients [30]. The latter, however, are primarily violations of laws on practicing medicine and professional medical

standards and cannot be prevented simply by regulating the quality and safety of tissues and cells for clinical use.

For the purpose of this document, we define illicit practices in the field of human tissue and cells as any practice performed in violation of one or more legal requirements or guiding principles, as set down in international legally binding instruments (see **Section 3**) that are related to the donation and/or human application of tissue and cells of human origin (see **Table 2**).

Table 2. Areas of potential unethical activities in the field of tissues and cells

Violation	Related legislation/principles
Procurement of tissue/cells without free, specific and informed consent (living donor) or without the authorisation required in a given jurisdiction, for the purpose of: • **Clinical use** • **Research** • **Further processing as innovative therapies (e.g. in the EU, following under the regulatory frameworks of medical devices or advanced therapy medicinal products)** **Use of surgical residues without free, specific and informed consent**	• Directive 2004/23/EC (Article 13) • Council of Europe recommendation (2006)4 • Convention on Human Rights and Biomedicine and additional protocols (CETS 168,186,195,203)
Violation of body integrity beyond the necessity to procure tissue or cells	• Council of Europe recommendation (2016)6 • Convention on Human Rights and Biomedicine and additional protocols (CETS 168,186,195,203)
Unlicensed storage, processing, distribution, testing	• Directive 2004/23/EC (Article 6) • Directive 2006/86/EC (Articles 3 and 4)
Breach of legal requirements for traceability, donor evaluation, testing, processing, storage and distribution	• Directive 2004/23/EC (Article 8) • Directive 2015/565/EC (Article 1, sub paragraph 2)
Excessive reimbursement or compensation of living donors or a third party in return for the donation of human tissues or cells	• Directive 2004/23/EC (Article 12) • Council of Europe Convention on Human Rights and Biomedicine (Article 21) • Additional Protocol on transplantation of organs and tissues of human origin (Article 21)

Distribution of unauthorised tissue and cell products (e.g. from unlicensed tissue establishments, illegal imports, brokers)	• Directive 2004/23/EC (Articles 6 and 9(3)) • Directive 2015/566/EC (Article 3)
Promotion of tissue- and cell-based experimental treatments without evidence of safety and/or efficacy	• WHO Guiding Principle 10 • Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin (Articles 4 and 6)

4.1 Results from the SOHO V&S project

In 2011, a report on illicit activities involving tissues and cells was prepared as part of an EU-funded project entitled "Vigilance and Surveillance of Substances of Human Origin (SOHO V&S)"[2] [13]. This report aimed at providing EU MS Competent Authorities responsible for tissues and cells with guidance on detecting/identifying, investigating, managing and communicating such activities.

In order to evaluate the experience with illicit activities related to tissues and cells, a questionnaire was developed as part of this project. The questionnaire was submitted to EU Competent Authorities, as well as to several other third countries, during 2010. The scope of the questionnaire was *Directive 2004/23/EC* on tissues and cells used in transplantation and assisted reproduction.

The questionnaire elicited 26 responses from 22 EU MS, 3 European non-EU countries (at the time Croatia had not yet joined the EU) and 1 non-European country[3]. An analysis of all the responses showed that many questionnaires were incomplete due to the fact that MS had limited insight into the matter. Some findings, however, could be highlighted:

- The majority of countries had legislation in place related to illicit activities, which was applicable to human tissue and cells. Those who did not have any legislation in place indicated that they considered it necessary or were working on it.
- Twelve countries indicated having had actual experience with illicit activities over the previous 5 years. In addition, 15 countries had experienced misleading and unsubstantiated claims related to the beneficial effects of cell and tissue transplants.

[2] Grant Agreement Number: 20091110. Funded under the EU Second Programme of Community Action in the Field of Health.

[3] Belgium, Croatia, Cyprus, Czech Republic, Denmark, Germany, Estonia, Iceland, Spain, Finland, France, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Sweden, United Kingdom, United States of America.

Eighteen countries had reported these incidents to other agencies and/or the general public.

- Seventeen cases of illicit were reported which dealt with gametes (sperm, oocytes, embryos), cord blood/tissue and bones/musculoskeletal tissue. Of these, nine were confirmed as constituting illicit activities and the others were still under investigation at the time the questionnaire was being completed. Most of the illicit activities had occurred during the procurement/donation stage of the process.
- Sanctions were imposed where cases of illicit activities had been identified, but it is notable that criminal and administrative sanctions are under the sovereignty of each MS and not EU institutions. Non-harmonised legislation in this regard means that an activity that is criminalised in one MS might not be so in another jurisdiction.

4.2 Interpol survey

At the request of the French Health Authority, a similar survey was developed by Interpol for Law Enforcement Agencies in 2012. In total, representatives from 43 countries completed this survey, most of them from policy-making agencies. One third of the respondents (14) reported cases of illicit with tissues and cells. These reports were based not only on questionnaires, but also on the Interpol database, scientific literature and other open sources. Only 50% of the respondents found legislation in their country sufficient in these matters.

The types of tissue and cells subjected to illicit activities in these reports were bone (including demineralised bone), tendons and ligaments, ocular tissues (corneas and sclera), skin, human placenta, cord blood for autologous use and gametes.

4.3 Case reports

One of the most cautionary examples of a large-scale fraud is the case of Biomedical Tissue Services Ltd (BTS), where intentional misconduct with tissue donors turned out to be highly lucrative and led to a risk of harm to patients. Between 2002 and 2005, BTS distributed tens of thousands of illegally obtained and improperly processed tissues throughout the world. BTS acquired tissues from cooperative funeral homes in the New Jersey area without any authorisation, and produced false death certificates and infectious disease test results. The Food and Drug Administration (FDA) estimated that 13,000 patients had ultimately received tissues processed by BTS. Not all hospitals kept records of which tissues had been implanted and in which patients, so the impact on recipients' health remains largely unknown.

The FDA responded to the BTS scandal by strengthening the regulations governing tissue procurement. However, within a year, another organisation supplying improperly obtained and processed tissues, and using an almost identical *modus operandi*, was discovered to be operating in North Carolina, under the name Donor Referral Services [31].

In Europe, similar practices have been brought to the European Court of Human Rights: the removal of tissue from a deceased man's body without the knowledge or consent of his wife amounted to degrading treatment [32]. The applicant was a Latvian woman whose husband had died in a car accident. After the autopsy had taken place, it emerged that tissue had been removed from the body prior to the funeral without her knowledge or consent. Under a State-approved agreement, the tissue had been sent to a pharmaceutical company in Germany to be modified into bio implants. During the course of the investigation, it was established that in 1999 tissues had been removed from 152 people; in 2000, from 151 people; in 2001, from 127 people; and in 2002, from 65 people. In exchange for the supply of tissue to the company in Germany, the forensic centre involved had organised the purchase of various items of medical equipment, instruments, technology and computers for medical institutions in Latvia.

The Court underlined that, in the special field of organ and tissue transplantation, it had been recognised that the human body had to be treated with respect even after death. Indeed, international treaties, including the *Convention on Human Rights and Biomedicine* and its *Additional Protocol on Transplantation* [16, 17], were drafted to protect the dignity, identity and integrity of "everyone" who had been born, whether at the time living or dead. The Court stressed that respect for human dignity formed part of the very essence of the European Convention.

Between 2009 and 2012, concerns were raised about illegally obtained tissues in forensic institutes in Ukraine; these were intended for the German and US markets and processed by for-profit tissue processors in both countries [33]. Although relatives of the deceased accused the forensic institutes of falsifying consent forms and/or obtaining more tissue than originally agreed upon, the police investigation could not substantiate illegal activities according to Ukrainian law. The processors stopped acquiring human tissue from Ukraine after negative publicity.

Recently, the financial gains made by abortion clinics as a result of selling foetal waste material for research purposes have come under public scrutiny. Although these practices have been going on for decades, ownership of the remains of the foetus and the necessity for consent from the mother has not been regulated in several European countries and therefore these practices continue despite the fact that in other countries they are considered to be a violation of principles and legal requirements.

Practices at some European sperm banks have also come under scrutiny. Among them, the direct sale of sperm samples to women for home insemination. In addition, because several MS prohibit

anonymous gamete donation (with the purpose of protecting the right of the child to know its parent), distribution of anonymous sperm to some countries is considered illegal.

Stem cell therapy brings a new challenge to the field because of the fraudulent practice of offering cures for almost every known disease using stem cells from different sources (autologous, embryonic, allogenic), sometimes obtained and implanted without fulfilling any legal or quality requirements, and in all cases without any evidence of efficacy of these treatments [34].

5 Potential and actual consequences of unethical activities from the perspectives of society and public health

5.1 Risks for recipients

The most important risk for recipients of tissues or cells obtained through illicit and unethical activities is the lack of control of the quality and safety of the tissue or cell products. Risk are increased by incorrect donor histories, doubtful procurement circumstances, incomplete documentation and traceability, inadequate processing, storage and labelling and lack of vigilance and recall options. The consequences may be diverse but can potentially seriously jeopardise the clinical outcome of the patient.

As is the case with organ trafficking, and in particular due to less stringent acceptance criteria, there is an enhanced risk of viral, bacterial or fungal infections transmitted via grafts procured in the context of illicit and unethical practices. In the past, several diseases have been transmitted via tissues and human cells: bone allografts have transmitted hepatitis viruses, tuberculosis and human immunodeficiency virus (HIV-1) [35]. Corneas have transmitted rabies, herpes simplex viruses, bacteria and fungi. Heart valves have been implicated in transmitting tuberculosis and hepatitis B. HIV-1 and cytomegalovirus seroconversion have been reported in patients receiving skin from seropositive donors. Creutzfeldt-Jacob disease has been transmitted by dura and pericardium transplants and several bacteria, such as *Treponema*, have been transferred through tissue. There are also potential dangers associated with stem cell therapy, such as malignant transformation of the implanted cells [36].

When illicit and unethical practices occur in the form of financial inducement to donors (or their families), there may be a risk of potential living donors not adequately considering and evaluating the potential risks related to the donation procedure or of donors or their families not disclosing relevant medical or behavioural information that would, under normal circumstances, preclude donation. This can also motivate intermediaries to withhold information for fear of losing fees.

While it cannot be stated that these complications are more frequent or particularly severe in the

context of illicit and unethical practices with tissues and cells, inappropriate donor (and recipient) selection and substandard practices applied to the procurement, processing and allocation of human tissues and cells are more likely to result in harm to patients.

Desperation may lead patients to search for alternative treatment options for a substantial number of diseases. In this context, advances in the field of stem cell therapies have been accompanied by the promotion of the clinical use of tissues and cells of human origin with no scientific evidence in terms of efficacy and safety. On occasion, patients travel outside of their country of origin in search of these "miraculous" treatments that violate fundamental ethical principles and quality and safety standards (this is the so-called stem cell tourism).

5.2 Consequences for donors or next of kin

The procurement of tissue and cells without consent, or with consent based on insufficient information, may cause severe psychological stress to the living donor and/or deceased donors' families. In particular, the idea that parts of the body "live on" elsewhere, or that the body of the deceased has been violated, often for financial gain, can cause trauma for donors (e.g. repeated and uncontrolled oocyte donation) and their next of kin.

Excessive damage to the deceased body, in the case of unprofessional procurement of tissue, may cause stress during the funeral and leave a permanent stain on relatives' memories of the donor. Other medical considerations include inadequate care and treatment of living donors after procurement of tissue or cells, including donation-related complications. Linked to the lack of appropriate clinical follow up, there is a possible absence of full traceability from donors to recipients and vice versa, as well as failure to record and report serious adverse events and reactions.

5.3 Consequences for the healthcare system

Successful tissue and cell donation and transplantation programs depend on public trust and support. The confidence of the general public in the donation system for tissue and cell products, in a context where the principle of voluntary unpaid donation is legally endorsed, is already threatened by the fact that certain human products are distributed via commercially used channels for pharmaceuticals and medical devices. Furthermore, the public has been shocked on several occasions by incidences of illicit medical practices where unfounded cures were promised by applying human materials.

Against this background, illicit and unethical practices pose an even bigger threat to public trust and support. Not only will scandals related to such practices cause a drop in confidence in all types of donor-derived products, but it will also result in a reluctance to donate bodily materials at all.

Ultimately this will affect the availability of tissue and cell grafts, and jeopardise the availability of organ and blood donors as well.

It is worth noting that desperate patients (as is the case with organ transplantation) who would like to find a solution for their disease are easy prey for illicit and unethical practices with human tissues and cells.

In the end, when financial gain plays a role, the allocation of human tissues and cells according to clinical needs no longer takes priority and this introduces inequality in access to treatment. Patients who benefit will tend to be those who can afford to pay. In addition to financial incentives to donate, there may be coercion, fraud and abuse of donors, as well as long-term medical, social and financial harm to living donors.

Finally, the risk of transmitting infections or other diseases with tissue or cells obtained through illicit and unethical practices does not only endanger the recipients, but may also affect others that are in contact with the recipients thus constituting a serious public health threat.

6 Conclusions

- The volume of tissue and cell donation and transplantation activities in Europe is substantial and the sector is developing fast, being subject to technological innovations and increasing commercial interest.
- The scarcity of donor material and the potential for financial gain from human tissues and cells for human application may encourage illicit activities. Although some cases of have come to light, the true dimension of the problem remains unknown in the absence of systematic and coordinated efforts to define and monitor these practices (last inventory in 2015).
- Illicit activities with tissue and cells may pose a risk to the individual health of both the donor and the recipient, by causing harm through unnecessary procurement procedures, facilitating the transmission of diseases (which also poses a risk to public health) or applying therapies that have not been tested in terms of safety and quality for the individual.
- Illicit activities may jeopardise public trust and willingness to altruistically donate tissue and cells and therefore limit the availability of these essential healthcare provisions for patients.
- The confidence of the general public in the donation system may be undermined by unethical but very lucrative medicinal procedures, in which treatments with tissues and cells offer unproven cures.

- The existing international legal framework provides ample provisions to ensure good practices and the quality and safety of tissues and cells, e.g. by specifying consent and authorisation requirements, prohibiting financial gain and creating the obligation of sanctions/penalties in cases of violation of such provisions. These provisions and sanctions, however, have not yet been implemented in all European countries and most of those found to be violating these requirements have not been subject to sanctions.
- Despite the existing legal framework, the interpretation of what constitutes illicit practices differs between countries; this may result in tissue- and cell-related activities being acceptable in one country while illegal in a neighbouring one. Moreover, there is no international agreement on which illicit practices are of such severity – because they violate fundamental human rights and freedoms, such as that of self-determination, dignity and integrity and/or because they pose important threats to public health – that they should be subject to criminalisation and made consistent with trafficking in tissues and cells. International agreement and coordinated efforts against trafficking in human tissues and cells are imperative in this field where transnational activity is frequent.

7 Recommendations

1. The principle of the prohibition of making financial gain with the human body or its parts should be the paramount consideration in relation to the donation of tissues and cells of human origin. All national legislations concerning the donation and human application of tissues and cells should conform to this principle.
2. The definition and interpretation of what constitute illicit activities, as well as the need for adequate sanctions against these practices, should be agreed at international level. In particular, international agreement should be reached on which illicit activities involving human tissue and cells are of such severity – because they imply the violation of fundamental principles and/or pose important threats to public health – that they should be criminalised.
3. Collaboration between international organisations, as well as national and international law enforcement agencies, such as Interpol and Europol, are indispensable where illicit practices are detected or suspected at an international level or where is the potential to have international consequences.
4. Cooperation among customs authorities, law enforcement agencies and Health Authorities should be strengthened, particularly during ongoing investigations. To coordinate the identification and management of suspected cases, clearly defined roles, training and education for all involved parties and adequate resources should be set in place.

5. Donors and recipients of tissues and cells, and the general public, should be informed of donors' rights and the legal context of donating, processing and distributing human materials for medical and research purposes, including (acceptable) commercial involvement.
6. Healthcare professionals should continue to promote standards for ethical practices in the field of tissues and cells. Professional societies should have a leading role in the development and dissemination of such professional codes of ethics.
7. It is essential to start collecting reliable data on illicit activities involving human tissues and cells. There is limited knowledge of the scale of the problem since little and fragmentary information about the number of trafficked tissues and cells and victims of illicit practices is available from official sources. This hinders both the quantification of illicit practices and also their qualitative description. The data should be disaggregated by sex in order to assess whether and to what extent the processes disproportionately affect women and girls. States should make efforts in terms of data collection in relation to illicit practices and commission an international body to systematically monitor and report international data and exchange good practices for the prevention and prosecution of such activities.

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Annex 1. Questionnaire to compile information on experience of illegal and fraudulent activities with tissues and cells.

1.	Please provide the number of suspected IFA cases related to tissues and cells your CA/MS has been involved in the last 5 years	
2.	What, in your opinion, are the strengths and weaknesses of the IFA management system in your MS? Please summarise. **strengths:** **weaknesses:**	
3.	Do you have any experience in dealing with misleading advertising in the use of tissues and cells (i.e. unsubstantiated claims)? If **Yes**, please summarise	☐ **Yes** ☐ **No**
4.	Do you have procedures to communicate suspected IFA cases to other agencies/the public? If **Yes**, please summarise	☐ **Yes** ☐ **No**
5.	Have you had any experience with a "virtual" tissue establishment that is involved in import/export? If **Yes**, please summarise	☐ **Yes** ☐ **No**

Annex 2. Examples of cases related to consent matters

Case	Year	Reason for case	Decision/settlement
Beleno v. Tex. Dept. of State Health Servs., No. SA-09-CA-188-FB, United States District Court for the Western District of Texas	2009	Parents sued state for use of leftover blood samples that were collected for new-born blood screening and were used in research for which parents had not given consent.	Case settled out of court. State destroyed all existing leftover specimens.
Adams v. King County, 192 P. 3d 891 (Wa. 2008)	2008	Organ donor's organs were sent to medical research institute for research. Family sued, contending that donor's consent was limited to transplantation.	Court held that family had a claim based on their interest in proper treatment of body; not a property interest.
Washington University v. Catalona, 490 F 3d 667 (8th Cir. 2007)	2007	Washington University refused to relinquish custody of tissue obtained for research purposes when one of the investigators (and some of the donors) requested that the samples be transferred to another institution.	Court held that donors made a gift of their samples and did not retain a right to direct that they be transferred elsewhere.
Havasupai Tribe v. Arizona State University, Case No. CV2005-013190, Superior Court of Arizona, Maricopa County	2004	Native American tribe filed lawsuit claiming samples given to local universities for diabetes research were used for studies on inbreeding, schizophrenia, metabolic diseases, alcoholism and population migration.	Case settled out of court. The University of Arizona's Board of Regents to pay $700,000 to the tribe members, provide other forms of assistance to the impoverished Havasupai and return the blood samples.
Greenberg v. Miami Children's Hospital Research Institute, 264 F. Suppl. 2d, 1064 (SD Fl. 2003)	2003	Plaintiffs donated samples for research which led to development of new diagnostic test. Plaintiffs sued after learning that research institution was licensing the test.	Patients have no property right in tissue voluntarily donated for medical research.
Application nº 61243/08 by Dzintra ELBERTE v Latvia	2001	After the autopsy had taken place, it emerged that tissue had been removed from the body prior to the funeral without his wife knowledge or consent. More cases were discovered later	Although relatives of the deceased accused the forensic institutes of falsifying consent forms and/or obtaining more tissue than originally agreed upon, the police investigation could not substantiate IFA according to Ukrainian law
Mansaw v. Midwest Organ Bank, 1998 U.S. Dist. LEXUS 10307 (W.D. Mo. 1998)	1998	Father sued for rights to control the removal of tissue and organs from his deceased son's body.	Court acknowledged father's property interest, but held that it was minimal.

Moore v. Regents of University of California, 793 P.2d 479 (Cal. 1990)	1990	Patient's cells were used for research without his knowledge or consent. Patient sued after learning that research institution had developed cell line and realised economic benefit.	Court held that patient did not have property right in excised tissue, but could pursue a breach of fiduciary duty claim.
York v. Jones, 717 F. Suppl. 421 (E.D. Va. 1989)	1989	Couple signed agreement regarding procedures for freezing their fertilised eggs, and permitting use for research if they no longer desired to initiate a pregnancy. Later the couple sought to have the prezygote transferred to another medical school for implantation.	Court ruled that the relationship was that of bailee/bailor and the couple did have property rights and could repossess the prezygote.