

INTRODUCTION

The European Society of Human Reproduction and Embryology (ESHRE) welcomes the European Commission's Proposal for a Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application, following the fundamental revision of the EU legislation on Blood, Tissues and Cells (BTC).

As the 'voice' of human reproduction and embryology professionals, ESHRE played an active role throughout the drafting phase of the proposed SoHO Regulation and effectively supported the revision of ambiguities, gaps, and shortcomings identified in the current BTC legislation. The issues raised were presented in a number of our previous position statements, together with recommendations for the field of medically assisted reproduction (MAR).

While ESHRE appreciates that the European Commission took into account and positively addressed many of our remarks in its SoHO Regulation Proposal, we take this opportunity to share additional views on the proposed legislation, including the elements of the proposal that could still be improved and clarified. A large variety of substances now fall within the scope of this regulation, each of which has its particularities that need to be recognised; this can prove challenging at times.

1. HARMONISATION OF PRACTICES

First and foremost, ESHRE welcomes the European Commission's efforts to allow for and ensure **higher harmonisation of practices in the field of MAR across European Member States** by proposing a joint regulation to replace the current BTC Directives 2002/98/EC and 2004/23/EC. As we urged in the past, it remains of utmost importance within our field that the authorisation process of new MAR technology/methodology and establishments, together with the data collection and the inspections' quality, content, and evaluation methods, are harmonised at the EU level.

2. DEFINITIONS AND TERMINOLOGY

However, one critical shortcoming of the proposal is that its **definition of a 'substance of human origin' (SoHO) does not currently account for embryos, given that embryos** are not collected from the human body but derived from it. Because MAR and fertility-related treatments involve the manipulation of sperm, oocytes and embryos, it remains without question that the high quality and safety standards to be set by the regulation to protect donors, recipients, and offspring from MAR need to apply to embryos too.

→ **We call on the legislators to correct the definition of a 'substance of human origin' (Article 3(5)) and clearly include embryos as SoHOs under this umbrella term. We propose the following for consideration:**

- 'substance of human origin' (SoHO) means any substance collected **or originating** from the human body in whatever manner, whether it contains cells or not and whether those cells are living or not. For the purposes of this regulation, SoHO does not include organs in the sense of Article 3, point (h), of Directive 2010/53/EU;

Another important definition that requires amendment is the one of 'offspring from medically assisted reproduction'. Experts at **ESHRE strongly disagree with using the term 'offspring' to refer to both fetuses and children born**. This term should only describe children that have already been born following MAR, not fetuses resulting from MAR.

→ **We urge the legislators to change the definition of 'offspring from medically assisted reproduction' (Article 3(11)), so that it adequately reflects the medical reality of a MAR practice:**

- 'offspring from medically assisted reproduction' means **fetuses and** children that are born following medically assisted reproduction;

ESHRE is appreciative of the **revised and newly proposed definitions of ‘within couple use’ and ‘third party donation’** to replace the current terminology referring to ‘partner donation’ and non-partner ‘donation’, which is in use within the scope of Directive 2004/23/EC and its implementing legislation. Nonetheless, this **distinction needs to be clear, together with the use of the terms ‘recipient’ and ‘donor’ in MAR throughout the entire legislative text**; mainly the definitions in Article 3. Provided that the SoHO Regulation will be directly applicable across all EU Member States and translated into 24 official languages once in effect, we find it critical that its text is clearly interpretable by all relevant stakeholders, especially health professionals and inspectors conducting audits of MAR establishments. We wish to prevent the improper use of terminology, which often results from extrapolating the use and meaning of these terms from other SoHO fields to MAR.

→ **We call for clarification of the terms ‘donor’ and ‘recipient’ in the field of MAR, either in the legislative text of the SoHO Regulation or through other accompanying documents provided by the European Commission to make such information publicly available.**

In our professional opinion, in the context of ‘within couple use’ (Article 3(63)) in MAR:

- the person supplying their own oocytes for a MAR treatment should be considered a ‘partner’ and only defined as a ‘recipient’ at the time of the embryo transfer or intrauterine sperm insemination, and not during the stimulation and procurement phase, given the revised definition of this term; while
- the person supplying their own sperm should be defined as a ‘partner’, not a ‘SoHO donor’, with such clarification added to the definition in Article 3(8).

→ **We propose that the definition of a ‘SoHO donor’ (Article 3(8)) is adapted to indicate that the terms ‘donation’ and ‘donor’ are no longer used for ‘within couple use’ treatments in MAR, nor when referring to individuals who are cryopreserving their own gametes for fertility preservation. We suggest the following option for consideration:**

- ‘SoHO donor’ means any person who has presented themselves to a SoHO entity with a view to making a donation of SoHOs, whether the donation is successful or not; **the person supplying sperm for within couple use is not considered a ‘SoHO donor’, but a ‘partner’.**

→ **We further propose that the persons taking part in a ‘within couple use’ treatment in MAR are both referred to as ‘partners’ and the definition of ‘within couple use’ (Article 3(63)) is adapted accordingly**

- ‘within couple use’ means use of reproductive cells for medically assisted reproduction from two persons (**‘partners’**) with an intimate physical relationship, where one person supplies their own oocytes and the other person supplies their own sperm.

In the context of ‘third party donation’ (Article 3(62)) in MAR, it needs to be clear from the SoHO Regulation that:

- the person is defined as a ‘recipient’ when they receive embryos (from own or donated oocytes and/or from donated sperm), or when they are inseminated with donated sperm; and
- the person is defined as a ‘donor’, as provided in Article 3(8), when they presented themselves to a SoHO entity with a view to making a donation of SoHOs, whether that donation is successful or not.

We also find it important to emphasize that **partners undergoing a ‘within couple’ MAR treatment should not be mistaken for or referred to as any kind of donors under the SoHO Regulation.** While we see the intention of the legislators in Article 53(1) on Standards concerning SoHO donor protection to exclude partners in ‘within couple use’ from its scope, it needs to be clear in the text to avoid ambiguity. The donation of reproductive cells in MAR is defined in the proposal as a ‘third party donation’. Therefore, **the provisions strengthening donor protection should concern ‘third party donors’ explicitly; the term ‘allogeneic donors’ is not used or applicable in the MAR field.**

→ **We strongly advise that Article 53(1) refers to the collection of SoHOs from both ‘allogeneic donors and third party donors’, not only ‘allogeneic donors’, to account for donations in our field and to protect third party donors in MAR.**

With reference to Article 3(18), providing the definition of ‘release’, we would like to highlight that, in the field of MAR, **the ‘defined quality criteria’ for release of SoHOs or SoHO preparations can be applied to the processes, but not to the biological material itself.** As the experience in our field shows, inseminating with suboptimal sperm samples or transferring morphologically suboptimal embryos may both lead to the birth of healthy children, with no increased risk of adverse outcomes for the mother and child.

3. DONOR, OFFSPRING AND RECIPIENT PROTECTION

A very positive element of the proposed SoHO Regulation is its **extended and strengthened scope regarding the protection of third party donors and offspring born from MAR**. ESHRE is pleased to see that the proposed SoHO Regulation aims to assure the safety of the entire donation process in MAR and protect donors before, during, and after donation. We also find it essential that the offspring is to be protected whether the sperm, eggs, or embryos used to assist the reproduction come from within couple use or third party donors.

ESHRE recognizes that particularly the following developments will be in a positive direction and highly relevant to our field:

- **mandatory third party donor health evaluations;**
- mandatory registration and follow-up of third party donors subjected to a surgical procedure in order to donate, donors who are treated with hormones to facilitate donation, and those who donate on a frequent and repeated basis **(i.e., risk-proportionate approach to donor monitoring after third party donation);** and
- **mandatory reporting concerning third party donors and the offspring born from MAR, including serious adverse occurrences (SAOs) reporting,** which is proposed to be mandatory for the offspring from donated sperm, eggs or embryos, and shall additionally entail reporting of genetic conditions transmitted to the offspring as SAOs.

ESHRE also appreciates the efforts to regulate the conditions for **compensation and reimbursement to donors for losses related to their participation in donations**, including the obligation of national authorities to set and/or approve an upper limit of these fixed rate allowances at the national level to ensure their financial neutrality and compliance with standards that prevent the provision of financial incentives or inducements to promote donations. However, ESHRE is rather **cautious about leaving the definition of this upper limit solely to the Member States without any further boundaries or guidelines on a wider scale**. Given the large existing differences between EU countries, this provision may still contribute to inequities and encourage donors to travel across borders instead of donating gametes in their home country.

→ **We urge the legislators to identify and propose solutions for finding a common denominator or some other value of proportion to guide national authorities in setting the upper limits for compensation and reimbursement allowances to donors across EU Member States (e.g., an economic index of a country).**

Regarding the protection of recipients, ESHRE welcomes that Article 58(10) of the proposed regulation shall constrain SoHO entities from applying SoHO preparations to recipients without proven benefit, unnecessarily, and from advertising or promoting particular preparations to potential recipients or health care professionals using information that is misleading (in particular, as to the potential use and benefits to recipients of the SoHO concerned). ESHRE acknowledges this as a positive element that could hopefully **address and help mitigate the use of unvalidated add-on procedures for MAR**.

We further wish to point out that while we generally support **the proposed hierarchy for implementing standards on donor, recipient, and offspring protection (Articles 56 and 59) and the involvement of European scientific expert bodies (the ECDC and EDQM) in this endeavour**, some elements of this hierarchy still need clarification. On the one hand, we are pleased to see that the importance of having a more flexible regulatory framework was recognised, as it should allow for a more efficient and responsive uptake of the most up-to-date scientific evidence and guidelines. On the other hand, **we find it imperative that the conditions of the ECDC and EDQM involvement are specified to ensure there is an appropriate level of expertise and transparency in their work**, if they are to be responsible for publishing the safety and quality guidelines applicable across all SoHO fields.

→ **The SoHO Regulation and/or other accompanying documents should provide clearly defined requirements for the involvement of ECDC and EDQM in the development and updating of the technical guidelines under its scope.**

For any future reference, it is also of utmost importance that, given the wide range of SoHOs covered, **the ECDC and EDQM technical guidelines describe the standards concerning donor, recipient, and offspring protection, and how these apply to specific SoHOs and respective fields in more detail**. It will be critical to define, for instance, the requirements for donor and offspring follow-up in MAR or the notion of 'frequent and repeated' donation (Article 53(3)) of gametes, when compared to blood or other types of non-reproductive tissues and cells for which these standards might greatly differ.

Still on the hierarchy for standards on donor, recipient, and offspring protection, Article 56(4)(b) and Article 59(5)(b) of the SoHO Regulation Proposal suggest that guidelines published by an expert society, like ESHRE, could also set the mandatory standards for MAR and thus be followed by SoHO entities. That is if the national competent authorities accept them as achieving an 'equivalent' level of safety and quality as is set by the EDQM and ECDC technical guidelines. Nonetheless, **the role of expert medical societies and our guidelines in this regard is not sufficiently clear** from the proposal.

→ **We call on the European Commission to clarify the role that medical societies and our evidence-based guidelines could play under the scope of this hierarchy; given that, as professionals, we have a complete and detailed view of the technical aspects and practical implications in our respective field, and the publication of guidelines is a valuable component of our activities.**

4. EXPERT AND PATIENT INVOLVEMENT

Overall, ESHRE is appreciative of **the extended role that experts may play within the scope of this regulation**, including the assessments of SoHO preparations, inspections of SoHO entities and establishments, as well as expert participation at the meetings of the SoHO Coordination Board.

However, in line with our previous point on the ECDC and EDQM role, **we would still like to see more explicit provisions on the involvement of experts from medical societies, such as ESHRE, in the development and update of the ECDC and EDQM guidelines** that are to be at the core of the SoHO Regulation. At the moment, there is no formal requirement for these expert bodies to consult and cooperate with experts from medical or scientific societies in relation to their guidelines on SoHOs; our involvement as a society for the field of MAR, although having worked very well, is currently rather ad hoc.

→ **Consequently, we would like a more formal requirement to be defined, for instance, in a cooperation agreement between the European Commission and these European expert bodies; so that at least two experts from each SoHO field (i.e., representatives of medical or scientific societies) are involved in the development and update of the ECDC and EDQM technical guidelines.**

ESHRE additionally supports **active patient participation in the SoHO Coordination Board**, for instance, by inviting patient organisations, like Fertility Europe, and other representative groups to join its meetings as observers. Since the provisions of Recital 38 and Article 67 on the SoHO Coordination Board are both quite open in this regard, we would like to see that the involvement and role of patients in the SoHO Coordination Board is more clearly described in the future rules of procedure or the implementing legislation of this regulation.

5. QUALIFICATIONS AND SPECIALISED TRAINING OF INSPECTORS

ESHRE further welcomes that, in line with our prior recommendations, inspectors of SoHO entities and establishments are now proposed to not only possess evidence of their formal qualifications in a relevant field, but shall also undergo a specific induction training, complemented by **a specialized training for inspection of specific types of establishments (e.g., MAR clinics and IVF laboratories)** and a continuous training throughout their careers (Article 32). We expect this will ensure that **the selected inspectors have the necessary understanding and expertise required to perform inspections within the field of MAR**, which is not always the reality experienced under the current BTC Directives. It also remains of utmost importance that the inspectors stay up to date with the most recent developments and technical guidelines applicable to the MAR field. This should hopefully be achieved through their continuous training and contribute to a higher harmonisation of practices across and within Member States.

→ **To support the endeavour, ESHRE strongly encourages competent authorities and inspectorate bodies to collaborate with experts from medical societies and professional associations from the respective SoHO fields when developing the training programs for inspectors and authority officials.**

6. DATA COLLECTION

Last but not least, ESHRE supports **the extended requirements for data collection**, as outlined in the proposal; for instance, regarding the collection of donor follow-up data and activity data of SoHO entities. We are also greatly appreciative of **the role that the international registries may play within the scope of the SoHO Regulation**, such as taking over certain tasks related to the collection and submission of data to the online EU SoHO Platform.

When it comes **to the design of the proposed SoHO Platform**, ESHRE welcomes the efforts of the European Commission to follow a participatory approach in its design and **involve key stakeholders, including expert societies like ESHRE**. Among other aspects that might arise along the way, we find it critical for the future utility of this platform:

- to primarily introduce **harmonised definitions of the items or parameters** to be included in the databases;
- To design the EU SoHO platform in a way that **allows the identification of new challenges and clinical outcomes related to novel technologies**; and
- to have an **online platform that can be easily and efficiently linked to other SoHO registries**.

→ **We encourage the European Commission to continue working with key stakeholders, including SoHO establishments and expert societies (such as ESHRE), in designing the EU SoHO Platform, and thus develop a tool that reflects the needs of its users and achieves the set objectives of more harmonised data collection across EU Member States.**

ABOUT ESHRE

ESHRE is a European non-profit organisation with international membership, whose main mission is to promote the study and research of reproductive science and medicine as well as the treatment of infertility. Established in 1984, the Society now comprises more than 9.000 members and has become the leading Society in reproductive science and medicine worldwide. Our members are medical professionals, scientists and researchers working in reproductive science, reproductive medicine and embryology. We work in close partnership with the patient organisation Fertility Europe.

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