SoHO-Regulation Perspective Lab

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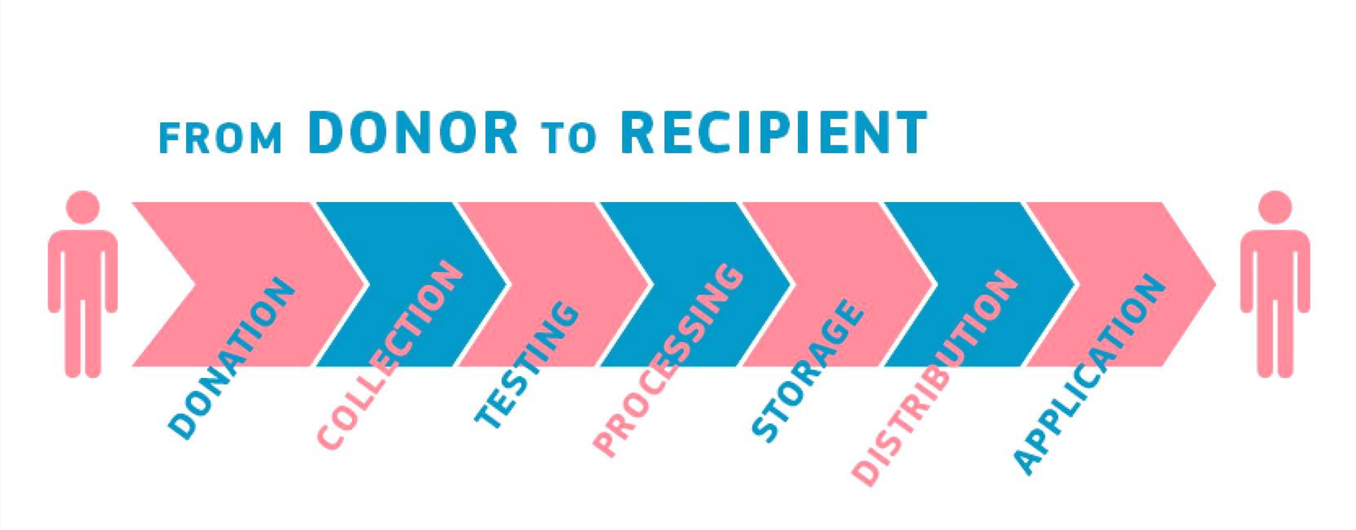
European Society of Human Reproduction and Embryology

Regulation 2024/1938 - scope

Covers the **activities that are considered to have a direct impact on the quality, safety and effectiveness of SoHO** → from the potential donor to the application of SoHO and clinical outcome

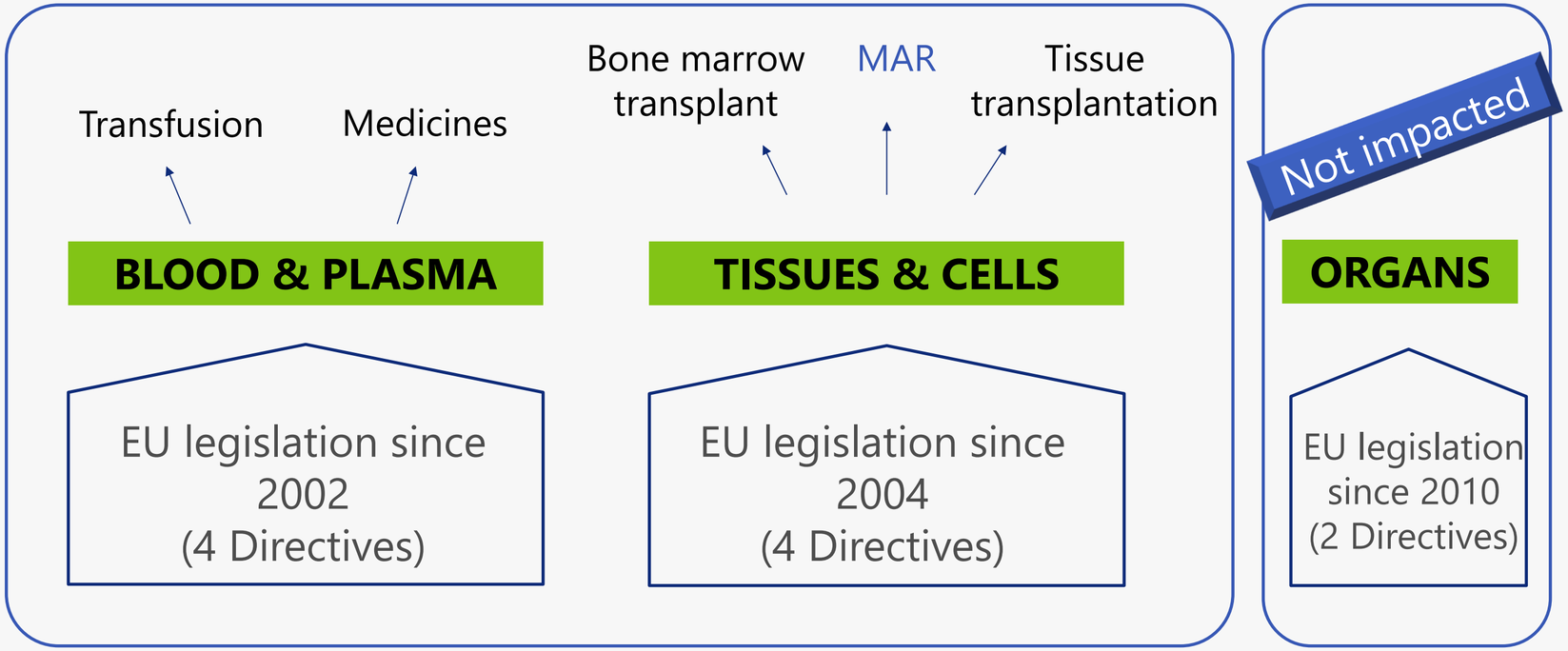


SoHO
= any substance collected from the human body
= oocyte

SoHO Preparation
= cryopreserved oocytes

Reproductive SoHO
= Sperm, oocytes, ovarian and testicular tissue, and embryos

Regulation 2024/1938 - scope



Replaced by a single "Regulation on standards of quality and safety for substances of human origin"

Regulation 2024/1938 - scope

(55) '**EDQM SoHO monograph**' means a specification of the critical quality parameters of a particular SoHO preparation defined by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM);

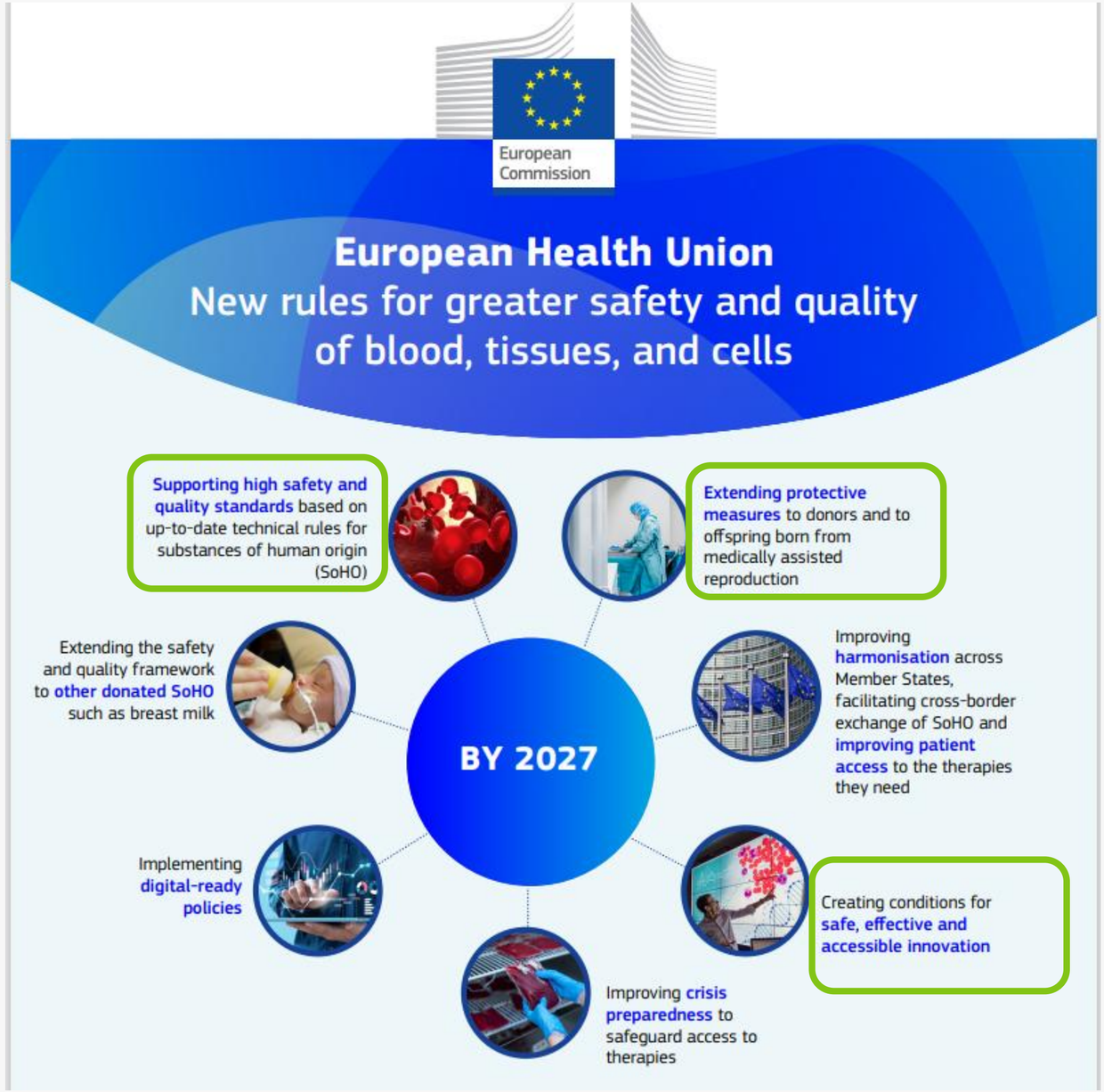
(18) As the **release of SoHO** is a critical step that allows SoHO to be moved from a 'quarantined' to an 'available for use' status, it should be considered as a SoHO activity.

(2) '**critical SoHO'** means a SoHO for which an insufficient supply will result in serious harm or risk of serious harm to recipients' health or in a serious interruption in the manufacture of products regulated by other Union legislation, as referred to in Article 2(6), where an insufficient supply of such products will result in serious harm or risk of serious harm to human health;

Article 64 - **Supply alerts for critical SoHO**

1.Critical SoHO entities shall, without undue delay, send a SoHO supply alert to their SoHO competent authorities in the event of significant shortages of supply of critical SoHO, indicating the underlying reasons, the expected impact on recipients and any mitigating actions taken, including in relation to possible alternative supply channels if appropriate.

The SoHO Regulation



The SoHO Regulation

Supporting high safety and quality standards based on up-to-date technical rules for SoHO

The SoHO Regulation - Recital 49

EDQM Guidance

ECDC Guidance

National/ equivalent Guidelines

Professional guidelines

Scientific evidence, ..

With regard to standards concerning the protection of SoHO donors, SoHO recipients and offspring from medically assisted reproduction, this Regulation should provide rules for their implementation. As risks and technologies change, these rules should facilitate an efficient and responsive uptake of the most up-to-date guidelines, based on available scientific evidence, for implementing the standards set out in this Regulation. For the purposes of this Regulation, reconstructive surgery should not be considered as an aesthetic use. In the absence of Union legislation describing particular procedures to be applied and followed to meet the standards set out in this Regulation, following the guidelines of the European Centre for Disease Prevention and Control (ECDC) and the EDQM should be considered an appropriate means to demonstrate compliance with this Regulation and the standards thereof to ensure high level of quality, safety and effectiveness. SoHO national authorities are involved in the process of establishing those guidelines through their participation in the governance bodies of both the ECDC and the EDQM. Member States should be able to adopt other guidelines, as a reference for SoHO entities located in their territory. When adopting such other guidelines, Member States should verify and document that those guidelines achieve compliance with the standards set by this Regulation. In cases of detailed technical issues for which neither Union legislation nor the ECDC and the EDQM, nor other guidelines, have defined a technical guideline or rule, SoHO entities should apply a locally defined rule that is in line with relevant internationally recognised guidelines and available scientific evidence and is appropriate to mitigate any risk identified.

The SoHO Regulation - Recital 49

Level 1

Implementing
Legislation

Level 2

EDQM
Guidance

ECDC
Guidance

National / equivalent
Guidelines

"Equivalent" Guidance, deemed by the CAs to achieve equivalent standards

Level 3

Professional guidelines
(ESHRE Guidelines and others)

Scientific evidence,
..

Detailed technical issues
⇒ based on international standards or scientific evidence

The SoHO Regulation - Article 27, 56 and 59

EDQM (or ECDC) Technical guidelines

Will be included in a specific module of the EU SoHO Platform.

Other guidelines adopted by the Member State

Will be included in a specific module of the EU SoHO Platform with information on equivalence.

Other guidelines or technical methods

Included in a specific module of the EU SoHO Platform ?

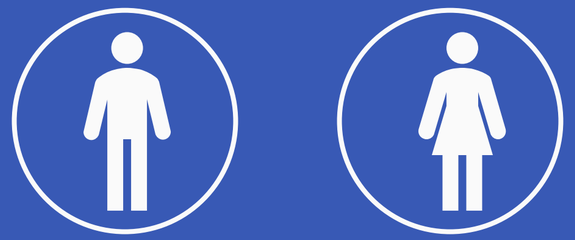
➢ If SoHO entities can demonstrate during inspections that they are following these guidelines, inspectors shall consider the standards of the Regulation to be met.

➢ SoHO entities need to provide a justification during inspections that these guidelines or methods are adequate to achieve the level of quality and safety set out in each specific standard for which they decided to follow other guidelines or technical methods. This justification may be based on a demonstration of equivalence with ECDC/EDQM guidelines.

The SoHO Regulation

Ensuring protective measures to donors and to offspring born from MAR

Terminology MAR treatments



DONOR (Third-party)

Someone who is not in a (sexual) relationship with the person(s) going through MAR treatment

RECIPIENT

Person who receives SoHOs (embryos or sperm), irrespective of if these are from a partner or a donor

OFFSPRING

Born children

WITHIN RELATIONSHIP USE

Allows less stringent criteria for donors donating for within relationship use

In the lab: Any handling of tissues and cells is covered by the SoHO Regulation.

The SoHO Regulation - Article 57 and 58

The SoHO Regulation sets the following **high-level standards for SoHO entities**:

Mitigating the risk of communicable disease transmission from donors by:
- Testing donors for communicable diseases
- Taking measures that reduce/eliminate potential communicable pathogens
- Defer donors with high risks (when risks cannot be minimized)

Mitigating the risk of transmission of serious genetic conditions from donors to offspring in MAR by:
- Review health and family history (refer if risk)
- Routinely test donors for certain genetic conditions
- Test donor relevant to the genetic conditions in the patient/couple (matching)

Mitigating the risk of contamination of SoHO from other SoHO from different persons or from the environment, personnel, equipment or materials

Mitigating the risk that any reagents and solutions added to SoHO might be transferred to recipients and have a harmful effect on their health

Mitigating the risk that any SoHO activity performed reduces the clinical effectiveness of SoHO (i.e., in MAR, the chances of a pregnancy and live birth)

Mitigating the risk that SoHO cause an unexpected immune reaction in recipients

Mitigating any other avoidable risk to the recipient or offspring health and dignity, in accordance with national law

Complying with national legislation on limits to the number of offspring from MAR, to be monitored by donor registries, in accordance with national law

Using technologies that reduce the risk of human error

The SoHO Regulation - Article 57 and 58

The SoHO Regulation also lists a number of things that SoHO entities **shall not do**:

- apply SoHO preparations to recipients without proven benefit, except in an approved clinical outcome monitoring plan in an application for preparation process authorisation
- apply SoHO preparations unnecessarily
- advertise or promote particular SoHO using misleading information
- use allogeneic SoHO (i.e., SoHO from a person other than the recipient) for purposes other than the prevention or treatment of a medical condition or for MAR

Examples

=> Using technologies that reduce the risk of human error

EDQM GUIDE

⇒ Provides good practice guidelines for Quality and Risk Management
⇒ SoHO entity should select (Key) Performance Indicators

ESHRE GUIDANCE:

Human Reproduction Open, pp. 1–17, 2017
doi:10.1093/hropen/hox011

human reproduction open

ESHRE PAGES

The Vienna consensus: report of an expert meeting on the development of art laboratory performance indicators[†,‡]

ESHRE Special Interest Group of Embryology[1,*] and Alpha Scientists in Reproductive Medicine[2,*]

Table IV KPIs for the ART laboratory.

KPI	Calculation	Competency value (%)	Benchmark value (%)
ICSI damage rate	$\frac{\text{no. damaged or degenerated}}{\text{all oocytes injected}} \times 100$	≤10	≤5
ICSI normal fertilization rate	$\frac{\text{no. oocytes with 2PN and 2PB}}{\text{no. MII oocytes injected}} \times 100$	≥65	≥80
IVF normal fertilization rate	$\frac{\text{no. oocytes with 2PN and 2PB}}{\text{no. COCs inseminated}} \times 100$	≥60	≥75
Failed fertilization rate (IVF)	$\frac{\text{no. cycles with no evidence of fertilization}}{\text{no. of stimulated IVF cycles}} \times 100$	<5	
Cleavage rate	$\frac{\text{no. cleaved embryos Day 2}}{\text{no. 2PN/2PB oocytes on Day 1}} \times 100$	≥95	≥99
Day 2 Embryo development rate	$\frac{\text{no. 4-cell embryos on Day 2}}{\text{no. normally fertilized oocytes}^a} \times 100$	≥50	≥80
Day 3 Embryo development rate	$\frac{\text{no. eight cell embryos on Day 3}}{\text{no. normally fertilized oocytes}^a} \times 100$	≥45	≥70
Blastocyst development rate	$\frac{\text{no. blastocysts Day 5}}{\text{no. normally fertilized oocytes}^a} \times 100$	≥40	≥60
Successful biopsy rate	$\frac{\text{no. biopsies with DNA detected}}{\text{no. biopsies performed}} \times 100$	≥90	≥95
Blastocyst cryosurvival rate	$\frac{\text{no. blastocysts appearing intact}}{\text{no. blastocysts warmed}} \times 100$	≥90	≥99
Implantation rate (cleavage-stage)[b]	$\frac{\text{no. sacs seen on ultrasound}^c}{\text{no. embryos transferred}} \times 100$	≥25	≥35
Implantation rate (blastocyst-stage)[b]	$\frac{\text{no. sacs seen on ultrasound}^c}{\text{no. blastocysts transferred}} \times 100$	≥35	≥60

[a]Defined as oocytes with 2PN and 2PB on Day 1.
[b]Based on total number of embryos transferred to *all* patients in the reference group, not just those for whom an implantation occurred.
[c]Definition reached after discussion, as some felt that no. fetal hearts / no. embryos transferred was a more meaningful indicator.
KPI, key performance indicator.

The SoHO Regulation

Ensuring protective measures to donors and to offspring born from MAR

Activity data collection and reporting - Article 41

SoHO entities shall collect and report data relating to any of the following SoHO activities: SoHO donor registration; collection; distribution; import; export; human application.

The data collected pursuant to paragraph 1 shall comprise the data set indicated on the EU SoHO Platform.

Data? To be defined by the SCB (starting point = ”MAR harmonisation data set”)

This task could be performed through national or international registries, **e.g. ESHRE EuMAR**

The SoHO Regulation

Creating conditions for **safe, effective and accessible innovation**

Authorisation of SoHO preparation processes - Article 39

Current

Processes that are currently approved/authorized by the competent authorities do not need a new authorization. **However**, they need to be registered (by the clinic) on the SoHO platform before August 2027. To be confirmed by the CAs and made public.

Authorisation of SoHO preparation processes - Article 39

New

Before implementing a new preparation process into the clinic, an application for authorisation must be made to the competent authorities.

If already authorised in another SoHO entity (and acceptable):

=> verify equivalence

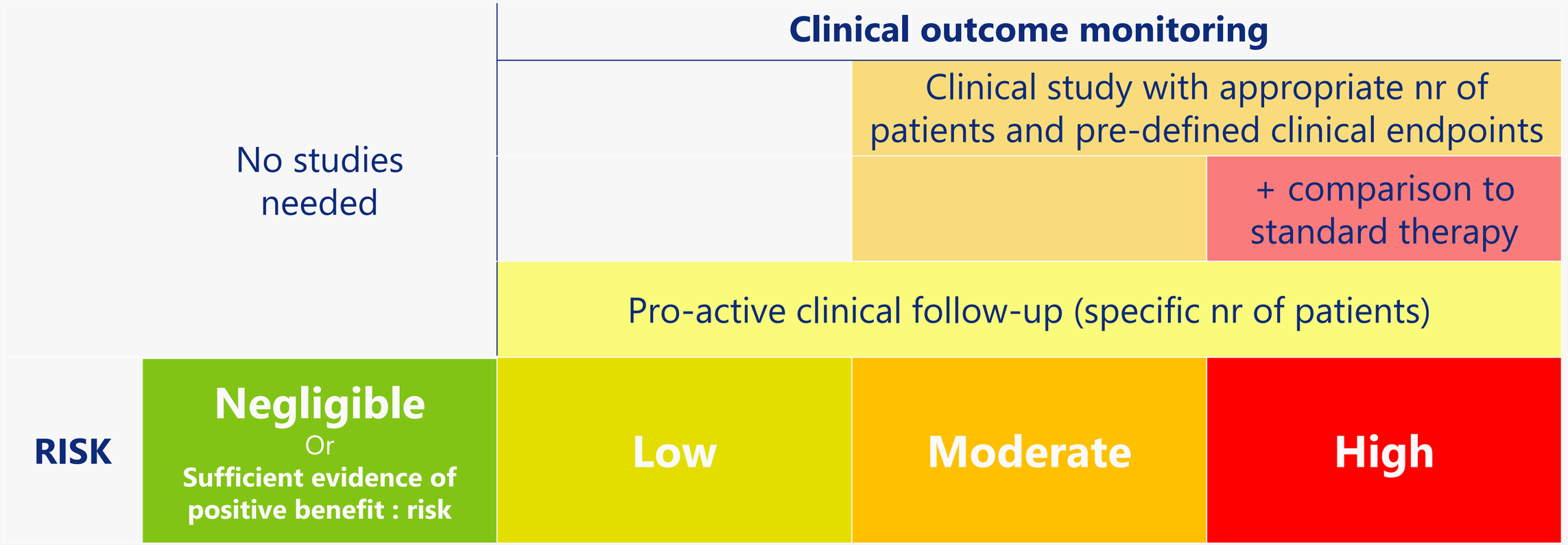
Authorisation of SoHO preparation processes - Article 39

Prep

Systematic **Benefit : Risk Assessment**

(evidence available on safety, quality and effectiveness)

Authorisation of SoHO preparation processes - Article 39



Study summaries registered on SoHO Platform

Authorisation of SoHO preparation processes - Article 39

Prep

Systematic **Benefit : Risk Assessment**

(evidence available on safety, quality and effectiveness)

Prep

Submission of an application, including laboratory validation and other safety, quality and effectiveness data and, where needed, a clinical outcome monitoring plan

Assessment 1

Assessment of the application by the competent authority

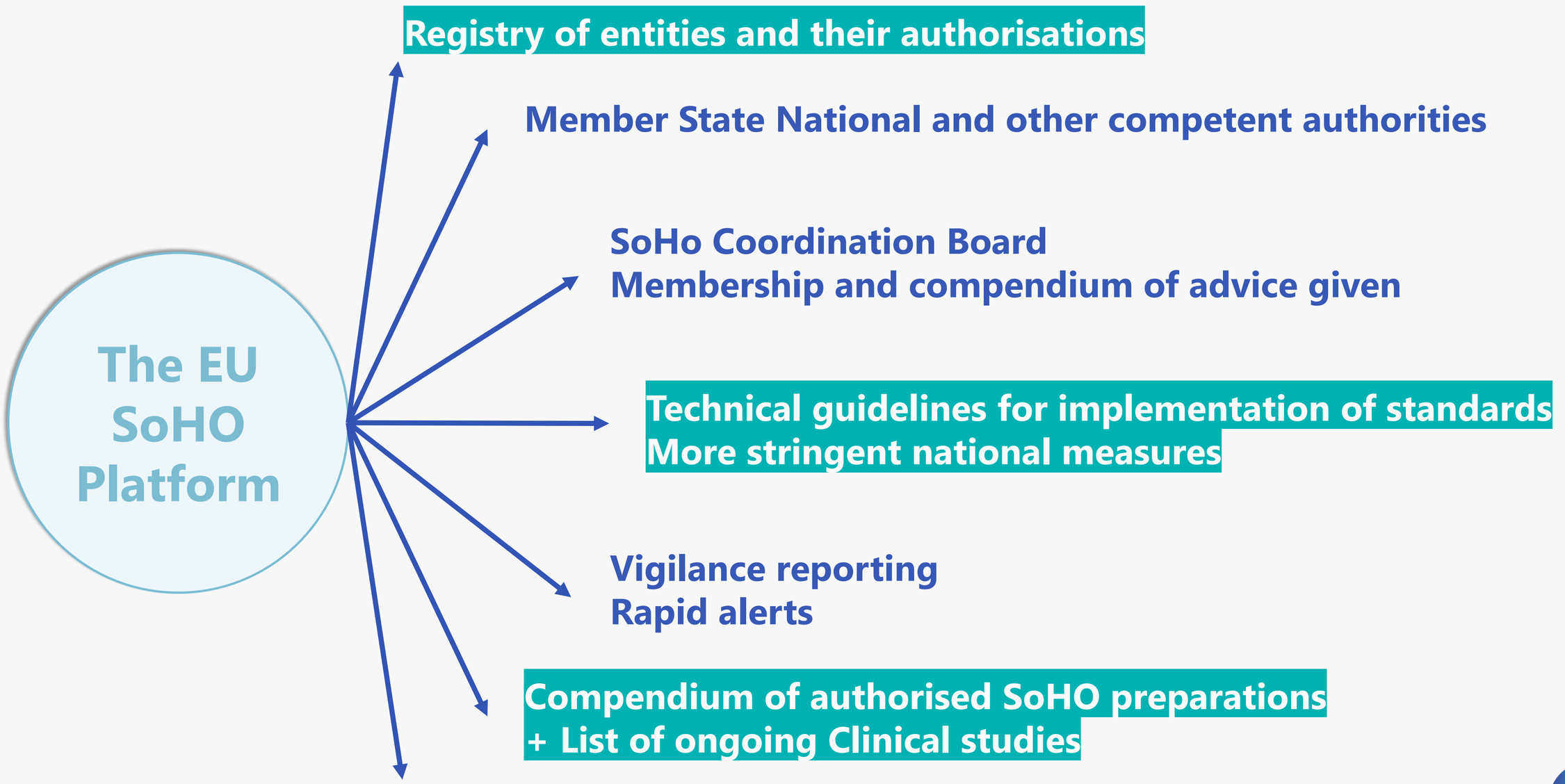
- **Refuse authorisation**
- **Grant authorisation for the SoHO preparation**
- **Grant an approval of the Clinical Outcome Monitoring plan or request an amended plan**

Assessment 2

Assessment by the competent authority of evidence of safety, quality and effectiveness data gathered in clinical outcome monitoring

- **Grant authorisation**
- **Refuse authorisation**

The SoHO Platform



To do list

Upon finalization of the SoHO Platform – and before August 2027

- Register as SoHO entity
- Register all current SoHO authorisations for preparation processes to SoHO platform, to be confirmed by CA

Quality management - SOPs

- Have a Quality management system in place
- **Follow the EDQM (ECDC) Guide for your technical processes** → *Highly recommended*
- Apply for SoHO authorisation for all (new) preparation processes to CA, including risk-benefit assessments, and clinical follow-up → *mandatory – but more information to follow*
- Go through regular inspections by the competent authorities
- Send an annual report on the activities to their CAs, or to a national or international registry → *mandatory – but more information to follow*

Key read

eshre

More to follow…

SCB working groups:

- registration of entities and authorisation of establishments
- authorisation and assessment of SoHO preparations
- inspections
- vigilance and traceability
- supply
- regulatory questions.

The SoHO Platform

Organisational support to SoHO Competent Authorities in Member States for the implementation of Regulation 1938/2024
€ 5 400 000

Supporting the implementation of the new SoHO regulation – "to facilitate the implementation of the new SoHO Regulation by the professional sector"
€ 3 500 000
⇒Training for professionals
⇒Technical assistance and supporting measures
⇒Awareness and capacity building activities

Thank you !

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