Executive Summary – ENG

Stem cell research has progressed substantially since the enactment of the Swiss Stem Cell Research Act (StRa) two decades ago, warranting its review and modernisation. This project aimed to provide an up-to-date overview of the bioethical and regulatory considerations for informing such policy revisions.

Methodologically, the project was divided into three Work-Packages. **WP1** conducted a structured and methodologically robust identification and synthesis of the relevant literature on ethical dimensions of EmRe (Embryonic Research): research involving embryos, human embryonic stem cells (hESCs), human induced pluripotent stem cells (hiPSCs), and stem cell-based embryo models (SCBEMs). The rapid literature review included 94 publications in the final analysis, which were analyzed using conventional qualitative content analysis facilitated by the software MAXQDA. The resulting coding frame was developed inductively from the data, while only the highest-level thematic categories were generated deductively to reflect entity-specific ethical considerations. **WP2** was based on a legal analysis of a group of selected European countries whose regulatory framework on EmRe attempted to operationalize the ethical and governance issues related to this type of research. Through an analysis of legislation, governmental reports and secondary sources on the legal situation, a profile describing the governance of EmRe for seven countries was developed. **WP3** supplemented the findings of WP1 and WP2 through selected expert interviews, focusing particularly on emerging developments in EmRe that are underexplored in current literature or not yet reflected in regulatory frameworks. This ensured that, despite the project's breadth and compressed timeline, no significant ethical or regulatory issues was overlooked. The findings of the interviews were integrated directly in the presentation of the results of the ethical and legal WP.

For the ethical issues, our analysis culminated in the development of a comprehensive ethics matrix designed to inform evidence-based policy-making. Although the emergence of iPSCs and SCBEMs has introduced novel ethical challenges, many longstanding concerns continue to underpin contemporary debates. One of the most prominent issues discussed in **Theme one** is to which degree of moral status and protection the entities are entitled, and on what basis such moral considerations should rest. Perspectives on the moral status of embryos or embryonic material vary widely, ranging from considering them as just collections of cells with no moral status, to attributing to them the same moral status as fully developed human beings, with numerous intermediate positions in between. Another related central debate concerns the temporal limits of EmRe research, exemplified by the ongoing discussion around the 14-day rule. Additional recurrent ethical discussions in this context address which embryos – only supernumerary embryos from IVF treatments or also embryos created specifically for research – may be used for research purposes and, if so, under what specific conditions (e.g. principles of subsidiarity and proportionality). **Theme two** gathered the ethical debates specific to research with human embryonic stem cells. Central to these discussions is whether the use of embryonic stem cells differs ethically from research involving embryos themselves, and the complicity critique: While many researchers using hESCs work exclusively with established cell lines and are not directly involved in embryo destruction, opinions diverge on whether this absolves them of moral responsibility. Some argue that the absence of causal involvement negates culpability, whereas others maintain that such use sustains a research enterprise dependent on the destruction of embryos, thereby constituting indirect complicity. **Theme three** discussed ethical considerations specific to iPSCs, their potential advantages as they are not stemming from embryonic source, but on the other hand also ethical challenges e.g. regarding donors' rights and control specific to iPSCs: The relative ease of deriving generation of iPSCs from any somatic cell of a person – including biological material shed in everyday contexts, such as skin cells or hair follicles – creates the potential for generating cell lines

without a donor's explicit consent or even awareness. This raises profound issues of autonomy, privacy, and ownership of biological material. **Theme four** laid out ethical considerations regarding SCBMEs, such as the challenge to find appropriate terminology which is itself a matter of ethical debate and carries significant ethical implications and the challenging categorization of SCBEMs: SCBEMs differ significantly in both their complexity and in how closely they replicate complete "natural" embryos, – and hence it is argued that the different kinds of SCBEMs are also not morally equivalent. However, the question then is whether or when they should be treated equally as "natural" human embryos, meaning which features and capacities are ethically relevant for assessing moral status (e.g. sentience, consciousness, potentiality etc.). **Theme five** synthesizes cross-cutting ethical considerations that transcend specific entities. It entails e.g. crucial discussions around informed consent, genetic privacy and data protection, as well as debates around commercialization of human tissue, public trust and translational issues, when moving from research to clinical application.

For the overview of how different legal systems implemented governance for EmRe, our analysis produced a detailed account of a selected number of countries. For **Belgium**, the regulation of EmRe is based on a liberal framework which allows both conducting research with supernumerary embryos and also the creation of embryos for research. This is based on two established and well-coordinated laws, one on embryo research and the other on Medically Assisted Reproduction. Moreover, a strong governance system is in place. A specifically designed commission for embryo research helps not only to evaluate research projects involving the use of embryos, but it also proactively collaborates with reproductive clinics and research centres to coordinate the use of embryos. Many safeguards are in place, including the 14-day rule, and the fact that each research project involving embryos needs to be conducted in collaboration with a university clinic and needs to receive a second approval also by regular ethics committees. The fact that patients can donate embryos for broad domain of research and not only for specific research projects has made many embryos available for research. Points of potential improvement concern better coordination between the centres with available embryos, whereas an active discussion on legislating for SCBEMs is not lively. In **France**, a distinctive feature of EmRe law is the continuous evolution and progressive liberalization over the years. At the moment, EmRe is permitted only with supernumerary embryos and within other safeguards (e.g.14-day-limit). Governance functions are performed mainly by a central agency responsible of supervising the use of embryos and medically assisted reproduction. This examines and gives permissions for embryo research, whereas research with hESC is only subject to a simpler notification scheme. To obtain embryos, a complex system of yearly reminders is organized, whereby every couples having supernumerary embryos stored is asked if they want to keep preserving them or consider donating for research. If donated for research, the consent normally covers projects approved by the central agency, but it is not tied to a specific one, thus making it more similar to the model of broad consent. For the future, there are some calls to expand the 14-day limit and to further differentiate legal pathways for SCBEMs, although French regulation is one of the few that already mentions them. In **Germany**, research with embryos is not permitted and the whole regulation of EmRe is thus quite restrictive. Despite several debates on the issue, the fact that embryos are considered protected constitutionally makes lawmaking on their use very difficult. The only achieved compromised is to permit research with hESC as long as these were derived abroad. Even for these, a special permission needs to be obtained from a centralized commission with specific governance expertise. There is some pressure to discuss a relaxation of the regulation, but this remains out of reach at the moment – despite some calls to give more prominence to the principle of freedom of research. **Italy** is another example of a very restrictive country, where a mix of legal hurdles and legal vacuums make EmRe extremely difficult. Indeed, the law forbids any research with embryos and does not regulate the research with (imported) hESC. Funding for the latter research is difficult to find given the legal vacuum

and the majority of the research on stem cells is thus with iPSCs. There some proposals to liberalise or at least complete the regulatory environment, but no concrete legal plans at the moment. The **Netherlands** have a balanced regulatory framework, respecting the principles of the Oviedo Convention, but also introducing dynamic elements (e.g. a clause allowing easier removal of some legal limits). Research with supernumerary embryos is possible and subject to the standard safeguards (14-days limit). Embryos are procured from fertility clinics with rather standardized consent forms. Oversight is exercised by a specialized commission, which evaluates instead of regular ethics committees. There are currently various legal reforms under consideration, and special attention to developing explicit rules for SCBEMS. **Sweden** is a paradigmatic example of very liberal regulation, with EmRe possible and widely practiced since decades. Rules are quite minimal and there is also no specialized body examining embryo research: it falls within the competence of regular ethics committees. Some doubts exist on the interplay with biobanking regulations and a few plans exist to reform the law in the future to accommodate the specific needs of SCBEMs. The **United Kingdom** is a key country for the development of EmRe and its regulation. Indeed, many of the basic principles and safeguard widespread in other countries permitting embryo research were developed here. EmRe is permitted but well regulated through a system of licenses dispensed by a central regulatory and oversight authority. Embryos can be created for research or procured from fertility clinics (supernumerary embryos). For the latter, only specific consent to individual project is practiced. Moreover, a parallel system exists for the governance of hESC, which also comprises a different regulatory authority and a centralized biobank. This creates sometimes some issues, and the interaction of different authorities is debated in respect to the potential future regulation of SCBEMs. Moreover, there is also a current project to explore the possibility to extend the current 14-day-limit.

In the **Critical Discussion** of the results, we highlight some relevant cross-cutting issues that relate to both the ethical and legal findings. First, we underscore that finding a balance between the ethical issues raised by EmRe is delegated, by states that allow this kind of research, to the institutional commissions in charge of approving single projects. There are, however, significant differences in how these commissions are organized, which means that Switzerland would have to choose amongst different options (single examination by specialized or regular ethics committee or double examination by both). Second, we reflect on the issue of informed consent, which is highly debated as a central element to enforce, in case embryos or other bodily material is donated for research. In some countries, patients can donate supernumerary embryos only for specific research projects, whereas elsewhere a donation for broad domains of research is possible. If Switzerland changes rules on EmRe, this issue is another ethically relevant policy crossroad to consider. Third, we focus on the many doubts still in place about the exact definitions of SCBEMs and different sub-categories within them, and the ethical relevance of this uncertain differentiation. In terms of policy, the classification and regulatory definition of SCBEMs is also creating doubts in many of the countries analysed. For Switzerland, this is also bound to remain a contentious issue in policymaking on EmRe. Fourth, we highlight the differences in the ethical conceptions of the definition of embryos and how these are reflected in regulatory implementations. Some countries refrained even to provide a binding definition of embryo in the law. Definitions are relevant – and should be consistent – especially in a field like EmRe, where they also determine the applicable regulatory path. Finally, we remark on how EmRe and MAR are ethically very connected, which also means that regulatory reform in both fields should be coordinated.