RAND EUROPE

State-of-play and future trends on the development of oversight frameworks for emerging technologies

Part 2:
Technology oversight report

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Research snapshot

Wellcome commissioned RAND Europe to undertake a study on the state-of-play and future trends of the development of oversight frameworks for emerging technologies. The specific objective of the study is to identify and analyse a suite of oversight frameworks and mechanisms that are in use, in development or under debate in different jurisdictions across the globe for a set of emerging technologies. The study is designed to inform a range of policy and research-focused stakeholders, offering a suite of tangible emerging and established oversight examples that can inspire future emerging technology oversight. The technologies of interest are organoids, human embryology, engineering biology and neurotechnology, as well as artificial intelligence (AI) (specifically its application and use as a research tool) and data platforms.[1]

The study findings are presented in two related documents: the global technology landscape review report, which provides an in-depth analysis of global research and innovation (R&I) developments occurring within each technology area, identifying key trends, challenges and opportunities; and the technology oversight report (this document), which examines notable oversight mechanisms that are either established or under development across a selection of global jurisdictions, offering key learning and insights that could inform future technology oversight discussions.

1 The study addresses AI and data platforms together and as 'transversal' to the other four technology areas (i.e. it considers how they are impacting these technologies and their resulting implications for oversight).

The technology oversight report used a mixed-methods approach, combining targeted desk research, stakeholder interviews, a strengths–weaknesses–opportunities–threats (SWOT) analysis, and an online expert elicitation exercise. An extended summary has also been developed that encapsulates the key findings from both reports.

This study takes an expansive view of technology oversight, covering a spectrum of options with differing levels of accountability, obligation and enforcement. These range from mechanisms such as legislation, regulations and treaties to non-regulatory standards, ethical guidance, codes of conduct and self-regulatory frameworks. For each technology, the study maps and examines a variety of oversight frameworks across multiple jurisdictions to assess how technology is being used, while keeping issues such as safety, privacy and risk mitigation at the forefront.

A series of 16 overview vignettes (four per technology) have been developed as part of this study, outlining notable oversight developments in four globally influential jurisdictions that are often at the leading edge of technology developments and governance debates: the United Kingdom, the United States, the European Union (EU) and international forums. The overviews provide a holistic view of oversight taking place in these jurisdictions. These were supplemented by 12 case study vignettes (three per technology area) detailing additional examples of oversight mechanisms across the globe. These offer evidence from a diverse selection of specific use cases of both emerging and established technology oversight in different cultural and social contexts. Collectively, these vignettes provide a deeper insight into the key oversight conversations occurring, and pinpoint areas where Wellcome and other stakeholders might effectively contribute.

We summarise the key points of discussion related to the oversight of the different technology areas below.

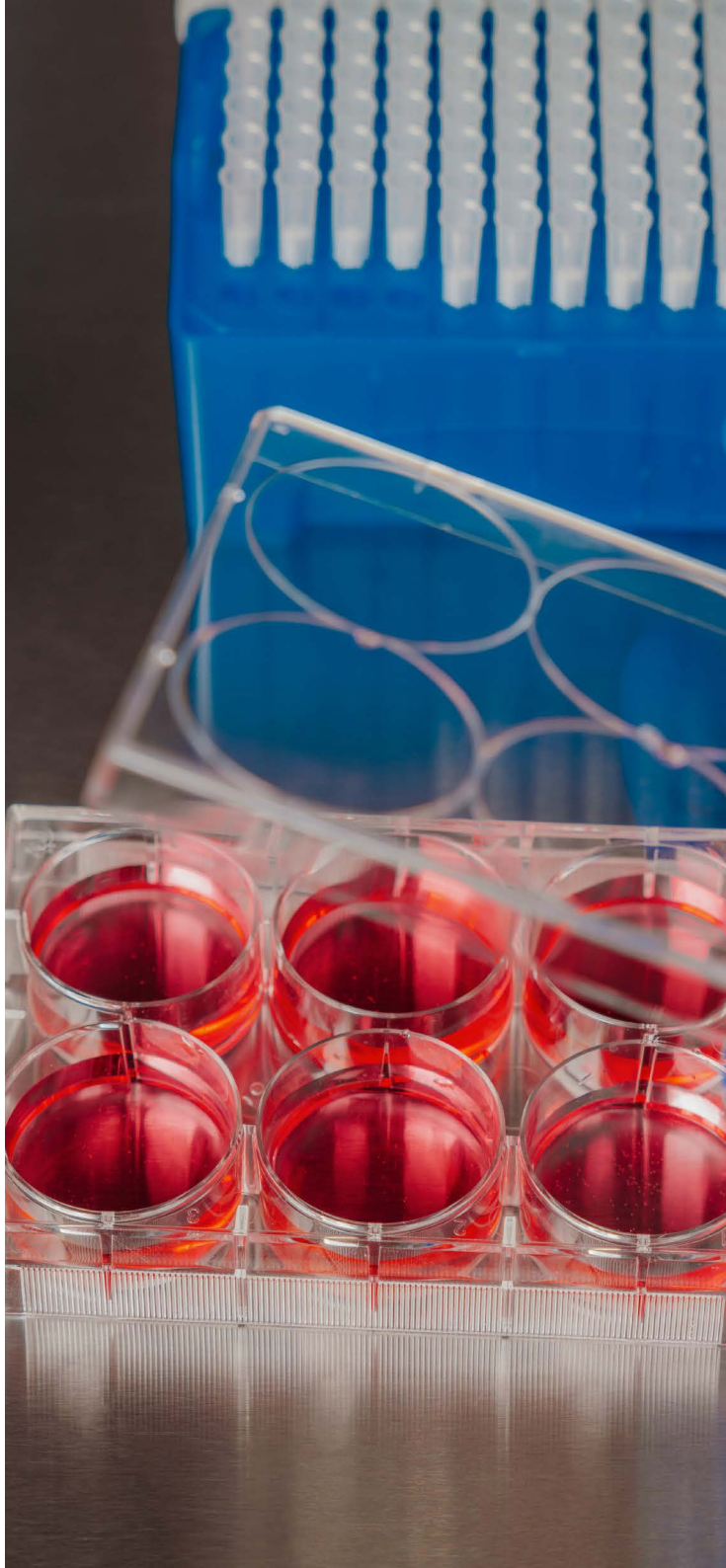
Key areas of debate related to the oversight of organoid research and innovation:

There is a lack of specific regulatory frameworks for organoids. For example, in the United Kingdom, the current oversight of organoid research relies on broader stem cell and biomedical regulations, with no specific legal framework solely for organoids; the Human Tissue Act (2004) governs the use of human cells but does not cover organoids themselves.

Neural organoids present new ethical challenges linked to conducting research on organoids with the potential for advanced neural activity, especially around donor consent, which is not covered by existing oversight mechanisms. New emerging mechanisms such as Japan's consent-to-govern approach and risk organoid framework are gaining traction as a supplementary oversight mechanism.

Variations in international regulations are creating barriers for collaboration. For example, regulatory requirements differ between the United States, which has stringent Food and Drug Administration (FDA) oversight, and the EU, where frameworks are fragmented across member states. Meanwhile the UK's Medicine and Healthcare products Regulatory Authority (MHRA) is working on specific guidelines for the clinical use of organoids, especially in advanced therapy medicinal products. The role of international organisations is potentially important to support standardisation and alignment on some aspects of organoid research.

The potential for reidentifying donor genetic material through advanced genomic sequencing techniques raises concerns about privacy and data protection, especially as organoid research advances in personalised medicine.



Key areas of debate related to the oversight of human embryology research and innovation:

Oversight mechanisms such as the United Kingdom's Human Fertilisation and Embryology (HFE) Act and the US Dickey-Wicker Amendment were established in the 1990s. These frameworks were not designed for cutting-edge developments such as stem cell-based embryo models. Updating these frameworks to include emerging technologies such as AI in embryo selection and advanced genetic techniques could ensure that regulations keep pace with innovations, while addressing new ethical concerns.

Oversight is primarily seen at the national level, allowing for a legislative landscape tailored to unique cultural and social norms, which appears to be essential for a politically and culturally charged topic such as human embryology. Human embryology research is often shaped by such cultural and social norms, rather than scientific drivers.

Disparate regulations across countries complicate international collaboration. For example, countries subscribing to the Oviedo Convention face strict restrictions on embryo research, while others such as the United States have decentralised and varied oversight across states. However, less formal oversight in the form of publication requirements, databases and repositories has provided direct support to embryologists for research and collaboration.

A key limitation in current oversight is the inflexibility of hard law mechanisms to adjust to developments in research and public interest, as shown by the calls for a statutory definition of embryos: while such a definition could provide regulatory clarity, it could potentially lead to inflexible oversight that cannot keep up with progress.

Key areas of debate related to the oversight of engineering biology research and innovation:

Disparate oversight mechanisms globally are creating obstacles for international collaboration in engineering biology, which is compounded by the vast number of sectors involved. International mechanisms such as the Cartagena Protocol could be adapted to ensure alignment across diverse applications and jurisdictions.

Engineering biology spans multiple sectors, leading to fragmented oversight with long approval timelines. For instance, in the EU, regulations such as Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) apply inconsistently across industries, creating confusion and conflicting incentives for research and commercialisation. Implementing cross-sector collaboration through initiatives such as the UK's Regulatory Horizons Council and Engineering Biology Sandbox Fund can potentially streamline oversight, accelerate approvals, and improve dialogue between regulators and innovators.

Engineering biology advancements, especially in AI-enabled biotechnologies, can increase the potential for biosecurity threats. Current oversight mechanisms (e.g. the Biological Weapons Convention) are insufficient to assess and manage these risks, particularly the potential for malicious use. Strengthening biosecurity measures through international collaboration, such as the International Biosecurity and Biosafety Initiative for Science, could address gaps in risk management and better monitor the evolving threats posed by engineered pathogens.

AI integration in engineering biology poses challenges to data privacy, accuracy and ownership. Existing frameworks, such as the General Data Protection Regulation (GDPR), are not designed for the nuanced requirements of AI-driven biological research.

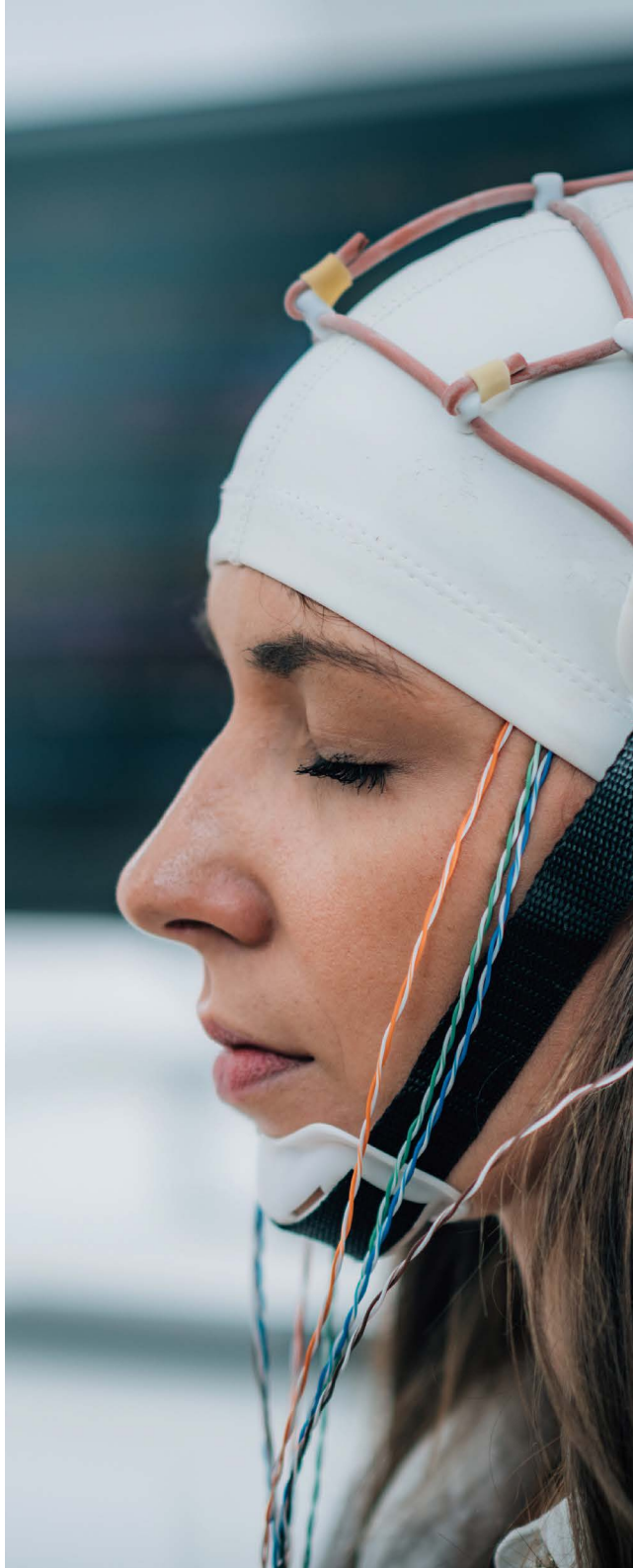
Key areas of debate related to the oversight of neurotechnology research and innovation:

Current regulations in jurisdictions such as the United Kingdom, United States and EU largely depend on broader frameworks for medical devices, data privacy and research ethics. These frameworks do not specifically address the unique challenges posed by neurotechnologies such as brain–computer interfaces (BCIs) and neural implants, which are generating new forms of data and have potential for cognitive influence.

Neurotechnologies generate sensitive neurodata, raising privacy concerns and issues of consent. Traditional frameworks such as the GDPR in the EU and the Health Insurance Portability and Accountability Act (HIPAA) in the United States do not explicitly address the nuances of neurodata, which creates risks for the misuse or unauthorised exploitation of this information, such as in a discriminatory fashion by employers or the services sector. Ethical guidelines focused on neurorights, such as Chile's constitutional amendments, offer a proactive model for addressing these challenges.

Neurotechnologies developed for medical purposes (e.g. BCIs for rehabilitation) can potentially be repurposed for military or surveillance applications, leading to significant ethical and security concerns. Current oversight mechanisms are reactive and do not adequately prevent dual-use scenarios. Developing international guidelines, such as the proposed Neurological Innovation and Defence Act in the United States, could help pre-emptively regulate the dual use of neurotechnologies, ensuring their applications remain ethical and beneficial.

There are limited mechanisms for the post-market surveillance of neurotechnology devices. This can lead to 'device abandonment', where manufacturers fail to maintain or repair devices, creating risks for users, especially those with implanted devices. Strengthening post-market oversight and surveillance systems, particularly for medical devices and consumer neurotechnology, could help manage long-term risks.



Considerations for the future oversight of emerging technologies:

This report proposes eight priority considerations for stakeholders engaged in technology R&I, to support the development of the broader R&I and technology oversight ecosystem in the future. These priority considerations – as a set of cross-cutting actions – are also relevant for a wider audience, encompassing individuals and groups with a vested interest in the oversight of emerging technologies such as policymakers, industry professionals, funders, researchers and the public. More details underpinning these considerations can be found in Chapter 7.

Priority consideration 1: Develop comprehensive process maps and establish networks of interconnected oversight mechanisms to support stakeholders in effectively navigating the labyrinth of relevant mechanisms in the technology oversight landscape.

Priority consideration 2: Ensure that equity considerations are prioritised and integrated into all aspects of technology oversight to promote fairness and inclusivity.

Priority consideration 3: Identify and establish common ground for practical and actionable international alignment to harmonise governance practices across borders.

Priority consideration 4: Intensify efforts to develop internationally coordinated risk mitigation strategies as part of implementing oversight mechanisms to address global challenges posed by emerging technologies.

Priority consideration 5: Support the implementation and scaling of innovative oversight mechanisms to effectively manage the complexities and dynamics of emerging technologies.

Priority consideration 6: Facilitate proactive public involvement in the development of oversight frameworks to ensure transparency and accountability.

Priority consideration 7: Incorporate adaptive practices into oversight processes to foster continuous learning, flexibility and agility in response to technological advancements.

Priority consideration 8: Integrate anticipatory strategies into oversight frameworks to prepare for and address future developments in emerging technologies.

Chapter 1
Introduction

Emerging technologies such as AI and biotechnology are redefining the boundaries of science and innovation. Governments, private sector and third sector organisations across the globe are increasingly recognising the potential for science and technology to impact economic growth and societal prosperity, committing greater funding and resources to research and development (R&D) in science and technology. The Organisation for Economic Co-operation and Development (OECD) recently emphasised how emerging technologies can contribute to significant benefits in fields as diverse as health, energy, climate, food systems and biodiversity (OECD 2024a). However, with this potential comes significant risk, as unregulated advancements can lead to unintended ethical, human rights, societal and security consequences.

A clear understanding of current and future oversight mechanisms in emerging science and technology across the globe is essential for effective research and innovation. Appropriate oversight can also ensure that technology advancements provide benefits to society (Gunashekar et al. 2019). This report examines the state of global oversight mechanisms, spotlighting the gaps and opportunities that demand urgent attention. By examining how some leading jurisdictions approach the governance of cutting-edge fields such as organoids and human embryology, the study reveals not only the shortcomings but also the transformative potential of well-crafted, forward-looking oversight. Investing time in understanding these developments is crucial for shaping a future where technological breakthroughs are safe, ethical and accessible to all. This report is intended as a useful reference guide for navigating and steering developments in emerging technology oversight.

1.1. Objectives of the study

The specific objective of the study is to identify and analyse a suite of oversight frameworks and mechanisms that are in use, in development or under debate in jurisdictions across the globe for a set of emerging technologies: engineering biology, human embryology, organoids, neurotechnology, AI and data platforms. Given that AI and data platforms are relevant to a wide range of domains and applications, they are addressed as ‘transversal’ to the other four technology areas (Figure 1).

The study findings are presented in two related documents: the global technology landscape review report and the technology oversight report (this document). the global technology landscape review report provides an in-depth analysis of global R&I developments, identifying key trends, challenges and opportunities. This report examines notable oversight mechanisms that are either established or under development across a selection of global

jurisdictions. The two reports should be read alongside each other. An extended summary that encapsulates the key findings from both reports has also been developed.

Figure 1. Technology areas covered by this study

Source: RAND Europe analysis.

This study uses an expansive interpretation of technology oversight, as conceptualised in a previous study (Gunashekar et al. 2019). For each technology area, a variety of oversight frameworks are mapped and examined, covering a spectrum of options with differing levels of accountability, obligation and enforcement. These range from mechanisms such as legislation, regulations and treaties to non-regulatory standards, ethical guidance, codes of conduct and self-regulatory frameworks created by professional/industry bodies, industry or the research community (see Figure 2).

1.2. Outline of the report

- **Chapter 2** summarises the methodological approach used for this study and its limitations.
- **Chapters 3 to 6** provide an overview of recent developments in the oversight of research and innovation on organoids (Chapter 3), human embryology (Chapter 4), engineering biology (Chapter 5) and neurotechnology (Chapter 6), focusing on four key jurisdictions of interest: the United Kingdom, the United States, the EU and international forums. This is followed by case studies of oversight mechanisms in a selection of global jurisdictions that include Australia, Chile, China, Japan and South Africa.
- **Chapter 7** provides an overall assessment on key learnings for the future of oversight mechanisms for emerging technologies, as well as concluding remarks.

Figure 2. Spectrum of oversight approaches and key stakeholders

Source: RAND Europe analysis.

Chapter 2
Overview of research approach

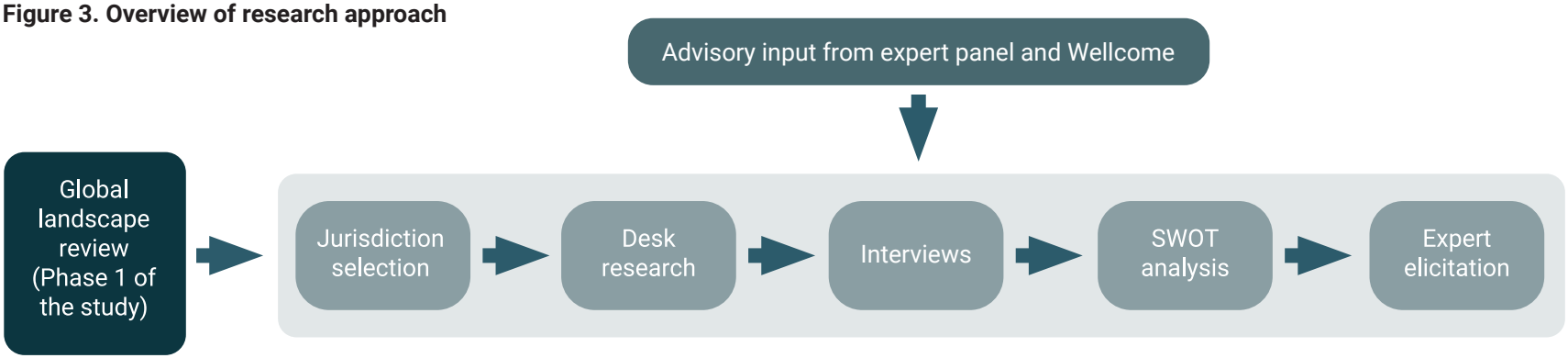
This chapter summarises the research methods used in the study, as illustrated in Figure 3 below. A detailed description of the methodology and limitations of the analysis is provided in Annex D.

2.1. Jurisdiction selection

The study used multiple parameters[2] analysed in the accompanying landscape review report to reflect on potential jurisdictions that could provide insightful evidence on oversight mechanisms. With these insights, and in consultation with the expert panel[3] and Wellcome, jurisdictions were selected and analysed in the following ways for each of the four technology areas:

- Development of a high-level overview of technology oversight developments taking place in four key jurisdictions acknowledged for their notable influence on developments in the specific areas

Figure 3. Overview of research approach



Source: RAND Europe analysis.

2 Parameters included government investment, R&I activity and policy influence.

3 An expert advisory panel was convened at the project inception stage consisting of six subject matter, policy and legal experts across the technology areas.

of technology: the United Kingdom, the United States, the EU and international forums.

- Development of specific case studies examining oversight mechanisms in a selection of jurisdictions across the globe spanning different societal and cultural contexts, and diverse types of oversight mechanisms.

2.2. Desk research

For the development of the high-level overviews, desk research was conducted using broad search terms for a given technology in combination with the jurisdictions of interest. The study aimed to strike a balance in capturing a breadth of oversight mechanisms, acknowledging that these would be restricted to what are considered the most important/prevalent rather than an exhaustive list of all mechanisms. Google Scholar/Google searches and snowballing[4] were used to identify relevant articles. Sixteen high-level overviews outlining oversight developments in the United Kingdom, United States, EU and international forumsforums were developed for the four technology areas. Desk research for the development of the 12 case studies (three per technology area) consisted of a more targeted approach focused on the specific oversight mechanisms and selected jurisdictions (e.g. oversight of neural organoids in Japan).

2.3. Stakeholder interviews

Three scoping interviews were conducted with experts with general expertise in emerging technology oversight to guide the development of the high-level overviews. A further eight interviews were conducted with topic experts to fill in gaps from the desk research while constructing the case studies. The interviews were semi-structured and conducted online. Annex E outlines the interview questions used to guide the interviews.[5]

2.4. SWOT analysis

The insights from the high-level overviews and case studies were analysed through a strengths–weaknesses–opportunities–threats (SWOT) framework that was used to assess the status of technology oversight across the globe and highlight key challenges, gaps and discussions in each sector.

2.5. Expert elicitation

The SWOT analysis was fed into an interactive online mural board. The team invited 27 experts in the relevant technology areas to engage with the mural board over a three-week window and provide feedback and validation of the aggregated SWOT analysis. Sixteen experts from a range of international organisations and universities participated in the online elicitation exercise.

4 Snowballing, also known as citation chaining, is the process of searching the references and/or citations of a list of articles to identify other relevant material.

5 Throughout the report, the insights from the interviews have been anonymised and cited using unique interviewee identifiers (INT_01, INT_02, etc.).

Chapter 3
Current organoid oversight developments

To guide the reader, this chapter is structured as follows.

Box 1. Current organoid oversight developments: Key takeaways

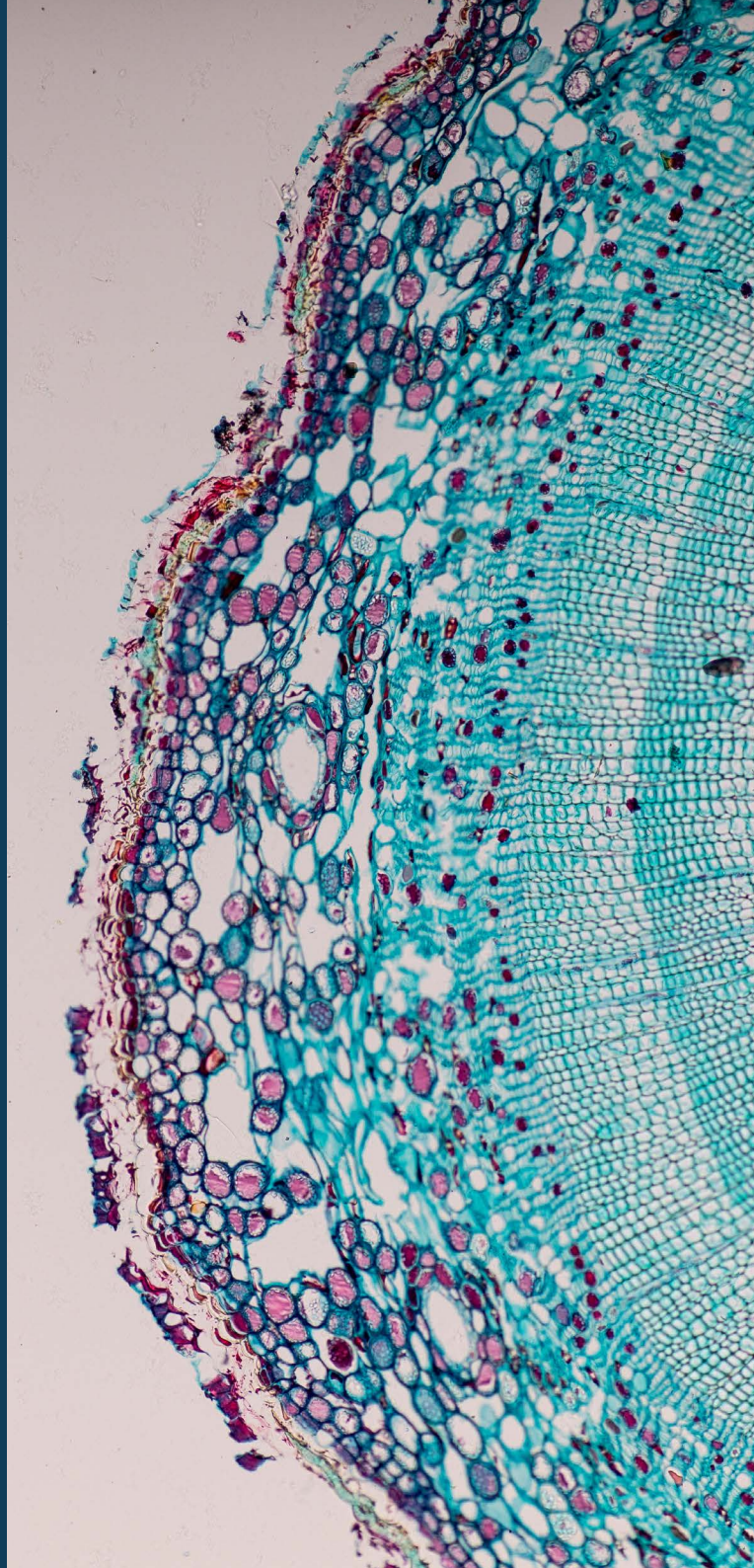
There is a lack of specific regulatory frameworks for organoids. For example, in the United Kingdom, current oversight of organoid research relies on broader stem cell and biomedical regulations, with no specific legal framework solely for organoids; the Human Tissue Act (2004) governs the use of human cells but does not cover organoids themselves.

Neural organoids present new ethical challenges linked to conducting research on organoids with the potential for advanced neural activity, especially around donor consent, which is not covered by existing oversight mechanisms. New emerging mechanisms such as Japan's consent-to-govern approach and risk organoid framework are gaining traction as a supplementary oversight mechanism.

Variations in international regulations are creating barriers for collaboration. For example, regulatory requirements differ between the United States, which has stringent Food and Drug Administration (FDA) oversight, and the EU, where frameworks are fragmented across member states. The United Kingdom's Medicine and Healthcare Products Regulatory Authority (MHRA) is working on specific guidelines for the clinical use of organoids, especially in advanced therapy medicinal products. The role of international organisations is important to support standardisation and alignment on some aspects of organoid research.

The potential for reidentifying donor genetic material through advanced genomic sequencing techniques raises concerns about privacy and data protection, especially as organoid research advances in personalised medicine.

Source: RAND Europe analysis.



3.1. Introduction

Organoids are three-dimensional structures that are derived from stem cells and are capable of self-organising into structures that mimic the key functional, structural and biological complexity of an organ. Rapid developments are occurring in organoid technology, with applications in disease modelling and drug testing leading to advancements in personalised medicine and novel therapeutic strategies. However, many oversight bottlenecks and challenges remain, potentially hindering positive momentum. A detailed assessment of the trends, challenges and opportunities associated with organoid research and innovation (R&I) is provided in the accompanying global technology landscape review report.

There are a lack of specific regulatory frameworks for organoids, which means that oversight is primarily provided through 'catch-all' biomedical oversight mechanisms. This could be problematic given the maturity of neural organoid research that has the potential to exhibit advanced neural activity, creating novel ethical concerns regarding their use in research. The potential for reidentifying donor material through advanced genomic sequencing techniques also raises concerns about privacy and data protection, especially as organoid research advances in personalised medicine. This impacts donor consent and privacy, which is not covered by existing oversight mechanisms. Variations in global regulations are also potentially creating barriers for collaboration, highlighting the role international organisations may need to play to support standardisation and alignment on research.

The first section of this chapter summarises the strengths and limitations of the emergent organoid oversight landscape, alongside key considerations for addressing the current gaps and bottlenecks. The subsequent sections present the evidence underpinning this assessment, outlining key oversight mechanisms across the United Kingdom, United States, EU and international forums, followed by case studies from Japan, Australia and the Netherlands that provide more detailed examples of how oversight could be progressed in this area.

3.2. Strengths and weaknesses of the organoid research and innovation oversight landscape

Strengths of organoid research and innovation oversight

National and regional regulatory frameworks for biomedical research influence organoid research as catch-all frameworks. The regulation of organoid research is a nascent field, and until recently there was no regulation focusing on organoids alone. Instead, organoids were included by proxy in frameworks that address, for example, stem cell research, cellular and gene therapy products, or biotechnologies more broadly. For instance, in the United Kingdom (except Scotland) the Human Tissue Act applies indirectly to organoids through general consent practices involved in human tissue use.[6] However, data protection and privacy oversight (e.g. General Data Protection Regulation (GDPR)) have provided consistent frames of reference with regards to consent and data usage within organoid research. Some experts note that this non-specificity could

6 Expert focus group input.

potentially be beneficial, providing just enough responsiveness to adjust to scientific and technological advancements.[7]

International forums provide advice to national regulators and researchers through ethical guidelines and principles, as well as expert advisory groups. For example, the European Group on Ethics in Science and New Technologies plays a role in informing regulations, including those involving organoids (section 3.5). Other international guidelines have provided an ethical framework for organoid research in the context of stem cell research (e.g. the International Society for Stem Cell Research (ISSCR) and the Declaration of Helsinki – section 3.6). Experts have noted that organoids are governed by both research ethics processes and clinical trial and medical devices regulations, creating multiple opportunities for oversight, but there are currently no additional ethics requirements for organoid-specific research.[8]

With the increasing use of and research into organoids, there has been some movement towards new, specific oversight. In the United Kingdom, for example, recent advancements include the ongoing MHRA development of specific guidelines for the clinical use of organoids, and the Nuffield Council on Bioethics' ethical guidelines for brain organoids (section 3.3). The United States outlines best practices for research involving organoids derived from human stem cells in guidelines from the National Institutes of Health (NIH) (section 3.4). There are also other proposals for oversight, including Japan's 'brain organoid'[9] risk framework (section 3.7, Case Study 1), although these have not yet been implemented.

Several proposed mechanisms involve non-regulatory, people-centred approaches designed to be agile to keep up with research progress. Other mechanisms to oversee organoid research involve 'bottom-up' approaches that enable clinicians, researchers and patients to interact with their personal data and/or increase their awareness and understanding of the topic. For example, researchers in the United Kingdom have suggested dynamic consent platforms that allow biological material donors to adjust their preferences over time, in tandem with technological progress or changes to public perception (section 3.3). Organisations such as stem cell research oversight committees (SCRO) have been established to review research proposals (section 4.4). These actions have been complemented with dedicated funding to promote training and develop organoid research in accordance with existing regulations, such as the United Kingdom's Imperial Biomedical Research Centre Organoid Facility (section 3.3).

The oversight of neural organoids has been accelerated with the emergence of organoid intelligence. As AI is applied to organoid research, both proactive and reactive oversight mechanisms are being put into place. Notably, the Baltimore Declaration guidelines have been highlighted as a potential framework for the formal oversight of organoid intelligence, while the US FDA has been preparing a regulatory framework for AI/software as a medical device (section 3.4).

7 Expert focus group input.
8 Expert focus group input
9 Neural organoids is used interchangeably with 'brainoids' and 'cerebral organoids' in the literature.

Opportunities in organoid research and innovation oversight

Neural organoids have stimulated new approaches to donor consent. Japan's multi-tiered oversight of neural organoids includes a 2024 'brain organoids' risk framework proposal aimed at improving consent processes and increasing public awareness and understanding of the risks associated with neural organoid research (section 3.7, Case Study 1). The framework considers the potential for consciousness and the moral status of organoids. In theory, this could bridge the knowledge gap between human studies – which 'rarely capture the earliest stages of disease development' – and animal studies – which have limited genomic equivalence or ability to 'recreate human-specific processes'.[10] It is one of the increasingly novel and agile mechanisms being proposed to leverage organoid developments and enhance organoid research and its clinical translation.

Developments in organoid research are paving the way for rapid translation to clinical settings. For example, organoids can be used for rare disease and infectious disease modelling. Some researchers and activists are also hopeful of the potential of organoid models to reduce the use of animal models in research given the current science and policy effort on using alternatives.[11] These opportunities require an enabling regulatory environment to ensure that translation and clinical implementation is not slowed down.

Threats and weaknesses of organoid research and innovation oversight

Organoids showcase complexities and risks that are not yet accounted for in existing regulations. Currently, organoids are not given the same ethical considerations as human subjects in research. However, they present several complexities related to informed consent, privacy of genetic information, agency, data reuse, as well as the additional risk and ethical implications of neural activity in neural organoids (section 3.1). New technologies, such as the convergence of organoids with AI and/or quantum, present risks not covered by current oversight mechanisms. These include the reidentification of specimens, posing a risk to donor confidentiality (section 3.1), or risks of consciousness in neural organoids resulting in research causing unintended harm.

Current regulations do not adequately ensure that organoid research equitably benefits all populations, and that research is free from bias. Issues such as addressing affordability, distribution and inclusive scientific collaboration must be addressed to avoid exacerbating existing health disparities by limiting the use of these innovations. There is a need for specific regulatory frameworks that directly address these complexities.

Harmonising existing international regulations is important for enhancing collaboration and maintaining consistent safety and ethical standards. Discrepancies in regulations between jurisdictions create barriers to international collaboration. This can increase the administrative burden and slow, or even prevent, research progress through collaboration. Similarly, clarifying the position of organoids

10 Expert focus group input.

11 Expert focus group input.

within existing regulations at the national level would ensure a consistent understanding of ethical requirements; one expert noted that the position of reproductive organoids 'requires rationalisation between HTA [Human Tissue Authority] and HFEA [Human Fertilisation & Embryology Authority]', as regulation is currently only targeted at live human embryos, and the position of organoids in this space is unclear.[12]

Challenges to organoid development and oversight at both the research and clinical level are not always considered. Experts mentioned the need for continued investment in basic research on human development, particularly with brain organoids, while barriers to the clinical translation of organoid research are linked to oversight challenges.[13] Regulations must address challenges in scalability, reproducibility and safety to facilitate this clinical translation (section 3.5).

Without tailored oversight to address these weaknesses, threats may emerge from the misuse or misunderstanding of organoids. There is a risk that commercial interests might overshadow ethical considerations, leading to the potential exploitation of donors or misuse of organoid technologies. Public misunderstanding or misinformation about the nature and purpose of organoid research may create unfounded barriers to this type of research. Proposals for informed consent and training could mitigate this but have not yet been implemented. These oversight mechanisms must be appropriate to avoid impeding research with unjustified red tape.[14]

12 Expert focus group input.
13 Expert focus group input.
14 Expert focus group input.

Given the current state-of-play in organoid oversight, this study proposes the following **key considerations** that could potentially be taken forward by decision makers:

Support and scale emerging mechanisms of oversight:

Neural organoids showcase complexities and risks that are not yet accounted for in existing regulations. Given the emergence of multiple updated mechanisms and processes to manage donor consent and privacy, and to deal with the moral status of neural organoids, a concerted effort is needed to support these emerging mechanisms and take them from conceptual frameworks to practical frameworks that can be adopted and scaled. To complement the current debates that are focused on generating new ideas to address oversight challenges, effort is also needed to scale and implement emerging ideas.

Develop demarcation and clarity between oversight for research and oversight for clinical application:

Organoid development and oversight have needs at both the research and clinical level, which are not always considered nor clear. For instance, the EU Tissues and Cells Directive, which pertained to both research and application, was replaced in 2024 with the EU Regulation on Substances of Human Origin (SoHO), which only pertains to clinical application. There is a need for more clarity and demarcation between oversight for research versus application, where appropriate.

3.3. Oversight of organoids in the United Kingdom

Figure 4. Illustrative oversight examples of organoids in the United Kingdom

Source: RAND Europe analysis.

Current oversight mechanisms in the United Kingdom

In the United Kingdom, the oversight of organoid research is primarily managed through a combination of existing regulations and oversight frameworks that address stem cell, microbiological and biomedical research more broadly, as listed below:

- The 'removal, storage, use and disposal of human tissue', including organoids derived from human cells, is governed by the HTA under the **Human Tissue Act** (UK Government 2004) and **the Quality and Safety of Organs Intended for Transplantation Regulations** (NHS 2024).
- Standards for procuring and processing tissues and cells intended for clinical applications, including organoids, are set by the **Human Tissue (Quality and Safety for Human Application) Regulation (2007),** which transposes the **EU Tissue and Cell Directive (2004)** into UK law. It is also enforced by the HTA, which licenses and inspects institutions that store and use human tissue for research purposes.

- For organoids developed for therapeutic applications, the MHRA (MHRA 2024) regulates clinical trials and the approval process to ensure they meet safety and efficacy standards. It follows the **Human Medicines Regulation (2012),** which provides the primary legislative framework for the regulation of medicines in the United Kingdom.
- The storage and supply of embryonic and other stem cell lines used in research and clinical application, including in organoid research, is carried out by the **UK Stem Cell Bank** (NIBSC 2024) under the **Human Tissue Act (2004),** with HTA oversight.
- **Research ethics committees** under the **Human Tissue Act (2004)** are responsible for reviewing the ethical aspects of research projects involving human tissues to ensure that they meet ethical standards and have appropriate consent.

Emerging oversight mechanisms in the United Kingdom

A range of emerging informal and formal oversight mechanisms are shaping the landscape of organoid research and development. These mechanisms differ in how they address the unique challenges associated with organoid research:

- With the increasing potential of organoids in personalised medicine, the MHRA is in the process of developing more specific guidelines for the clinical use of organoids, particularly in the context of **advanced therapy medicinal products (ATMPs).**
- With growing innovation in organoid research, there have been discussions regarding the **UK Stem Cell Bank** remit to specifically include organoids in the same way as stem cell lines, ensuring standardised practices for depositing and withdrawing organoid lines for research purposes (NIBSC 2024). Currently, the voluntary steering committee reviews applications to consider ethics.
- The **Nuffield Council on Bioethics** is an independent body examining ethical issues in biology and medicine. While it does not directly create or enforce regulations, it influences and informs policy and regulation through its recommendations and reports. It has recently written new ethical guidelines for neural organoids, which emphasised the necessity for policymakers to increasingly collaborate closely with scientists and ethicists to keep pace with rapid technological advancements (Nuffield Council on Bioethics 2024a).

Other mechanisms of relevance in the United Kingdom

- **The Human Fertilisation and Embryology (HFE) Act** (UK Government 2008), enforced by the HFEA, licenses and monitors clinics that carry out in vitro fertilisation (IVF), mitochondrial donation, donor insemination and human embryo research. This is relevant to the oversight of embryoid research.
- **The Stem Cell-Based Embryo Model (SCBEM) Code of Practice** (Cambridge Reproduction 2024) has been developed by a diverse working group of academics, regulators and lawyers to set out standards for researching embryo models in a lab setting. It prohibits their implantation in humans. The models are considered as a type of organoid, i.e. embryoid, and hence the code of practice will be of relevance to embryo-focused organoid R&I.
- **Dynamic consent platforms** are an oversight mechanism relevant for organoid research, as they allow donors of biological materials to adjust their preferences over time as the research progresses or attitudes change (Teare et al. 2021). Organoid research can evolve rapidly, and new applications that might not have been anticipated at the time of initial consent may occur later on. This approach to consent can ensure continuous agreement

on the use of cells, which is a concern in the current regulatory landscape.

- **The Data Protection Act** (UK Government 2018) controls how personal information is stored and used, and is the country's implementation of the **GDPR** (European Union 2016). It demands controls on data handling and personal data derived from organoid research.
- The Imperial Biomedical Research Centre Organoid Facility has been established as a research and training hub to stimulate the development and application of organoids in alignment with UK regulations. While not an oversight mechanism, it has been established to stimulate innovation in organoid technology by helping researchers navigate regulatory compliances (NIHR 2024).
- **The ISSCR Guidelines for Stem Cell Research and Clinical Translation** address the international diversity of cultural, political, legal and ethical issues associated with stem cell research and its translation to medicine (Lovell-Badge et al. 2019).

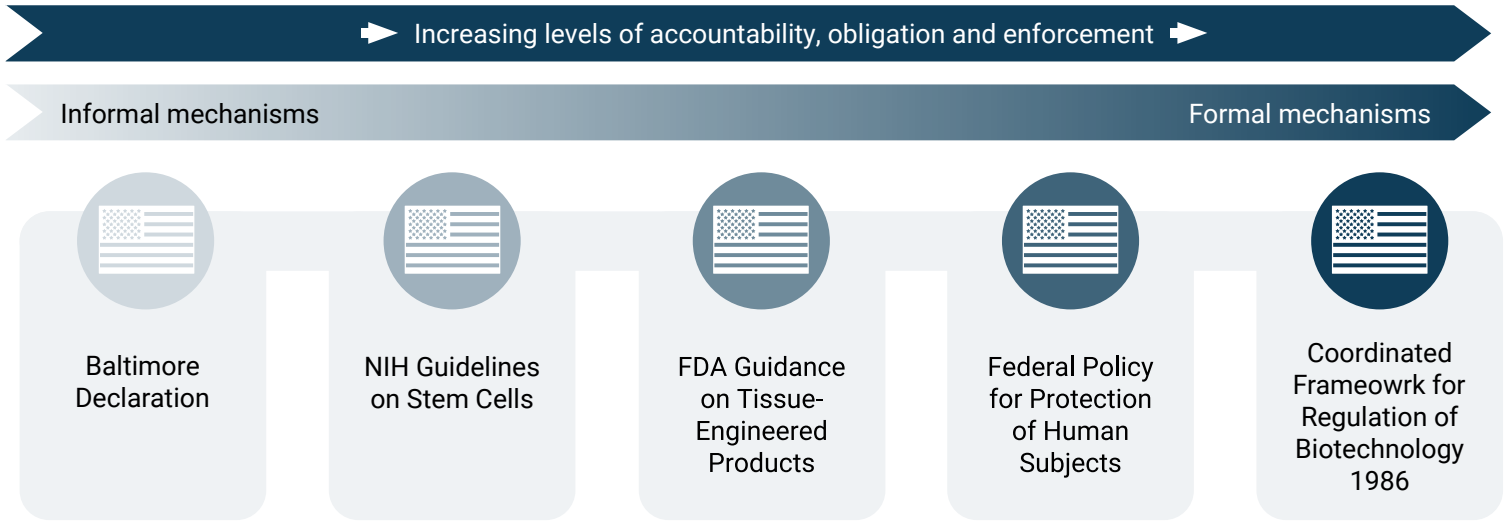
Uncertainties associated with organoid oversight in the United Kingdom

Current UK regulations primarily address broader categories of biomedicine and stem cell research, exposing gaps on emerging topics of dynamic consent, maintaining donor privacy and navigating ethical dilemmas on the use of neural organoids.

- **Specificity in oversight mechanisms.** UK regulations lack specificity in oversight mechanisms directly applicable to organoids. For instance, materials created outside the human body that consist of or include human cells are explicitly excluded from the HTA's remit, meaning that while the stem cells used to create organoids are regulated, the organoids themselves are not. This brings challenges for determining the ownership of these organoids once an individual's cells are donated and transformed into organoids.
- **Data protection and donor confidentiality.** Human-derived cells and data are commonly 'de-identified' so that they cannot be traced back to the donor patient, meaning that they are no longer subject to regulations on human participants in research (Boers and Bredenoord 2018). However, new sophisticated genomic sequencing techniques can allow for the reidentification of cells, meaning that new regulations that consider the potential for specimen reidentification and that still ensure donor confidentiality could be needed.
- **Regulation of neural organoids.** The development of neural organoids with complex neural structures that can model human cognition and neural activity present challenges for oversight. Currently, given the lack of maturity of organoids, they are not given the same ethical considerations as human subjects in research. However, as the technology evolves, oversight frameworks will likely need to adapt to consider the moral significance of organoids' human-derived nature and their potential for complex neural activity and features associated with consciousness (National Academies Press 2021).

3.4. Oversight of organoids in the United States

Figure 5. Illustrative oversight examples of organoids in the United States



Source: RAND Europe analysis.

Current oversight mechanisms in the United States

The US regulatory framework governing organoid research is informed by federal regulations designed for general biomedical research, but it is also applicable to the specific aspects of organoid research. The key aspects of this framework are:

- The **Coordinated Framework for Regulation of Biotechnology 1986** (updated in 2017) is a comprehensive federal regulatory policy for biotechnologies in the United States (US EPA 2017a). It clarifies regulatory responsibilities and ensures that biotechnological advancements, including organoids, are developed and implemented safely and effectively, while adhering to ethical standards. Oversight of this policy is distributed between the FDA, the Environmental Protection Agency (EPA) and the United States Department of Agriculture (USDA).
- The regulation of cellular and gene therapy products, including those derived from organoids, are overseen by the FDA's Center for Biologics Evaluation and Research (CBER), which primarily operates under the **Federal Food, Drug, and Cosmetic Act (FD&C Act)** (US FDA 2018) and the **Public Health Service Act**. The

CBER oversees various stages of development, production and distribution of organoid technologies including:

  - **Preclinical and clinical oversight.** Reviews trial protocols to ensure that they appropriately assess safety and efficacy.
  - **Product approval.** Reviews data from trials and manufacturing processes.
  - **Manufacturing regulations.** Sets and enforces standards for medical products, including those involving organoids.
  - **Post-market surveillance.** Monitors effectiveness in real-world settings and ensures ongoing compliance with regulatory standards.

- Oversight mechanisms have been developed to accelerate the development of medical products. The **21st Century Cures Act (2016)** aims to accelerate new innovations and advances by streamlining the approval process for new FDA medical products. This includes measures particularly relevant to organoid-based technologies that can lead to novel therapeutic methods or drug testing platforms.
- The protection of rights of human subjects involved in research is regulated by the 2018 **Federal Policy for the Protection of Human Subjects ('Common Rule').** While organoids are not categorised as human subjects, the initial collection of human cells or tissues to create organoids falls under this framework. This policy is enforced by institutional review boards at research institutions, and covers research undertaken with US government funding, including the NIH.
- National standards for the protection of certain health information are set by the 2008 **Standards for Privacy of Individually Identifiable Health Information ('Privacy Rule')** under the 1996 **Health Insurance Portability and Accountability Act (HIPAA)** (CDC 2024). Any personally identifiable information derived from tissue donors must be handled according to these regulations, which includes the deidentification of data used. These are enforced by the Office for Civil Rights (OCR) at the US Department of Health and Human Services (HHS), which carries out compliance reviews and investigates complaints. Additionally, state-level laws such as the **California Consumer Privacy Act (CCPA)** (State of California Department of Justice 2024) and **the Virginia Consumer Data Protection Act** (Usercentrics 2024) are expanding the scope of data protection for genetic data, which research initiatives in those states must also comply with.
- The **NIH (2017)** has guidelines for research involving human stem cells and organoids derived from these cells. Compliance with these guidelines is mandatory for institutions seeking NIH funding, and they serve as a model for ethical research conduct.

Emerging oversight mechanisms in the United States

As the field of organoid research continues to evolve, both in complexity and potential applications, new oversight mechanisms are being discussed and developed to address the unique challenges it presents:

- **Guidance for tissue-engineered products, which includes organoids**, is currently being developed by the **FDA** (BioPharm International 2024). A draft guidance has been issued covering human- and animal-derived materials used in the manufacture of ATMPs, with the focus primarily on safety and quality improvements.
- A **regulatory framework for AI/machine learning (ML)-based software as a medical device** has been proposed by the

FDA. This is designed to regulate the AI and ML technologies increasingly being integrated into biomedical applications, including organoids, particularly brain organoids.

- The **Baltimore Declaration** (Hartung et al. 2023) serves as informal guidelines advocating for the responsible exploration of organoid intelligence, emphasising the potential of human brain organoids for advancing neuroscience and biotechnology. The informal approach laid out by the Baltimore Declaration could inform more formal oversight mechanisms as it provides a foundational framework that emphasises ethical guidelines, transparency and the protection of organoids and donor interests as the field progresses. The declaration began in the United States but is now international.

Other mechanisms of relevance in the United States

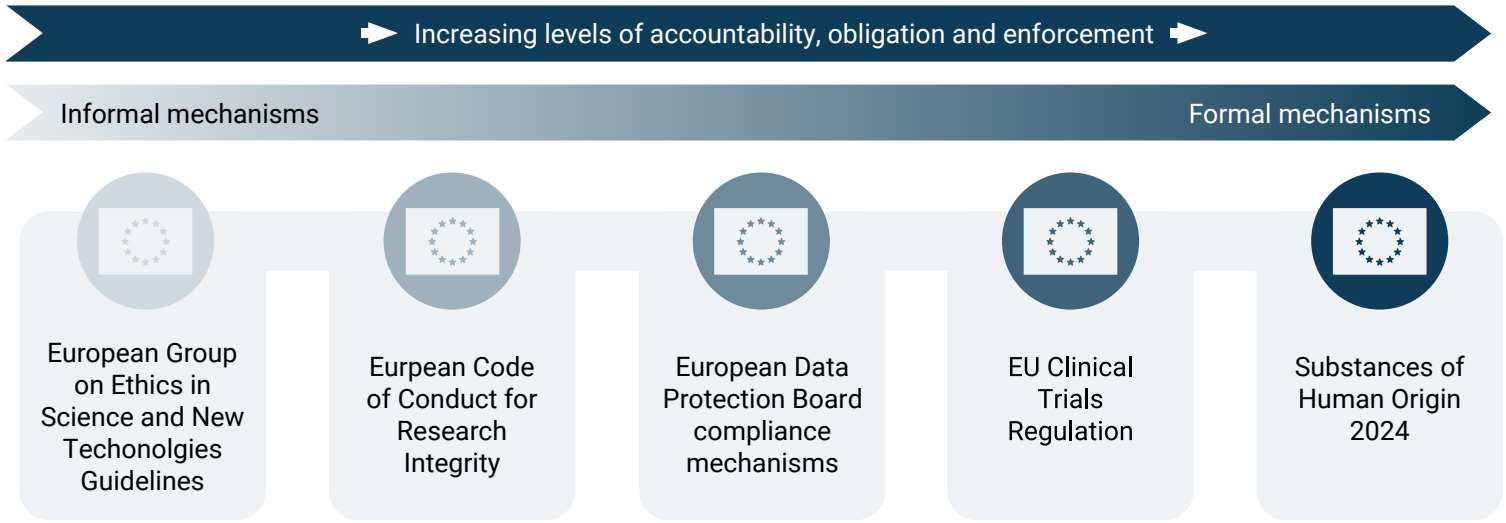
- The 2008 **Genetic Information Nondiscrimination Act (GINA)** protects the privacy of genetic information to ensure that Americans cannot be discriminated against based on their genetic information in health insurance and employment. It is relevant to organoid research primarily because it provides protections that could influence how genetic information derived from organoids is handled.
- The 2024 **Executive Order on Preventing Access to Americans' Bulk Sensitive Personal Data and United States Government-Related Data by Countries of Concern** protects US citizens' sensitive personal health data, including genetic information used in organoid R&I (White House 2024a).
- Oversight mechanisms that address the potential of the dual use of research in life sciences, including the development of organoids, are **the Biological Weapons Convention (BWC)** (formally known as the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction), which has been signed by the United States. This ensures that biological research, including potentially organoids, does not contribute to the development or proliferation of biological weapons (United Nations 2024). The US government has also implemented the **Policy for Oversight of Life Sciences Dual Use Research of Concern** (2012), which establishes review processes for research projects that may pose dual-use threats.
- **ISSCR stem cell guidelines** address the international diversity of cultural, political, legal and ethical issues associated with stem cell research and its translation to medicine (Lovell-Badge et al. 2019).

Uncertainties associated with organoid oversight in the United States

- **Specificity in oversight mechanisms.** Donor consent is a key challenge in the use of organoids. This is especially the case for neural organoids as they are not fully covered by general stem cell or human subject research guidelines, which are the main oversight mechanisms for organoid research in the United States. There is no bespoke guidance on ethical issues such as donor consent specifically tailored to the complexities of organoid use, including the potential for creating organoid models with neural activity. While this concern is highlighted and in part addressed by the **Baltimore Declaration**, it has not yet been addressed in any current oversight mechanisms.
- **Clinical translation.** As organoid research increasingly moves toward clinical use, US regulatory frameworks must address challenges in scalability, reproducibility and safety, especially against the backdrop of efforts being undertaken to scale other biomanufacturing processes in the United States.

3.5. Oversight of organoids in the European Union

Figure 6. Illustrative oversight examples of organoids in the European Union



Source: RAND Europe analysis.

Current oversight mechanisms in the European Union

In the EU, the regulatory landscape for organoid research is multifaceted, including EU-wide regulations and national legislation that reflect each member state's specific stance on ethical considerations in biomedical research. EU-wide regulations are stringent and play an important role in setting overarching standards for organoid research across member states. Key oversight mechanisms include:

- Standards for the quality and safety of human tissues and cells, including those used in organoid research, are established in the **EU Tissues and Cells Directive (2004).** These directives set rigorous standards for the procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for use in humans. In July 2024, the **Substances of Human Origin Regulation (SoHO)** was published as a replacement to this directive. As a regulation it will be applied directly, in contrast to directives that must be implemented nationally. Although the replacement regulation still applies to organoids, unlike the previous directive it only applies to the clinical research of organoids and not in any other context such as discovery research.

- The conduct of clinical trials in the EU, including those that might involve organoids, for testing the safety and efficacy of new drugs is governed by the **EU Clinical Trial Regulation 2014** (European Commission 2014). These regulations ensure that clinical trials are conducted according to high ethical and scientific standards.
- The evaluation and safety monitoring of medicines in the EU is regulated by the **European Medicines Agency (EMA),** which is the primary route for the authorisation of medicines in the EU. The EMA is a centralised EU agency, with the implementation and enforcement of related directives devolved to individual member states. There is no provision for organoids unless they are part of therapeutic products or used in preclinical trials for drug testing.
- Frameworks for handling and protecting personal data in the EU, including genetic information, are set by the **GDPR.** Given the potential for organoids to contain genetic information about the donor, regulations that influence data protection and privacy strongly influence organoid research.
- Ethical questions arising from science and new technologies, including organoids, are addressed by the **European Group on Ethics in Science and New Technologies** (European Union 2021a), an independent advisory body established by the European Commission. Although it does not directly create or enforce policy or regulation, it plays a significant role in informing regulation.

Emerging oversight mechanisms in the European Union

Current discussions and development of oversight mechanisms for organoid research and innovation primarily surround the updating of existing regulatory frameworks to better suit the needs of organoid research:

- The European Group on Ethics in Science and New Technologies is actively involved in **evaluating the ethical implications** of emerging technologies. It has released an opinion on the ethics of genome editing, which is often involved in organoid research, that suggests the development of specific ethical guidelines to address **consent and donor rights** when genetic alterations are involved (European Union 2021a).
- The EMA is leading ongoing discussions with researchers, bioethicists and industry stakeholders to explore how the regulatory pathways used for **Advanced therapy medicinal products** (**ATMPs)** could better accommodate new technologies, including organoid-based therapies (Iglesias-Lopez et al. 2019). The aims are to streamline the approval process, encouraging innovation in organoid research on drug development and therapeutic applications, while ensuring that safety standards are met. These discussions are likely to inform annexes or guidelines that can be integrated into the existing regulatory framework governing ATMPs.
- Data protection authorities across the EU are in conversation with the **European Data Protection Board** to ensure the compliance of genetic data, including data from organoids. The primary focus is on developing robust mechanisms for anonymising genetic data derived from biomedical technologies, such as organoids, that consider issues such as the possibility of reidentifying anonymised genetic data (Shabani and Marelli, 2019). There have been efforts to establish protocols for the sharing of such data with international research partners beyond the EU. These discussions may lead to supplementary guidelines under **GDPR** that specifically address data handling in organoid research to prevent breaches of personal data privacy.
- The European Parliament and the Council of the European Union reached a provisional agreement on 15 March 2024 to create a **European Health Data Space** that would enhance the infrastructure for sharing health data across Europe, including data used or collected in clinical trials and medical devices, and

pathogen genetic data. These types of data are highly relevant to organoid research and could provide a streamlined framework for accessing and using large quantities of relevant biological data, which is crucial for the validation of organoid models.

- The EU communication, **Building the Future with Nature: Boosting Biotechnology and Biomanufacturing in the EU**, outlined forthcoming efforts by the European Commission to enhance the regulatory environment for biotechnological interventions, including those relevant to organoid research (European Union 2024a).

Other mechanisms of relevance in the European Commission

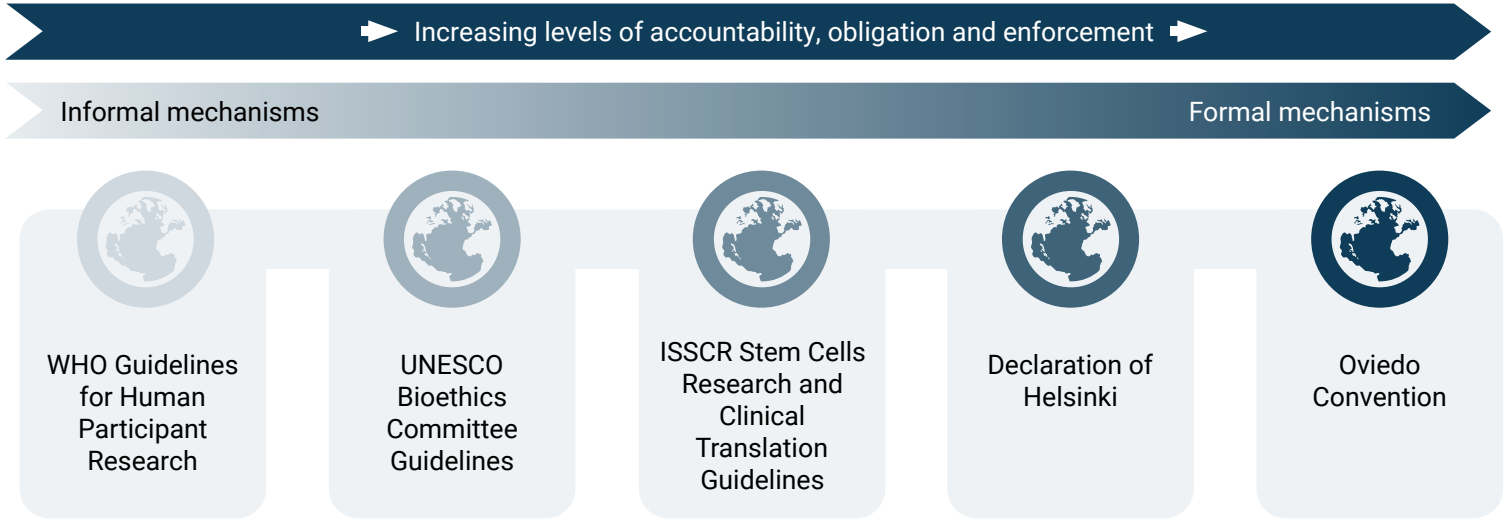
- The use of AI across the EU is regulated by the **European Union Artificial Intelligence (AI) Act 2024.** It categorises AI into different levels of risk, which dictates the regulatory requirements that each AI system must meet. Regulations involving AI in healthcare are likely to be considered high risk.
- Standards for conducting and reporting research are set by the **All European Academies' (ALLEA)** and the **European Commission's European Code of Conduct for Research Integrity**. This sets standards for the transparent reporting of research, which can also impact research on organoids.
- The 1997 **Convention on Human Rights and Biomedicine (Oviedo Convention)** is the first legally binding instrument to safeguard human rights in the face of emerging biomedical technologies. It outlines principles relevant to organoid research, such as consent and confidentiality.
- Organoid research often involves multinational collaborations. International bodies such as the **International Society of Organoid Research** and the **International Stem Cell Biobanking Initiative (ISCBI)** provide guidelines and standards for the global exchange of stem cells and related data, including stem cell-based organoids (Stacey and Healy 2021).
- The **ISSCR** addresses the international diversity of cultural, political, legal and ethical issues associated with stem cell research and its translation to medicine (Lovell-Badge et al. 2019).

Uncertainties associated with organoid oversight in the European Union

- **Specificity of guidelines.** Current EU regulations are generally designed for broad categories of biotechnologies and medical research. Organoids present particular challenges and opportunities, and existing EU regulatory frameworks do not fully address their unique properties and potential applications. There is a need for specific regulatory frameworks that directly address the complexities and nuances of organoid technology, particularly in relation to informed consent, governance and the ethical implications of complex neural activity in brain organoids. For instance, there is no oversight in place for gonadal organoids or the production of any gamete-like cells.
- **Harmonisation across contexts.** The regulatory landscape in the EU can be fragmented, with member states responsible for the implementation of relevant EU directives. A unified framework specific to organoid research could streamline research processes, reduce bureaucratic hurdles and ensure consistent ethical standards across the EU.
- **Informed consent.** EU regulations concerning the standards for informed consent do not specifically cover research involving organoids or related studies that use human tissues and cells, unless in a clinical context. This omission has resulted in variations at the national level regarding the legal requirements for the research use of human tissues, cells and related data (Shabani and Marelli 2019).

3.6. Oversight of organoids in international forums

Figure 7. Illustrative oversight examples of organoids in international forums



Source: RAND Europe analysis.

Current oversight mechanisms in international forums

- The **Declaration of Helsinki (2013)** sets ethical principles for medical research involving human subjects, including research on identifiable human material and data (in this case organoids) (WMA 2022). It emphasises informed consent, the protection of patient rights and the ethical conduct of research. The declaration serves as a cornerstone document in the field of research ethics, guiding researchers, ethics committees and regulatory bodies worldwide.
- The World Health Organization's (WHO) established guidelines on **standards and operational guidance for ethics review of health-related research with human participants** provide a broad framework for ethical considerations in biomedical research, including issues related to human subjects, consent and the use of human biological materials such as organoids (WHO 2011). WHO's guidance is influential in shaping national policies and regulations.
- The 2016 **International Ethical Guidelines for Health-Related Research Involving Humans** were developed by the Council for International Organisations of Medical Sciences (CIOMS) in collaboration with WHO. These guidelines provide ethical standards for health-related research involving humans (van Delden and van der Graaf 2017) and address issues such as informed consent, the use of human biological materials such

as organoids and the protection of vulnerable populations. While these guidelines are not legally binding, they are widely recognised and adopted by institutions and regulatory bodies worldwide. Compliance is often a prerequisite for funding and publication in scientific journals.

- The **Oviedo Convention** addresses ethical and legal issues in biomedicine, including the use of human biological materials (Andorno 2005). It provides a framework for the protection of human rights in biomedical research and clinical practice. It is the first legally binding instrument to safeguard human rights in the face of emerging biomedical technologies and outlines principles such as consent and confidentiality, which impact organoid research.
- The **ISSCR's** 2021 **Guidelines for Stem Cell Research and Clinical Translation** (Lovell-Badge et al. 2021) provide comprehensive recommendations for the ethical conduct of stem cell research, including organoid research. Key areas covered include research integrity, the ethical sourcing of human tissues, informed consent and clinical translation. While a soft oversight mechanism, the guidelines are widely recognised and adopted by researchers and institutions globally, including in the United Kingdom and the United States.
- **ISCBI** provides guidelines and standards for the global exchange of stem cells and related data, including stem cell-based organoids (Stacey and Healy 2021).

Emerging oversight mechanisms in international forums

- The WHO **Global Observatory on Health Research** is an initiative aimed at providing a comprehensive and up-to-date view of global health research activities, including those related to organoid research (WHO 2024a). WHO is continuously involved in global discussions about the ethical and regulatory challenges posed by new biotechnologies, including organoids. As the field quickly develops, this initiative can help identify emerging risks needing oversight.
- The United Nations Educational, Scientific and Cultural Organization (UNESCO) has a **Bioethics Committee** that addresses the ethical implications of biotechnologies. UNESCO has been discussing the potential need for international agreements or treaties to regulate organoid research. It advocates for the inclusion of diverse perspectives in these discussions, including those from low- and middle-income countries.
- The **Baltimore Declaration** was formed by an international community of scientists undertaking research on brain organoids. It emphasises the potential of human brain organoids for advancing neuroscience and biotechnology (Hartung et al. 2024) and serves as an informal guideline advocating for the responsible exploration of organoid intelligence. The Baltimore Declaration provides a foundational framework that emphasises ethical guidelines, transparency, and the protection of organoids and donor interests, and could inform more formal oversight mechanisms as the field progresses.
- **The consent-to-govern model** is an emerging ethical framework designed to address the complex issues surrounding the use of human tissues and cells in organoid research (Boers and Bredenoord, 2018). The model emphasises the importance of obtaining informed and ongoing consent from donors, ensuring that they have a say in how their biological materials are used throughout the research process. By emphasising informed and ongoing consent, transparency, and community engagement, this approach to consent aims to respect donor autonomy and build public trust in scientific research.

Other mechanisms of relevance in international forums

- The **Cartagena Protocol on Biosafety 2003** is an international agreement under the Convention on Biological Diversity (CBD) that governs the safe handling, transport and use of living modified organisms resulting from biotechnology that may have adverse effects on biological diversity, also considering risks to human health (United Nations 2000). The regulatory framework for the transboundary movement of living modified organisms can include genetically modified cells that are used for creating organoids.
- The **BWC** is an international treaty that prohibits the development, production and stockpiling of biological and toxin weapons. It aims to eliminate an entire category of weapons (United Nations 2024) and plays a critical role in shaping the ethical and regulatory landscape of modern biological research, including organoid research.
- The **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)** is an initiative that aims to harmonise regulatory requirements for pharmaceuticals, bringing together regulatory authorities and the pharmaceutical industry. It plays a critical role in shaping the regulatory landscape for pharmaceuticals, ensuring that new drugs are safe, effective and of high quality. Its guidelines and harmonisation efforts are directly relevant to organoid research, which holds promise for revolutionising drug development and testing (Singh 2015).
- Journals have **increasingly high publication standards**, including requirements for ethical approval, transparency in reporting, and considerations for the reproducibility and validation of research. As a result, publication standards for organoid research are increasing. For example, the journal *Nature* has updated its publication guidelines to emphasise transparency and reproducibility, which also impacts organoid research (Nature 2024).

Uncertainties associated with organoid oversight in international forums

- **Specificity of policies.** There is a lack of specificity in existing regulations and guidelines in international forums, as in the United Kingdom, United States and EU. While general ethical and scientific principles are often outlined, the unique characteristics and applications of organoids may not be fully addressed. Although there are international central oversight mechanisms, such as the **Declaration of Helsinki** and WHO guidelines on **standards and operational guidance for ethics review of health-related research with human participants**, they are not specific to organoids. This lack of specificity can lead to inconsistencies in ethical review processes and regulatory compliance, potentially compromising the rigour and reproducibility of organoid research, especially in the context of neural organoids.
- **Commercialisation.** As organoids move from the laboratory to commercial applications, issues related to intellectual property, benefit-sharing and ethical use become more pronounced. There is a risk that commercial interests might overshadow ethical considerations, leading to the potential exploitation of donors or misuse of organoid technologies. Regulatory frameworks must adapt to address these commercial dynamics, ensuring that ethical standards are maintained even as organoid research becomes increasingly integrated into the marketplace.
- **Public benefit and equitable access.** Ensuring that the benefits of organoid research are equitably distributed remains an area of uncertainty. There is a risk that advancements in organoid technology could exacerbate existing health disparities if access to these innovations is limited to certain populations or regions. Oversight mechanisms must consider how to promote public benefit. This includes addressing issues related to affordability, distribution and global collaboration to foster inclusive scientific progress.

3.7. Case studies of organoid oversight mechanisms

Case study 1:
Japan – A proposed framework for neural organoid research risk management

Table 1. Japan's brain organoid risk framework

Technology area:	Organoids
Oversight example:	Brain organoid risk framework
Type(s) of oversight mechanism(s):	Research framework
Jurisdiction:	Japan
Timescale:	First proposed in academic article published in 2024

Why is the oversight required?

As neural organoid research matures, broad donor consent has been suggested as being insufficient by stakeholders working in this sector. Oversight is required to address two core issues in the consent process: the inadequacy of broad consent approaches given the evolution of the materials taken from the donor, and the issue of consciousness and donor autonomy. Broad consent or 'consent-to-govern' approaches are becoming increasingly prevalent and have been suggested as being particularly relevant for organoids (Boers and Bredenoord 2018). This proposed mechanism suggests that while consent-to-govern approaches can be implemented, neural organoid research requires separate and project-specific consent. Adequate ethical oversight is necessary to prevent donors from inadvertently donating biological material for research they do not wish to participate in. This is also important to ensure public trust in organoid research.

While informing donors of how their cells will be used is an important element in gaining informed consent, it can be particularly challenging with neural organoid research as it contains both philosophical and moral uncertainties (Kataoka et al. 2024). To obtain fully informed consent these uncertainties must be effectively communicated to donors at the point of consent. Ethical oversight ensures that donors are fully informed about the potential risks and ethical implications, thus safeguarding their autonomy and moral integrity.

Most scientists and ethicists agree that organoids do not possess any form of consciousness due to their structural and functional simplicity (ISSCR 2024). However, the rapid pace of development in this area has led to the development of neural organoids that exhibit neural activity resembling that found in premature infants (Trujillo et al. 2018). This has highlighted the need for bespoke guidelines for neural organoid research that goes beyond those applicable to stem cell research in general (Lavazza and Massimini 2018).

How is the oversight mechanism being conducted?

A brain organoids risk framework has been proposed by Kataoka et al. (2024). It was developed during a five-year research programme at the Centre for Ethical, Legal, and Social Implications (ELSI) of Human Brain Organoid Research, and funded by the Japan Agency for Medical Research and Development (AMED) (Sawai, Tsutomu and Masanori Kataoka 2024). The framework introduces specific ethical principles for brain organoid research, focusing on the

epistemological and moral uncertainties, and the implications of the donor consent procedure.

To address concerns in brain organoid research, the framework includes three proposals for the consent procedure:

- **Develop specific consent mechanisms:** Broad consent is inadequate for brain organoid research because some donors may object to the creation of potentially conscious entities from their cells. To respect donors' autonomy and moral integrity, it is essential to provide project-specific informed consent for each research project. This ensures that donors are fully informed about the ethical oversight and uncertainties involved, allowing for their active and informed participation.
- **Incorporate epistemological and moral uncertainties into consent procedures:** Researchers should inform donors about the epistemological and moral uncertainties in brain organoid research when obtaining project-specific consent. Donors must have the opportunity to critically reflect on these uncertainties. If these uncertainties are not sufficiently emphasised, there is a risk of violating donor autonomy and moral integrity.
- **Develop a risk framework for brain organoids:** Donors should be assured that appropriate measures will be taken to protect the brain organoids during research. These assurances should be fulfilled through the implementation of precautionary measures to mitigate potential harm.

In Japan, the oversight of brain organoid research involves a multi-tiered approach that includes institutional, national and international guidelines, and ethical review processes. Relevant stakeholders to consider in the implementation and development of this proposed mechanism include:

- **Biobanks:** Regulations and policies set by biobanks storing organoids, or stem cell used to develop organoids, are particularly relevant to the specific consent mechanisms being developed.[15]
- **Institutional review boards and ethical committees:** Research proposals involving brain organoids are reviewed by institutional review boards at the institutions where the research is conducted. These boards assess the ethical implications and ensure compliance with national and institutional guidelines. Specialised ethical committees, such as those within universities and research institutions, provide additional layers of review, focusing on specific ethical concerns related to brain organoid research.
- **National and international guidelines:** Compliance with international guidelines, such as those from the ISSCR (ISSCR 2024), ensures that research aligns with global ethical standards. Japan has a history of taking early and proactive stances on life-science research and development (Regulatory Horizons Council 2022). The guidelines by the Japanese Society for Stem Cell Research align with those set by the ISSCR and provide comprehensive standards for ethical conduct in stem cell research. New oversight mechanisms must be embedded within these guidelines.
- **National organisations:** Other national organisations such as the Japanese Organoid Repository (JOR 2024) and AMED, which has funded the research programme developing Japan's brain organoid risk framework, are relevant stakeholders to involve.

15 INT_04.

- **Cell donors and the wider public:** These should be engaged in discussions about the ethical implications of research and the development of new ethical guidelines to ensure that their voices and perspectives are adequately reflected in the guidelines (Schicktanz et al. 2012). This is particularly relevant for this Japan's brain organoid risk framework, which proposes changes to the consent process for tissue donors.

What is the future trajectory for the oversight mechanism?

The proposal was published in early 2024 and is still in its **early stages of development and potential uptake.** The framework has not yet directly informed practice or regulations, but it has led to discussions amongst stakeholders and scientists.[16]

The Centre for ELSI of Human Brain Organoid Research, where the framework was developed, has been established to address the ethical considerations of brain organoid research. Stakeholders could look to this research centre to **update existing institutional and national guidelines to pursue research excellence and ethics in brain organoid research.** This includes aligning with the ethical standards set by the Japanese Society for Stem Cell Research and the ISSCR.

Japan's brain organoid risk framework could **impact the public perception of brain organoid research.** The purpose of the framework is to ensure the ethical conduct of brain organoid research, including the importance of obtaining fully informed consent that involves informing donors of the epistemological and moral uncertainties of organoids. While this requires a more demanding donor consent process, it could also ensure that donors are comfortable with the uses of their donated biological material. If this mechanism is integrated into guidelines and regulation, it could help preserve and enhance public trust in brain organoid research, and in organoid research more broadly.[17]

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Japan's brain organoid risk framework demonstrates the importance of **engaging with stakeholders in the development of research frameworks.** It has currently informed discussions in bioethics, including responses from scientists who agree with the need for changes in consent procedures and from those who question whether the potential for consciousness is relevant to consider at this point.[18] This suggests that incorporating stakeholders into the development of frameworks to ensure that they are framed in a way that promotes acceptability amongst scientists could be advantageous.

The framework also shows that **oversight mechanisms must be flexible and adapt** to evolving scientific knowledge and technological advancements. For example, new knowledge about moral and epistemological uncertainties in brain organoids can be integrated into consent procedures. The proposed framework's adaptability to different levels of epistemological and moral uncertainties associated with brain organoids as the field continues to progress is a useful framing in that respect.

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Case study 2:
Australia – A proposed research framework focused on moral principles underpinning organoid research

Table 2. Australia's morality based brain organoid research framework

Technology area:	Organoids
Oversight example:	Morality based brain organoid research framework
Type(s) of oversight mechanism(s):	Research framework
Jurisdiction:	Australia
Timescale:	First proposed in academic article published in 2019

Why is the oversight required?

As discussed above, there are limitations in current oversight mechanisms: while the relevant regulations and guidelines address issues related to the provenance, procurement, and handling of human tissue and stem cells, there are no specific research limits based on the maturity of neural organoids themselves and their corresponding moral status, nor do the ISSCR guidelines currently address these emerging ethical issues. Oversight is required to address several key challenges and gaps relating to the potential for consciousness and cognitive capabilities. This need has been highlighted by bioethicists, organoid scientists and the general public (Haselager et al. 2020). There has also been a growing agreement within the research community that bespoke guidelines are needed for neural organoid research beyond those pertaining to stem cell research in general (Lavazza and Massimini 2018).

How is the oversight being conducted?

The **morality based brain organoid research framework** has been proposed as an oversight mechanism by Koplin and Savulescu (2019) as a way of providing some boundaries and oversight on brain organoid research. The research framework is in its very early stages of development, with its application mainly being discussed amongst academic bioethicists and scientists.

The framework aims to balance scientific progress with the ethical treatment of brain organoids, considering the risk of harm associated with their potential consciousness. It suggests that brain organoids have different moral statuses depending on the levels of consciousness and cognitive abilities they exhibit. A broad challenge in the area of brain organoid development is defining what constitutes consciousness and cognitive abilities (Amadio et al. 2018). In this framework, Koplin and Savulescu (2019) use approaches to defining when foetuses are conscious 'by extrapolating from the threshold at which human foetuses begin to develop consciousness'.

Based on this, Koplin and Savulescu (2019) suggest dividing organoids into three different categories: 1) non-conscious brain organoids; 2) conscious or potentially conscious brain organoids; and 3) brain organoids with the potential to develop advanced cognitive capabilities. For non-conscious brain organoids, research should be regulated according to existing frameworks for stem cell and human biospecimen research. For conscious or potentially conscious organoids, there should be additional limitations guided by adapting the 'Three Rs' approach from animal welfare: reduce, refine and replace (DeGrazia and Beauchamp 2020). This includes using the minimum number of conscious brain organoids necessary, refining experimental

techniques to minimise harm and opting for non-conscious organoids whenever possible. Organoids with the potential to develop advanced cognitive capabilities should additionally be screened for advanced cognitive capacities they could develop and associated welfare needs should be addressed, ensuring that cognitive capacities are no more advanced than necessary to achieve the goals of the research and justifying the research purpose against the potential harms (Koplin and Savulescu 2019). See Figure 8 for a detailed description of the different levels of consciousness and research restrictions.

Figure 8. Different levels of consciousness and research restrictions regarding organoids

Equivalent stage of human *in vivo* brain development	Research restrictions
Non-conscious brain organoids (e.g., equivalent to fewer than 20 weeks' *in vivo* brain development)	Research should be regulated according to existing frameworks for stem cell and human biospecimen research
Conscious or potentially conscious brain organoids (e.g., equivalent to 20 weeks' *in vivo* brain development or more)	In addition to the above constraints, research should be subject to the following restrictions: 1. The expected benefits of the research must be sufficiently great to justify the moral costs, including potential harms to brain organoids. 2. Conscious brain organoids should be used only if the goals of the research cannot be met using non-sentient material. 3. The minimum possible number of brain organoids should be used, compatible with achieving the goals of the research. 4. Conscious brain organoids should not have greater potential for suffering than is necessary to achieve the goals of the research. 5. Conscious brain organoids must not experience greater harm than is necessary to achieve the goals of the research. 6. Brain organoids should not be made to experience severe long-term harm unless necessary to achieve some critically important purpose.
Brain organoids with the potential to develop advanced cognitive capacities (e.g., mature brain organoids capable of interacting with outside environment.)	In addition to the above constraints, research should be subject to the following restrictions: 1. Brain organoids should be screened for advanced cognitive capacities they could plausibly develop. In general, such assessments should err on the side of over-estimating rather than under-estimating cognitive capacities. 2. Cognitive capacities should not be more sophisticated than is necessary to achieve the goals of the research. 3. Welfare needs associated with advanced cognitive capacities should be met unless failure to do so is necessary to achieve the goals of the research. 4. The expected benefits of the research must be sufficiently great to justify the expected or potential harms. This calculation should take into account the implications of advanced cognitive abilities for brain organoids' welfare and moral status.

Source: Koplin and Savulescu (2019).

Australia's morality based brain organoid research framework has currently only been discussed within academic conversations on bioethics. As the framework is multifaceted, a range of stakeholders must be considered when considering opportunities for implementation into formal oversight mechanisms. These include:

- **Institutional review boards or human research ethics committees:** These bodies review and monitor research proposals to ensure compliance with ethical standards. They would need to adopt the new framework when reviewing research proposals, which would include evaluating the category that brain organoids would fall under and applying appropriate research limits.
- **National Health and Medical Research Council (NHMRC):** Provides the foundational ethical guidelines for the collection and use of human biospecimens. These do not currently contain guidelines on brain organoid research. Guidelines and the National Statement on Ethical Conduct in Human Research (NHMRC 2023) would need to be updated if the framework were to be implemented nationwide.
- **ISSCR:** Australia's national guidelines are closely aligned with the international guidelines set by the ISSCR, which have informed formal and informal oversight mechanisms on stem cell-based research (ISSCR 2024).
- **Human tissue donors and the wider public:** Capturing the voices and perspectives of tissue donors and the wider public is particularly important to ensure that they find the framework acceptable and that it promotes public trust in research (Schicktanz et al. 2012).

What is the future trajectory for the oversight mechanism?

The framework is still in the very early stages of consideration and implementation. While it has had **early influence in shaping and initiating discussions** in academic and bioethical circles, its integration into the Australian oversight landscape and practice is ongoing.

The **framework could impact institutional guidelines and practices.** It has started to influence discussions about the ethical oversight of brain organoid research in Australia, with one academic institution discussing its integration into its guidelines.[19] The framework is likely to gain more acceptance as the scientific community and regulatory bodies recognise the importance of addressing the unique ethical challenges of brain organoid research, and as the technology develops.

If the framework is adopted more widely by various research institutes **it could lead to the development of enhanced ethical guidelines proposed for adoption into** Australia's NHMRC research guidelines. The integration of guidelines for specific types of emerging biotechnology into national guidelines in Australia has already been observed for genomic research and the ethical use of biobanks (Australian Government 2017). These precedents indicate that the adoption of the new framework for brain organoid research by various research institutes could similarly lead to enhanced ethical guidelines within the NHMRC framework.

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Australia's morality based brain organoid research framework was developed in response to growing concerns amongst bioethicists and scientists that brain organoids could attain some degree of moral status if they develop characteristics such as consciousness, active pain pathways or self-awareness (Koplin and Savulescu 2019). However, there are difficulties in establishing what constitutes consciousness in organoids, and the moral challenges this brings, and there have been few concrete suggestions of research frameworks to address the issue (Amadio et al. 2018). Australia's new framework represents a novel approach that has gathered attention within academic discussions and amongst scientists and research institutions, with one academic institution considering implementation.[20]

The framework also represents lessons learned that can inform the further development of research frameworks:

- The framework demonstrates the **challenges of translating bioethical frameworks into practice.** While the framework has influenced academic discussions and prompted conversations about ethical guidelines in one research institution,[21] it has not made direct impact on practice or regulations, despite being published over four years ago and the authors remaining involved in conversations about the framework.
- The framework's **flexibility and adaptability to evolving scientific knowledge and technological advancements** has

19 INT_05.
20 INT_05.
21 INT_05.

been highlighted as a strength that allows it to remain relevant as the field progresses.[22] By categorising brain organoids based on their potential levels of consciousness and cognitive abilities, the framework provides a graded approach to ethical oversight, allowing the application of appropriate levels of limits. A graded approach ensures that ethical concerns can be balanced with scientific progress, which is important for a field such as brain organoids, where innovation is fast-paced with great potential, but where there are also strong ethical considerations.

- The framework demonstrates **the importance of involving stakeholders in proactive ethical considerations.** One of the framework's authors reported that the article presenting it received criticism from scientists working within the field of brain organoids.[23] As brain organoids do not currently exhibit consciousness, the framework was criticised for being alarmist and potentially undermining public acceptability of brain organoid research, thereby limiting scientific progress. **This suggests that future frameworks should integrate scientists and other stakeholders into their development and communication processes to improve understanding and enhance acceptability.** Increased acceptability from scientists and stakeholders can facilitate the informal adoption of the framework, even before it becomes embedded in official guidelines or regulations.

22 INT_05.
23 INT_05.

Case study 3:
The Netherlands – Organoid biobank guidelines for maintaining donor privacy and revisiting consent

Table 3. The Netherlands' Foundation Hubrecht Organoid Bank guidelines

Technology area:	Organoids
Oversight example:	Foundation Hubrecht Organoid Bank
Type(s) of oversight mechanism(s):	Guidelines
Jurisdiction:	The Netherlands
Timescale:	2013 – present

Why is the oversight required?

Organoid research involves the collection, sorting, cataloguing and storing of physical specimens, including material that contains genetic information, in a biobanking infrastructure. These practices give rise to variety of concerns that necessitate oversight, including **data governance and privacy, long-term sustainability of data, and managing access. The development and implementation of appropriate informed consent processes** constitute a longstanding ethical concern with organoid research, particularly brain organoid research. Particular issues include donor control/management of

future use cases, the varied relationships donors will have with their organoid specimens (Lewis and Holm 2022), the scope of autonomy in the absence of certainty (at the time of consent), and, for brain organoids, risks to the brain organoids themselves.

For neural organoids, informed consent is especially complex due to the possibility of organoid consciousness and autonomy linked to these structures (Kyoto University 2024). At the time of donation it is extremely difficult to inform donors of how donated materials will be used in future research, which makes it difficult to respect the donor's autonomy or right to self-determination during the consent procedure (Kataoka et al. 2024). Traditional consent takes two main forms:

- **Broad consent** is given for an unspecified range of future uses under limited restrictions. Some argue that broad consent should be not be applied to brain organoid research because of its controversial nature, largely relating to the 'consciousness problem' (Kataoka et al. 2024).
- **Project-specific consent** is given for a specified use case. As with broad consent, project-specific consent also suffers from the inability of researchers to provide definitive explanations regarding brain organoid research, resulting in inadequate informed consent (Kataoka et al. 2024).

Further concerns regard donors' potential **right to compensation** if drugs or therapies are developed using their specimens, or the **possible asymmetry** between donors' desire to use organoids to improve their health and the involved companies' desire to develop commercial products (de Jongh et al. 2022; Boers et al. 2016).

What is the oversight mechanism proposed?

The **Foundation Hubrecht Organoid Biobank** (FHOB) began in 2013 from a collaboration between the University Medical Centre Utrecht, the Royal Netherlands Academy of Arts and Sciences (KNAW) and the Hubrecht Organoid Biobank (previously the Hubrecht Organoid Technology). It is the world's largest collection of patient-derived organoids developed from adult stem cells. FHOB collects both healthy and diseased tissue for disease modelling, drug testing and development, and personalised medicine. It has published little specific information of its oversight practices with regards to consent and privacy, but states that its models undergo 'strict quality control measures to ensure that they adhere to the highest quality standards' (FHOB 2024). What is known about FHOB's oversight on brain organoid research can be drawn from a variety of affiliate institutions and inferred from industry and academic publications.

FHOB leadership worked with leading academics at Utrecht University to launch a project and proactively review the ethics of organoid research, spanning its development, storage and use in further research. This community of experts later launched a proposed governance framework for organoid biobanking, many aspects of which can be seen in **FHOB's standards on the ethical and transparent use of donated specimens and the consent process** to maintain the privacy and rights of donors (Boers and Bredenoord 2018).

These standards state that:

- All specimens are donated anonymously, voluntarily and with informed consent (Hubrecht Institute 2024).
- All specimens are coded so that samples are unidentifiable and the patient medical data is never provided unless there is specific consent in place to allow it, even then, it is anonymised (Utrecht University 2024).
- All uses of donated material require approval from the ethical board for biobanking, which ensures that the use of the donor

tissue complies with the permission given by the patient in their consent form (Utrecht University 2024).

The governance framework proposes that there should be a 'shift [in the] the focus of the consent procedure from the content to the context of future use, and to shift the ethical emphasis from initial consent to ongoing governance obligations, so-called "consent for governance"' (Boers and Bredenoord 2018).

In line with this proposal, FHOB set up a programme where patients and donors were involved to think about fair use, licensing and commercial aspects of organoid research. The consent and privacy processes established place the biobank's own processes, as an infrastructure, as part of the initial consent for patients to ensure the long-term interests of donors and other wider stakeholders involved (Utrecht University 2024).

What is the future trajectory for the oversight mechanism?

As organoid modelling and imaging technologies continue to develop, increasing amounts of data will be generated from specimens held at FHOB, and the research and application of the organoid technology derived from those specimens. The volume and complexity of data may result in unforeseen challenges for researchers and regulators (Rios and Clevers 2018). FHOB must remain responsive to new concerns and build on already profitable relationships with academics and bioethicists.

Patient-derived organoids may blur the line between research and clinical practice, as the organoids are used to first 'test' the efficacy of treatment before being introduced to the patient. Research and clinical practices are traditionally subject to different ethical–legal frameworks. As such, FHOB will need to account for the blurring of distinction between clinical research and practice in patient-derived organoids (de Jongh et al. 2022).

Organoids may be a future source of functional tissue useful for organ transplantation. Three ethical challenges may implicate future operations at FHOB:

- Transplantable organoid trials may not be justifiable due to safety concerns related to the exposure of unnecessary risks of transplanting regenerated organs – an entirely new concept (Hyun et al. 2020).
- It is currently impossible to forward transplantable organoids to the first-in-human phase of trials because current standards require that these trials yield benefits to participants. However, for now they only involve animals and thus do not guarantee the benefit of human participants. There is disagreement in the relevant literature on how to proceed, with some arguing that the traditional sequence of clinical trials is inappropriate for transplantable organoids in humans (Bredenoord et al. 2017), and others arguing that the trial design should include the combination of safety/efficacy outcomes that allow some chance of human participant benefit (Schneemann et al. 2020).
- There are psychological and societal concerns regarding the future success of organoid transplantation. The patient's perception of their composite body may change, and societal views of maladies such as organ failure may be rethought (Boers et al. 2019).

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

- **A reformed consent regime will need to include additional features**, including: project-specific consent procedures that include explicit information about brain organoid research, robust information about the potential for brain organoids (e.g. consciousness) and means of addressing it, and a risk

framework to guide ethical considerations and minimise potential harm (Kyoto University 2024).

- **FHOB's practices of working with academics and bioethicists and bringing together patient and donor values have been integral to its standards on the ethical and transparent use of donated specimens.** These standards are informed by the proposed governance framework developed through collaboration between FHOB and academic institutions.
- **The unpredictable development of organoid research, particularly neural organoid research, requires a consent paradigm that** goes beyond initial broad consent to include continuous oversight, participant engagement, benefit-sharing and privacy (Utrecht University 2024). The proposed governance framework developed in part by FHOB captures this concern by including consent for governance as an ongoing consent obligation.
- **A consent paradigm alone may not be sufficient** for using human tissue in organoid technology given the many pressing ethical concerns of commercial interests in organoid technology, the genetic linkage to donors, and the difficulties in discerning the appropriate consent regime (Boers et al. 2016). In addition to an expanded consent regime, FHOB implements ethical standards of practice, including anonymous donation, unidentifiable coding procedures and required approval from the ethical board for biobanking for any use of the donated material.

Chapter 4
Current human embryology oversight developments

To guide the reader, this chapter is structured as follows.

Box 2. Current human embryology oversight developments: Key takeaways

Oversight mechanisms such as the United Kingdom's Human Fertilisation and Embryology (HFE) Act and the US Dickey-Wicker Amendment were established in the 1990s. These frameworks were not designed for cutting-edge developments such as stem cell-based embryo models. Updating these frameworks to include emerging technologies such as AI in embryo selection and advanced genetic techniques could ensure that regulations keep pace with innovations, while addressing new ethical concerns.

Oversight is primarily seen at the national level, allowing for a legislative landscape tailored to unique cultural and social norms, which appears to be essential for a politically and culturally charged topic such as human embryology. Human embryology research is often shaped by such cultural and social norms, rather than scientific drivers.

Disparate regulations across countries complicate international collaboration. For example, countries subscribing to the Oviedo Convention face strict restrictions on embryo research, while others such as the United States have decentralised and varied oversight across states. However, less formal oversight, in the form of publication requirements, databases and repositories has provided direct support to embryologists for research and collaboration.

A key limitation in current oversight is the inflexibility of hard law mechanisms to adjust to developments in research and public interest, as shown by the calls for a statutory definition of embryos: while such a definition could provide regulatory clarity, it could potentially lead to inflexible oversight that cannot keep up with progress.

Source: RAND Europe analysis.

4.1. Introduction

Human embryology is a sub-field of developmental biology that concerns human development from fertilisation to birth. Advances in embryo research, genomic editing and IVF are exemplified by milestone discoveries such as the development of stem cell-based embryo model systems (SCBEMs) and mitochondrial replacement therapy. Improvements in reproductive health and the potential to correct inherited genetic disorders are being progressed. However, there are challenges and bottlenecks to the further pursuit of the technology, such as dated mechanisms of research oversight, and varied regulations and norms across the globe regarding acceptability and limits of using human embryos in research.

Oversight mechanisms such as the United Kingdom's Human Fertilisation and Embryology (HFE) Act and the US Dickey-Wicker Amendment were established in the 1990s and do not appear to be designed for cutting-edge developments such as SCBEMs. Updating these frameworks to include emerging technologies such as AI in embryo selection for IVF and advanced genetic techniques is critical to ensure that new techniques can be utilised for benefit and deployed in a safe manner. The inflexibility of hard law mechanisms to adjust to developments in research and in changing public interest and appetite for innovative treatments is a significant challenge. International collaboration can also be challenging as the embryology legislative landscape is tailored to unique cultural and social norms, which creates discrepancies in research guidelines and parameters. A detailed assessment of the trends, challenges and opportunities associated with human embryology R&I is provided in the accompanying global technology landscape review report.

The first section of this chapter summarises the strengths and limitations of the emergent human embryology oversight landscape, alongside some key considerations for addressing the current gaps and bottlenecks. The subsequent sections present the evidence underpinning this assessment, outlining key oversight mechanisms across the United Kingdom, United States, EU and international forums, followed by oversight case studies from China, Germany and internationally that provide more detailed examples of how oversight in this area could be progressed.

4.2. Strengths and weaknesses of the human embryology research and innovation oversight landscape

Strengths of human embryology research and innovation oversight

Pioneering oversight mechanisms in human embryology research have paved the way for other biotechnologies. Mechanisms to regulate human embryology have been considered since the 1990s, and many early legislations are still relevant to this day, for example the Warnock review of the ethics of human embryo research, the United Kingdom's Human Fertilisation and Embryology Act of 1990 (section 4.3), and the US Fertility Clinic Success Rate and Certification Act of 1992 (section 4.4). Human embryology oversight has largely been looked upon favourably by subject matter experts; experts involved in the focus group[24] agreed that international organisations have paved the way for other technologies, introducing standards and guidelines for responsible research in human embryology and gene editing. Some national jurisdictions are leading developments in

24 Expert focus group input.

the governance of emerging embryo technologies, providing strong models for other biotechnologies.

For human embryology, oversight is primarily provided at the national level – at times in alignment with international guidance that helps jurisdictions frame their legislations and guidance according to their personal ethical and cultural values. In the EU, oversight focuses on safeguarding human rights, safety and responsible research (e.g. SoHO regulation); however, EU institutions typically do not regulate on ethical standards as this is left up to the individual member states (section 4.5). International forums have safeguarded ethics and human rights within human germline genome editing through rules and guidance (e.g. ISSCR guidelines, National Academies' International Commission on the Clinical Use of Human Germline Genome Editing, Oviedo Convention), allowing nations to implement the guidelines in their own way (section 4.6).

Less formal oversight in the form of publication requirements, databases and repositories has provided direct support to embryologists. These softer mechanisms oversee human embryology research to complement formalised national and international regulations. The journal *Nature*, for example, provides clear guidelines and requirements for human embryology research publications (section 4.6).[25] Equally, databases, repositories and registries are available to complement regulations and guidance, serving as platforms for researchers and clinicians to report on their findings and treatments. For example, the EU hosts the largest register in the world (European IVF-monitoring Consortium Register, section 4.5), while open databases have been suggested as a way to address issues associated with the rise of AI in human embryology (section 4.7, Case Study 3).

Opportunities in human embryology research and innovation oversight

The recent wave of national and international oversight reviews shows the willingness of the sector to address new technologies and renewed ethical debates. Examples of new activities related to the ethical and regulatory scope of human embryology research include the debate on legal definitions of what constitutes a 'human or stem cell derived embryo' (sections 4.2 and 4.6), Germany's revisions to its Embryo Protection Act (section 4.7, Case Study 2), and the emergence of new technologies such as AI algorithms for embryo selection and ranking processes (section 4.6). The rise in ethical complications and incidence has also driven an increase in ethical practices being put in place, notably China's Ethical Measures (section 4.7, Case Study 1), the UK HFEA Code of Practice and the UK Stem Cell Bank (section 4.3).

The research community has broadly welcomed revisions to the 14-day rule, which allows for an extension of research into the undiscovered aspects of human embryo development. The extension of the ISSCR guidelines beyond the 14-day limit opens up research to understand issues such as why embryo implantation fails, which could aid the design of interventions to avoid failure, or help understanding of the early stages of organ development.

Softer oversight mechanisms are being proposed as a flexible route to address new technologies. IVF data faces challenges of aggregation and interoperability, posing hurdles to amassing sufficient quantities of accurate and usable data, threatening the reliability of AI training data. Oversight mechanisms involving working groups, sandboxes, advisory boards and repositories have been proposed to navigate these challenges. For example, a working group

25 One expert noted that compliance with the UK SCBEM Code is likely to be adopted by publications, funders and institutions (expert focus group input).

on AI in human embryology has been suggested by embryologists working in this field as the best way to generate guidelines or a checklist for responsible reporting. It has been noted that such a group, as well as ethical review committees, would need to be disciplinarily diverse and balanced so that any guidelines and/or checklists go beyond the computational requirements of AI systems.

On the IVF repository side, there is an opportunity to implement data solidarity principles to encourage 'bottom-up' oversight, where responsible research that appropriately protects privacy, enables access and promotes inclusion is encouraged. Establishing a data repository would require action and cooperation from governing bodies such as the HFEA in the UK, and from professional and academic bodies.

Embryo banks have also created an opportunity to enhance embryo donation, while regulatory sandboxes enable productive conversations between regulators and scientists in rapidly developing areas. The use of sandboxes was proposed in the HFEA consultation document as a change to the HFE Act (HFEA 2023).

Threats and weaknesses of human embryology research and innovation oversight

The relative inflexibility of hard law mechanisms to adjust to developments in research and public interest is the biggest weakness in current oversight. Experts noted a clear lag between developments in technologies and the review of regulations in response.[26] The added bureaucracy of acts and legislations limits the supply of embryos (an unintended consequence of the UK HFE Act). Softer oversight mechanisms, such as the introduction of ethical review committees, could be a better way to respond to developments in research and public opinion. One stakeholder noted that 'arguments are therefore raised that ethically freighted developments such as the licensing of a new HGGE [human germline genome editing] intervention should be decided by an expert scientific-clinical ethics body operating in a more transparent way than the HFEA's SCAAC.[27] In the realm of research, the SCBEM Code (which does not apply to human embryos but relates to human material which may be of ethical concern) provides for just such a devolvement. Without such mechanisms, conventional statutory frameworks appear unlikely to accommodate emerging technology.'[28]

Such potential overregulation of human embryology could pose a threat to scientific progress. As mentioned, the rigid nature of hard law mechanisms limits the responsiveness of such mechanisms to developments in human embryology research and technologies. With changes to the regulatory landscape stemming from ethical debates, changing public opinion and updates to international guidance, national and subnational oversight needs to be flexible and responsive. In some cases, this might result in more ethical review committees or new social contracts. Regulators must consider appropriate levels and types of oversight, and not necessarily assume that regulation is best.

Movement towards a statutory definition on embryos could provide regulatory clarity, but it may lead to inflexible oversight that cannot keep up with progress. Jurisdictions vary in terms of whether definitions of embryo are enshrined in law or if there are bespoke oversight mechanisms to address various aspects of embryos. Some

26 Expert focus group input.
27 Scientific and Clinical Advances Advisory Committee.
28 Expert focus group input.

experts note that with the emergence of embryo models there needs to be consensus on whether these models are considered under the umbrella of 'embryos'. Loopholes or lack of clarity on embryo definitions could lead to complications in IVF and/or confusion about ethical and regulatory scope regarding SCBEMs and heritable genome editing (if new genetic material is not introduced and it does not aim to change the human genome).

However, other experts argue that the loose definition is actually a strength, and that statutory definitions are not necessary when presented with empirical evidence of cells initiating a pregnancy being constituted as an embryo.[29] In the United Kingdom, the definition of the human embryo in the HFE Act is circular, 'a live human embryo', and classification would be in accordance with expert scientific understanding. By contrast, a rigid statutory definition 'would quickly be dated and [need to be] amended many years after the development in question'.[30] One expert noted that, 'the "adequate protection" requirements for Oviedo-subscribing states only extend to human embryos. If a[n embryo] model is, empirically speaking, a human embryo in the estimation of experts in the field, it will simply be one (under UK law) and regulated accordingly.'[31]

While variations to oversight between jurisdictions are expected, researcher confusion in navigating the landscape is a concern. The non-binding nature of international governance has contributed to the disparate regulatory landscape.[32] For example, legislation in many US states lacks clarity (section 4.4). Similarly, not all nations are signatories of the Oviedo Convention, showing the inherent cultural and political differences between the United Kingdom and the rest of Europe. This divergence is becoming more obvious with the revision of the ISSCR's 14-day rule, the interpretation of the Oviedo Convention's Article 18,[33] and the changing political and ethical standpoints of nations (e.g. Germany's Embryo Act, section 4.5.2).

Natural variation in oversight due to cultural and social norms has been accounted for to some degree in current oversight mechanisms. For example, the European Court of Human Rights anticipated variation under its 'margin of appreciation' doctrine.[34] Given that the international trade of embryos is not commonplace, international oversight variation is not much of a concern. The EU's SoHO regulation has recently allowed trade under common standards and inspections.[35]

However, weaknesses can occur within jurisdictions that lack state-level consensus, leading to oversight gaps and complications with researchers identifying relevant legislation (examples include the disparate US landscape and China's gaps in ethical oversight, sections 4.4 and 4.7, Case Study 1). The lack of international consensus could further complicate scientific research and collaboration efforts.

29 Expert focus group input.

30 Expert focus group input.

31 Expert focus group input.

32 For example, there is often a lack of consensus around the bioethics related to heritable genome editing.

33 Expert focus group input stated, 'Article 18, which provides that where the law allows research on human embryos, it must provide "adequate protection". What this means is elaborated in Germany in [two] significant and highly restrictive Acts: the Embryonenschutzgesetz and the Stammzellgesetz.'

34 Expert focus group input. Margin of appreciation is an international legal principle that allows countries to have different interpretations of certain issues and to make their own decisions on how to apply rights in their country.

35 Expert focus group input.

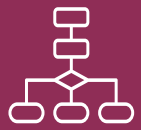
Safeguarding privacy in an increasingly digital space is a priority. Many issues beyond embryo definitions concern the impact of data sharing and governance. As IVF data concern personhood, infertility and family life, and are therefore socially, emotionally and politically charged, their governance is often subject to stronger privacy protections compared to other personal or health data, limiting potential for data linkage and reuse in research. For practices around data use and consent in assisted reproductive technologies (ART) and IVF, consent often does not include permissions for data reuse, which this study identifies as an oversight gap. The concern around privacy and data naturally extends to the use of AI in human embryology, with the training of AI/ML models that require access to diverse datasets increasing risks to privacy and safety (section 4.7, Case Study 3). However, it is unclear what has happened since the 2022 AI Fertility World Conference. Although there are guidelines and tools to avoid bias, ensure transparency and safeguard privacy in AI/human embryology research, they are not widespread or common practice.

New threats to equitable and accessible research are evolving alongside research developments. Historically, there has been a concern about the risk of misuse of human embryology technologies (e.g. CRISPR-Cas9)[36] for selective gene editing. An added complication is that there is no consensus over what constitutes misuse, and varying public opinion and oversight could confuse this further. However, with new technologies being developed, the risk to equity and accessibility of research has become a primary concern. In ART, for example, there is a question about how to disseminate these technologies to all who need them.

36 Clustered regularly interspaced palindromic repeats (CRISPR-Cas9) is a gene-editing technology that uses RNA (ribonucleic acid) as a guide to make precise edits in the genome. It is cheaper, faster and more accurate than previously discovered tools.

Given the current challenges and bottlenecks in human embryo research, this study proposes the following **key considerations** to be taken forward by funders and policymakers working in this sector:

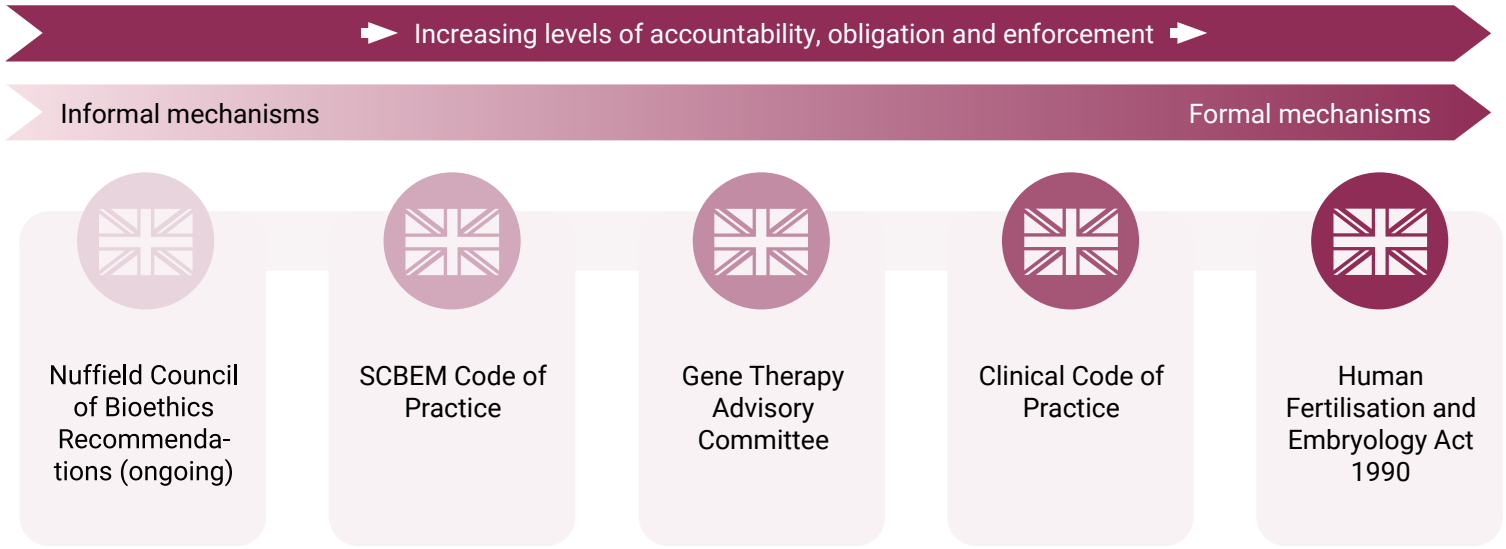
Given the vast variation in human embryology research oversight between jurisdictions, alongside international oversight by organisations such as ISSCR, confusion among researchers is a key concern. Embryologists and small and medium-sized enterprises (SMEs) collaborating/operating internationally need to have clearer pathways to progress research and receive support in navigating disparate mechanisms that their work may encounter.



The use of digitised datasets and ML algorithms for embryo ranking and selection illustrate the increasingly digital space that human embryology research occupies. In addition to the focus on clarifying legal definitions and ethical oversight in human embryology research, safeguarding privacy and generating transparency in algorithmic decision making should be a priority.

4.3. Oversight of human embryology in the United Kingdom

Figure 9. Illustrative oversight examples of human embryology in the United Kingdom



Source: RAND Europe analysis.

Current oversight mechanisms in the United Kingdom

- The **Human Fertilisation and Embryology (HFE) Act** of 1990 provides oversight of assisted reproduction treatments such as IVF and mitochondrial replacement techniques (also called mitochondrial donation), as well as research that includes the use of human embryos (UK Government 2023a; UK Government 2014). The HFEA has conducted a consultation on the act with a view to updating it in line with a variety of technological advancements, including new genome editing techniques. The HFEA is responsible for enforcing the act and for inspecting and licensing all UK fertility clinics and human embryo research centres, which must abide by a **Code of Practice**[37] to receive a licence (Cambridge Reproduction 2024). The act bans heritable human genome editing at present.
- The HTA regulates the storage and use of human tissues in a variety of settings, including post-mortem, education and research. It also oversees which tissues and cells may be

37 The Code of Practice is a set of standards detailing clinical practice and consent procedures amongst other aspects of fertility treatment provision and research.

transplanted to a human (EuroStemCell 2024). The functions of the HTA are covered by four pieces of legislation:

- **The Human Tissue Act 2004** (UK Government 2004).
- **Human Tissue (Quality and Safety for Human Application) Regulations 2007.**
- **Quality and Safety of Organs Intended for Transplantation Regulations 2012, amended in 2019 (EU Exit Regulations).**
- **The Human Transplantation (Wales) Act 2013.**

The first two acts listed above are particularly relevant to human embryology given that any clinical applications and the use of embryo-derived cells and tissues requires inspection by the HTA. The acts also specify the consent regime for the use of any tissue and cells derived from individuals.

- The UK Stem Cell Bank steering committee manages the ethical approvals and quality control of human embryonic stem cell (hESC) lines for research (as mentioned in the context of organoids research).
- The **Medicines for Human Use (Clinical Trials) Regulations 2004,** overseen by the MHRA, applies to clinical trials to ensure the efficiency and safety of medicines and therapies for use in humans. This includes stem cell/embryo tissue derived therapies and treatments (UKRI 2023).
- The Gene Therapy Advisory Committee is responsible **for reviewing all proposals for research that use human stem cell lines** in a clinical setting.

Emerging oversight mechanisms in the United Kingdom

- Recent advancements such as SCBEMs are not included in the legal definition of an embryo in many countries, with work underway by different countries to address gaps in oversight regarding the use and modification of SCBEMs in a laboratory setting. The United Kingdom is guiding developments in SCBEM governance with the Governance of Stem Cell-Based Embryo Models (G-SCBEM) project, which is a strategic initiative within the University of Cambridge in partnership with the Progress Educational Trust to establish the first governance framework for SCBEM research (University of Cambridge 2023). The project has examined the challenges and opportunities in this field and will set the foundations for an ongoing dialogue with the public and various stakeholders.[38] In July 2024, the **Code of Practice for the Generation and Use of Human Stem Cell-Based Embryo Models** was published to address oversight uncertainties, informed by the ISSCR guidelines (Cambridge Reproduction. 2024). The code proposes specialised oversight for SCBEMs, with each SCBEM culture to be reviewed rather than having a 'fixed [term] limit for culture', and research on human SCBEMs to proceed only under a number of conditions (e.g. consent, research benefits, appropriate justification and subject to review by the SCBEM Oversight Committee). The code also outlines standards in research and data collection.
- The Nuffield Council on Bioethics launched a project in 2024 to **explore the ethical and regulatory issues** raised by research using SCBEMs. The project will provide recommendations before the end of 2024 (Nuffield Council on Bioethics 2024b). The United Kingdom hosted the Third International Summit on Human Genome Editing

38 In April 2024, the project conducted a public dialogue on the governance of research that employs SCBEMs. The aim was to inform the Code of Practice being produced by the G-SCBEM project and to ensure that researchers' work maintains and promotes public trust.

in 2023.[39] The summit touched on research and **regulation related to human germline genome editing;** however, the primary focus was on adult genome editing therapies. A consensus emerged that further research and socio-political consultations are needed before new genetic technologies can safely be used in human embryos for the purpose of IVF/reproduction. The organising committee called for a continuing dialogue and international collaboration regarding the governance and regulation of heritable human genome editing technologies. Although there are major efforts to modernise the HFE Act, it is unclear whether any developments will occur on heritable genome editing as part of the HFEA amendments in development (HFEA 2023).

Other mechanisms of relevance in the United Kingdom

- In addition to the HFEA implemented act, the United Kingdom is bound by international obligations regarding human germline genome editing, such as the **Universal Declaration on Bioethics and Human Rights**, the **Universal Declaration on the Human Genome and Human Rights, and the International Covenant on Economic, Social and Cultural Rights**, some of which have been mentioned in the context of organoid research.
- The **Biotechnology Directive and the UK Patent Act 1990** are also relevant as they denote that the products, direct or otherwise, of human embryos are excluded from patentability.
- Embryologists have called for human dignity and rights to be prioritised **in the oversight of AI-assisted human embryology technologies**, such as when used to select IVF embryos. This is particularly relevant to data privacy and protection, where models and research should be operated with maximum transparency. Researchers have noted that international consensus on research guidelines and best practices is key in this regard (Medenica et al. 2022). Proceedings from the first **AI Fertility World Conference** in 2022 led to the creation of the International AI Fertility Society, which includes subcommittees addressing regulation, ethics and transparency, and responsible innovation (AI Fertility Society 2024).
- To support IVF research, including the development of AI models, some academics and clinicians are calling for an **open access and comprehensive data repository of embryo images** and data (Afnan et al. 2021). Such a repository would enable data aggregation at the scale necessary to develop AI models that are trained and validated on sufficiently diverse data. Establishing a data repository of this nature would require action and cooperation from governing bodies such as the HFEA in the United Kingdom and from professional and academic bodies such as the Academy of Clinical Embryologists (Afnan et al. 2022).

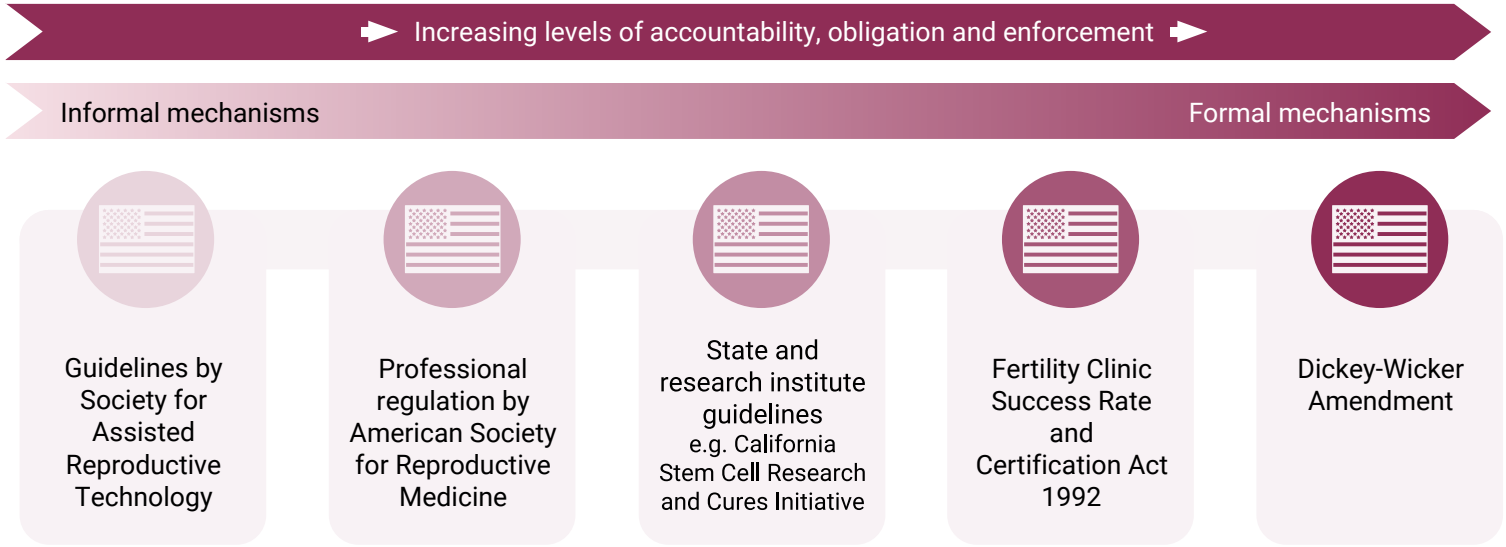
Uncertainties associated with human embryology oversight in the United Kingdom

- While current oversight mechanisms are fairly comprehensive, there are gaps and challenges regarding the burden and cost of compliance across multiple regulatory authorities (UK Government 2023a).
- Oversight gaps and uncertainties have also been exposed in the limited ability of current mechanisms to incorporate developments from emerging technologies, such as the creation of SCBEMs. This has created a need to revisit existing mechanisms such as the 14-day embryo rule and the legal definition of terms such as 'human embryo'. There is also a need to create linguistic and functional clarity on terms and concepts of what constitutes a stem cell derived embryo.

39 The summit took place at the Francis Crick Institute in London and was organised by the Royal Society, the UK Academy of Medical Sciences, the US National Academies of Sciences and Medicine, and the World Academy of Sciences.

4.4. Oversight of human embryology in the United States

Figure 10. Illustrative oversight examples of human embryology in the United States



Source: RAND Europe analysis.

Current oversight mechanisms in the United States

- The **Dickey-Wicker Amendment**, passed in 1996 by the US Congress, bans the use of federal funds on human embryo research (Matthews and Yang 2019). However, the oversight of human embryology research is generally decentralised in the United States.
- At the federal level, a combination of acts and organisations are involved in the oversight of ART. The Centers for Disease Control and Prevention (CDC), under the **Fertility Clinic Success Rate and Certification Act 1992,** collects and publishes data on ART procedures and their outcomes. The FDA, under a series of acts, approves drugs and devices used in ART and screens any reproductive tissues used in procedures. The Centers for Medicare and Medicaid Services (CMS) is responsible for implementing the **Clinical Laboratory Improvement Act 1988** to ensure the quality of laboratory testing.
- There is also **professional self-regulation,** with professional societies such as the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

having their own ethical and practice guidelines and membership requirements. Medical certifications are also provided by the American Board of Obstetrics and Gynecology or the American Board of Urology, with medical professionals needing to be periodically examined to retain their certification (ASRM 2021). The regulation of medical providers is primarily undertaken through state laws.

- There are several state laws for regulating human embryo research, with substantial differences. Legislation in many states lacks clarity and seems to allow the use of human embryo research with embryos not used for IVF. Overall, there is inconsistency between state laws, and it is challenging to understand what is allowed in research (Matthews and Yang 2019). Differences across states include:
  - » In six states it is prohibited to conduct embryo research; however, the state laws allows embryo-derived stem cell research and embryoid research.
  - » Twenty-one states (and the District of Columbia) do not have any policies on human embryo research and rely on federal policies, which means that embryo research is forbidden by default.
  - » Eighteen states allow embryo research, and California, Connecticut, New Hampshire, New Jersey and New York have specific permissive laws on human embryo and hESC research. For example, the **New York State Stem Cell Science** (NYSTEM) programme within the state's Department of Health included the 14-day limit in the consent forms used for the donation of embryos for research (Matthews and Yang 2019). The programme was defunded in 2022 (Matthews and Morali 2022). California organised the **California Stem Cell Research and Cures Initiative**[40] in 2004, which was a ballot initiative through which USD 3 billion was invested in stem cell research, overseen by California's Stem Cell Agency and the California Institute for Regenerative Medicine (CIRM) (Acosta and Golub 2016). The CIRM have released **Guidelines for Human Stem Cell Research** that include a 12-day limit on human embryo research, excluding frozen storage time (Matthews and Morali 2022).
  - » In Connecticut, stem cell research and experimentation on human embryos receives state funding. Connecticut's **Stem Cell Research Program** was established in 2005 and allows stem cell research, although forbids the cloning of humans (Connecticut State 2024). The Stem Cell Research Oversight Committee's (SCRO) role is to ensure that hESC and iPSC[41] research is well justified (University of Connecticut 2024). New Jersey specifically permits embryo research through its legislation,[42] allowing 'research involving the derivation and use of human embryonic stem cells, human embryonic germ cells and human adult stem cells, including somatic cell nuclear transplantation' (Matthews and Morali 2022).
- Some research institutions have their own laws. For example, although the state of Washington does not have a human embryo research policy, the University of Washington **bans 'in vitro**

40 Known as 'Prop 71' (Proposition 71), the identification on the ballot in 2004.

41 iPSC: human induced pluripotent stem cell.

42 Statute: NJ Rev. Stat. § 26:2Z-2, § 2C:11A-1 (2003).

culture of an intact human embryo for more than 12 days of development or until formation of the primitive streak, whichever occurs first' (Matthews and Yang 2019).

- Private companies funding embryo research also have different policies. For example, the Juvenile Diabetes Research Foundation follows **the 14-day-limit,** while other foundations that fund human embryo or hESC research, such as the New York Stem Cell Foundation, do not publicly outline a policy (Matthews and Yang 2019).

Emerging oversight mechanisms in the United States

- Changes and developments in oversight mechanisms following the ISSCR proposal to abolish the 14-day rule and the development of SCBEMs will likely have a variable influence on state laws given the diversity and nuances of oversight at the state level. At present, there are no emerging oversight mechanisms being proposed or discussed at the federal level.
- The degree of state-level challenges and changes is exemplified in the case of Alabama, where in 2023 three couples filed a death suit against IVF centres that accidentally destroyed their IVF embryos. The Alabama Supreme Court ruled that these embryos are 'children' and that the death suit can be pursued under the state's **Wrongful Death of a Minor Act.** This brought IVF to a halt in the state; however, in March 2024 a new bill was passed extending criminal and civil immunity to IVF clinics.

Other mechanisms of relevance in the United States

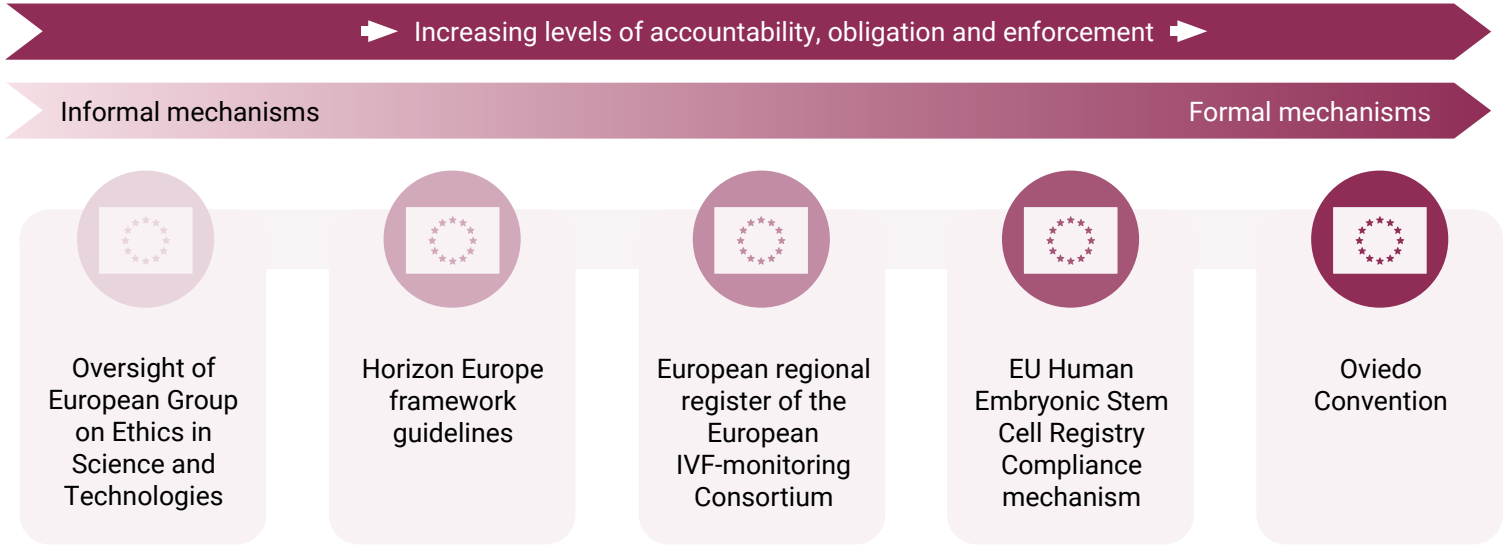
- The US Supreme Court's reversal of **Roe v. Wade** in 2022 removed the constitutional right to an abortion, passing authority to the states to determine abortion rights. This has implications for human embryology clinical research, such as the use of embryos in research.

Uncertainties associated with human embryology oversight in the United States

- Given that federal funding is not used for human embryo research, there are no associated oversight mechanisms, making the landscape of oversight extremely challenging and varied across the country. This creates **research collaboration barriers,** as well as **inequity in access to ART.**
- An analysis of all US states found that most laws did not directly discuss stem cell research as they were created to address matters such as abortion and reproductive cloning. **Definitions may vary substantially and thus researchers need to carefully consider state laws and local politics** to engage in embryo and stem cell research (Matthews and Morali 2022).
- **Misinterpretation and lack of consensus in terminology** have caused issues in other applications of human embryology in the United States, contributing to the controversial ban of mitochondrial replacement therapy, a form of IVF. While the treatment could have significant benefits to affected couples and to the future economy, it is considered a form of heritable genetic modification in the United States, and therefore banned (Pompei and Pompei 2019).

4.5. Oversight of human embryology in the European Union

Figure 11. Illustrative oversight examples of human embryology in the European Union



Source: RAND Europe analysis.

Current oversight mechanisms in the European Union

- The 1997 **Oviedo Convention** concerns bioethics and bans heritable human genome editing and the creation of embryos for research. It is the only legally binding instrument to embed human rights into biomedicine (Council of Europe 2024a; Andorno 2005). Article 13 of the convention states that 'an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants' (Council of Europe 2024a). It also states that modification of (for example) the embryo's genome for the benefit of a person born as a result must not be undertaken for the sake of descendants.
- In 2003, the EU proposed **ethical guidelines on funding EU research,** limiting **hESC research** to fighting major diseases. Proposals must pass stringent peer and ethical review procedures and will only be funded if the research has particular objectives and there is no other alternative. These guidelines

still exist in the current Horizon Europe framework programme (European Union 2021b). Compliance with ethical standards is verified in part by the **EU Human Embryonic Stem Cell Registry** (hPSC^{reg}, established in 2007), which stores scientific and ethical data on generated hPSC lines (Seltmann et al. 2016; Isasi et al. 2022). The **European Bank for Induced Pluripotent Stem Cells** (established in 2014), a similar repository for iPSC lines for international distribution, reviews related ethics.

- Oversight of ART in the EU is carried out through the **European regional register** of the European IVF-monitoring Consortium (EIM, established in 1997) and the European Society of Human Reproduction and Human Embryology (established in 1985) (De Geyter et al. 2020). As of 2020, the register comprised ART data from 40 EU countries, the largest register in the world. Data spans a wide range of technologies, from IVF to frozen embryo transfer and intrauterine insemination (IUI); however, reporting is not a legal requirement across members (Calhaz-Jorge et al. 2020; Vidalis 2022). More specific technologies such as mitochondrial replacement therapies are typically regulated at the national level (Johnson and Bowman 2023).
- Other EU-level oversight actors include the **European Society of Human Genetics** (ESHG), the **EMA**, and the **European Group on Ethics in Science and Technologies** (EGE) (Mahalatchimy et al. 2021).

Emerging oversight mechanisms in the European Union

- Published in July 2024, and superseding the EU Tissue and Cells Directive, the European Council adopted the new regulation on standard quality and safety procedures for **substances of human origin (SoHO)** intended for human application, medical and donation purposes (Elias et al. 2024). The regulation applies to embryos and embryo stem cells, under 'reproductive SoHO' (European Union 2024a; 2024b); however, it does not specifically cover donation for research purposes.

Other mechanisms of relevance

- In 2014, the EU banned heritable genome editing[43] in a clinical setting through the **EU Clinical Trials Regulation**; however, this does not extend to heritable genome editing in research (European Commission 2014).
- The 1998 amendment to the **Convention for the Protection of Human Rights and Dignity of the Human Being** added a protocol prohibiting the cloning of human beings (Council of Europe 1998).
- The **EU Legal Protection of Biotechnological Inventions Directive** (1998) bans the patenting of innovations that use 'human embryos for industrial or commercial purposes' (European Union 1998).
- The **European Health Data Space** was established in April 2024 to support the safety and quality of **SoHO**. It includes EU-supported national-level oversight of health data (e.g. training and IT) and allows patients access to their health data throughout the EU (European Union 2024a). As mentioned in Chapter 3 it also supports access to data for organoid validation.

43 Heritable genome editing forms a subset of germline gene editing.

Uncertainties associated with human embryology oversight in the European Union

- **Position of human embryology research within the scope of existing conventions and regulations:** There is a lack of clarity around whether all heritable genome editing research is banned under the Oviedo Convention, and whether *in vitro* research is allowed (Global Gene Editing Regulation Tracker 2024). Some scientists argue that heritable modification should be allowed if new genetic material is not introduced and if the research does not aim to change the human genome, and others argue that the ban is broad enough to encompass intentional modifications (Baylis and Ikemoto 2017; Vidalis 2022). Although the 2014 EU Clinical Trials Regulation banned germline gene editing in a clinical setting, it does not cover germline gene editing in research.
- **Unclear taxonomy regarding new developments and embryo status:** Recent advancements such as SCBEMs are not included in the legal definition of an embryo for many countries, and thus are not protected by embryo research regulations (Ball 2023). It is anticipated that embryo models, specifically SCBEMs, may reach a point of maturity where ethical distinctions with an embryo no longer apply, signalling a new frontier in the study of human embryology (Ball 2023).
- **Consensus between international, EU and national-level oversight:** The Oviedo Convention's impact on national laws varies across countries, with only 37 countries in the world having signed the convention (Global Gene Editing Regulation Tracker 2024). The Oviedo Convention's ban on embryo creation for research is in contrast to international ISSCR guidelines,[44] which permit embryo creation for research but limit timeframes for embryo development to 14 days (Isasi et al. 2022). This has led to diverging governance mechanisms in the EU and the reticence of the UK to sign up.
- **Ethics:** Human embryology converges human dignity, human rights, safety and other ethical issues. EU oversight focuses on safeguarding human rights, safety and responsible research, but member states rather than EU institutions typically regulate on ethical standards. For example, the Clinical Trials Regulation mandates ethical review at the member state level, which states will carry out according to national law (Mahalatchimy et al. 2021; Mahalatchimy 2010; European Commission 2014).[45]

44 For more information on international oversight, including discussion of the ISSCR guidelines, please see the section on international oversight of human embryology (section 4.6).

45 While formal ethical oversight usually falls under the responsibility of member states, EU research funding has stipulations to ensure that ethics are considered within EU-level research – see section 4.5.

4.6. Oversight of human embryology in international forums

Figure 12. Illustrative oversight examples of human embryology in international forums

Source: RAND Europe analysis.

Current oversight mechanisms in international forums

- **ISSCR Guidelines for Stem Cell Research and Clinical Translation.** The ISSCR (established in 2002) published guidelines on standards for stem cell research in 2006 (Lovell-Badge et al. 2021). In 2021, the ISSCR updated its guidelines to no longer limit the growth of human embryos in a research setting to 14 days. The guidelines propose that this limit could be extended or abolished to allow research on some crucial stages of embryo development, which may increase knowledge of the main causes of miscarriages and birth defects (Foreman et al. 2023). The update also launched the ISSCR Standards Initiative, outlining core principles and standards in human embryology research (ISSCR 2024). The ISSCR guidelines aim to harmonise the oversight and ethical conduct of human embryo research globally. Although not legally binding regulations, they have had implications on national policies and legislation (Matthews and Morali 2022; Xue and Shang 2022). The ISSCR intends to revisit its guidelines, with new updates expected in 2025.

- WHO's **Human Genome Editing: A Framework for Governance.** In 2021, WHO released a governance framework to address the ethical, social, legal and scientific issues associated with human genome editing. The framework touches upon heritable genome editing in the context of human embryology. It recommends establishing human genome editing registries to facilitate ethics reviews for clinical trials, and proposes that the Health Ethics and Governance Unit in the WHO's Science Division produces a set of ethical values and principles (WHO 2021a). Alongside the framework, WHO published a position paper (summary of findings) and recommendations[46] outlining the values and principles (Mills 2021; WHO 2021b).
- **International Commission on the Clinical Use of Human Germline Genome Editing**. In 2018, the US National Academy of Medicine, UK Royal Society, and many other academies of medicine and sciences from around the world convened an International Commission on the Clinical Use of Human Germline Genome Editing to develop frameworks and guidelines to help scientists and clinicians assess potential clinical use cases of heritable genome editing. The commission published a report in 2020 which highlighted pathways from research to the clinic, and specified stringent preclinical and clinical protocols for safety (National Academies of Sciences, Engineering, and Medicine 2020).
- **Nature publication policy.** In May 2018, the journal *Nature* released a new publication policy for human embryo and hESC research publications (Nature 2018). The policy requires papers on these subjects to provide an accompanying ethics statement highlighting ethical oversight and the consent process used in the work. For papers that could be perceived as controversial, the journal ensures that it is reviewed by an independent ethicist, in addition to the traditional peer review process.
- **ICMART[47] and WHO Revised Glossary on ART Terminology, 2009**. Following consultation with a multidisciplinary team, this glossary was expanded to 87 terms that include definitions of clinical and laboratory procedures, and outcome measures. The updated glossary standardises communication and understanding across regions and areas of expertise to facilitate data collection and monitoring (Zegers-Hochschild et al. 2009).
- **AI/data tools.** For AI and data platforms as related to human embryology, guidelines and tools to avoid bias and ensure transparency in research exist, but they are not widespread or common practice. Some examples include the **PROBAST tool**, which assesses the risk of bias (Moons et al. 2019), and the **TRIPOD tool**, which provides guidelines for transparent reporting (Collins et al. 2015).

Emerging oversight mechanisms in international forums

- The **2021 ISSCR guidelines update** classified SCBEMs as 'integrated' or 'non-integrated',[48] each requiring differing oversight processes, with integrated SCBEMs subject to additional ethical and scientific review due to their potential to form an entire embryo (Bhaskaran and Mutebi 2024). However, this classification has been met with criticism by some scientists

46 These outputs followed the 2019 reports on the first two committee meetings (WHO 2019b; 2019c).

47 ICMART: International Committee for Monitoring Assisted Reproductive Technology.

48 Integrated SCBEMs contain all components of a future embryo, whereas non-integrated SCBEMs only contain partial building blocks to study some aspects of embryo development.

given the overlap seen across the classifications in a research setting.

- Participants at the 2023 **Third International Summit on Human Genome Editing** called for continuing dialogue and international collaboration regarding the governance and regulation of heritable human genome editing technologies (Royal Society 2024).
- There are limited oversight developments regarding AI-enabled human embryology research and data platforms at the international level, with efforts focused on AI transparency and data solidarity in relation to applications such as AI-driven embryo selection for IVF. Due to the complex ethical implications of AI-assisted IVF, there has been an upsurge in **researchers calling for clarity and standards in research findings reported** (Curchoe et al. 2020). Such standards should consider issues including the validation and verification of databases used, and sample sizes (Salih et al. 2023).
- A **classification system for embryo selection** was proposed in early 2024 to provide clarity and consistency in the selection process to ensure 'subjectivity, explainability, and interpretability' (Lee et al. 2024). In 2023, a study ranking embryo quality against eight different algorithms was published, bringing together embryologists to agree on the parameters considered when determining embryo quality between different AI algorithms (Zaninovic and Rosenwaks 2020; Cimadomo et al. 2022). This work was led by researchers across Argentina, Denmark, Italy, Spain, Sweden, the United Kingdom and the United States.
- To support IVF research, including the development of AI models, there are **growing calls for an open access and comprehensive data repository of embryo images and data** (Afnan et al. 2022). Such a repository would enable data aggregation at the scale necessary to develop AI models that are trained and validated on sufficiently diverse data. To this end, data solidarity[49] principles have been suggested as a means of governance (Afnan et al. 2022).

Other mechanisms of relevance in international forums

Other mechanisms of relevance in international forums include:

- International declarations that impact the ethics (e.g. human dignity) associated with human embryology research include the 2005 **UNESCO Universal Declaration on Bioethics and Human Rights**, the 2014 **UNESCO International Declaration on Human Genetic Data**, the 1997 **Universal Declaration on the Human Genome and Human Rights**, and the 2005 **UN Declaration on Cloning** (UNESCO 2005; Mayor 2005; Yotova 2020).

Uncertainties associated with human embryology oversight in international forums

Uncertainties associated with human embryology oversight in international forums include:

- **Ethics.** In 2019, WHO released a statement recommending halting clinical applications of human germline genome editing until appropriate governance is in place due to technical and ethical concerns (WHO 2019a). The technical concerns cited

49 Data solidarity refers to 'an approach to the collection, use, and sharing of health data and data for health that safeguards individual human rights while building a culture of data justice and equity, and ensuring that the value of data is harnessed for public good' (Kickbusch et al. 2021).

related to the lack of precision of gene editing and the uncertainty of long-term effects; the ethical concerns related to changes to future generations without consent and the exacerbation of inequities if only some could access the technology. These concerns were echoed at the 2023 Third International Summit on Human Genome Editing, which advised that heritable human genome editing should be banned until it fulfils appropriate standards for safety and efficacy (Royal Society 2023).

- **Consensus.** The ISSCR guidelines do not represent comprehensive global consensus, with many varying views and a disparate national policy landscape (e.g. Switzerland has a 7-day limit and the French senate has proposed a bill for a 21-day limit). This lack of international consensus could complicate scientific research and collaboration efforts (Matthews et al. 2021). Some researchers note that as the guidelines focus on technology risks, they fail to appreciate the potential benefits to individuals and their rights (Thaldar and Shozi 2023). Experts have noted that stakeholder engagement and international discussions, as well as engagement with scientists, are needed to reach consensus on changes to the 14-day rule, taking into account different national, cultural and religious values (Hyun et al. 2016).
- **Embryo definition.** The legal definition of an embryo varies across the world, and many countries do not define embryos within their laws and guidelines (Xue and Shang 2022; Matthews and Morali 2020). This has created uncertainties when considering embryo models, which do not fall under the legal definitions or legal protections for embryos (Rivron et al. 2023; Ball 2023). Some argue that it could be beneficial to not have a legally adopted definition as this could make it challenging to be agile and adaptive in the face of new technologies.

4.7. Case studies of human embryology oversight mechanisms

Case study 1:
China – A legal mechanism for ensuring compliance with the 14-day rule

Table 4. China's legislative and punitive measures on the 14-day rule

Technology area:	Human embryology
Oversight example:	Legislative and punitive measures on the 14-day rule
Type(s) of oversight mechanism(s):	Legal mechanisms
Jurisdiction:	China
Timescale:	2023 – present

Why is the oversight required?

Prior to 2018, oversight of human embryology and associated technologies (including ART) was conducted through select mechanisms in China. These included:

- 2001 Measures of Administration of Assisted Human Reproduction Technology and associated Technical Standards of the Assistant Human Reproductive Technology (2001 ART Measures). Criminal penalties could be applied to cases that violated the measures and guidelines, with fines reaching CN¥30,000 (Zhang 2018).

- 2003 Guidelines for the Ethical Principles in Human Embryonic Stem Cell Research (Ethical Guidelines).
- 2016 Measures for Ethical Review of Biomedical Research Involving Human Subjects (2016 Ethical Review Measures).

Chinese stem cell research was regulated through the Ministry of Science and Technology's (MoST) 2003 Ethical Guidelines, and the National Health and Family Planning Commission's (NHC) 2016 Ethical Review Measures (Peng et al. 2020; Chen et al. 2022). The 2003 Ethical Guidelines applied to stem cells originating from the human embryo or germ cells, or from the transplant of a nucleus. Article 4 of the guidelines stipulated that any research on reproductive cloning was banned and that hESCs could not be created for research – although sourcing cells from surplus embryos or donated germ cells was allowed (Law of China 2003; Peng et al. 2020). The 2016 Ethical Review Measures complemented the 2003 Ethical Guidelines, but were limited to medical institutions and hospitals. They considered WHO's International Ethical Guidelines for Health-related Research Involving Humans and the World Medical Association's (WMA) Declaration of Helsinki.

Changes to oversight took place following events in 2018, when Chinese researcher He Jianku announced that he had successfully modified the genes of twin girls using CRISPR-Cas9. This led to an outcry from the scientific community, who voiced concerns about the ethical implications of such research given the unknown long-term impacts of gene modification. The 'CRISPR babies incident' exposed a number of gaps in oversight in China: experts across scientific and sociological research noted legislation was often outdated, and China suffered a disparate regulatory landscape, including 'blurred jurisdictional boundaries', where oversight differed between regions and existing regulations and guidelines were not a priority in the legal hierarchy (Song and Isasi 2020; Fabbri et al. 2023; Peng, et al. 2020).

This led to weak monitoring mechanisms and difficulties in identifying accountability between jurisdictions and regulatory agencies (Song and Isasi 2020). The incident also revealed loopholes in existing regulations, as Jianku was able to register the clinical trial retrospectively and did not disclose all of the details to his staff (Kuo 2018).

What is the oversight mechanism proposed?

Following the incident, China's National Health Commission released the **Measures for Ethical Review of Life Sciences and Medical Research Involving Humans** (referred to hereafter as the 'Measures') on 27 February 2023 – an update to the 2016 Ethical Review Measures (Government of China 2023a).

Four government agencies – MoST, National Health Commission, Ministry of Education, and the State Administration of Traditional Chinese Medicine – in consultation with a number of experts were involved in developing the Measures (Government of China 2023b). In 2020, the National Science and Technology Ethics Committee was established to implement ethical governance of the Measures (Zhang and Lei 2023).

Key aspects of the Measures include:

- **Extended scope and coverage.** The updated Measures apply to scientific activities on research participants, including human subjects themselves or human cells, personal data and behaviours (Government of China 2023b; Zhang and Lei 2023). The update notably extended the range of organisations covered under the Measures to include those involve d in clinical human embryology research, now applying to medical institutions, scientific research institutions and universities conducting scientific research (the latter two were not covered in the 2016 Ethical Review Measures).

- **New ethical review requirements.** The Measures stipulate that institutions must establish fully resourced ethics review committees or ensure that an external (regional) review committee is in place to oversee the research, which is subject to annual review (Article 25). Article 21 specifies that the committees must ensure research integrity, fairness and justice through a review of the social value of the research, aligning with existing regulations; rights, privacy and informed consent[50] protocols in place; risk–benefit analysis; and the appropriateness of the scientific protocol and research methods. Institutions must also file all information in the National Medical Research Registration and Filing Information System 'within three months of the establishment of the Ethics Review Committee' (Article 13).
- **Penalties for non-compliance.** While specific sanctions have not been introduced in the Measures, Articles 44–46 note that sanctions for failure to comply with the Measures will occur in accordance with regional or national legislation (Government of China 2023a). Legislation has been heavily updated since 2018, and the Measures now accompany a series of regulatory reforms (a Criminal Code and Patent Law) and new regulations (a Civil Code and Biosecurity Law). A number of oversight committees have also been established (Normile 2023), and in 2020 and 2021, civil and criminal penalties were introduced to ban human germline editing.

What is the future trajectory for the oversight mechanism?

Enforcement of the Measures still has several challenges ahead. The success of the Measures relies on the implementation of the ethical review committees and the enforcement of penalties, which many have remarked is lacking in the 2023 Measures (Wu and Kong 2023; Zhang and Lei 2023; Wang et al. 2023). Wu and Kong (2023) have noted that the current ethics review committees are 'executed with low efficiency and quality'. Without infrastructure or resources in place, there are concerns around the ability of institutions with few resources to comply, which may lead to worsened inequalities and disparities between institutions that could lead to some becoming incentivised to circumvent the Measures, carrying out research without complying with reporting and ethical review requirements.[51] The lack of cohesion between national and subnational/transnational institutes makes enforcement challenging (Wang et al. 2023; Liu et al. 2024).

While stakeholders have asked for a detailed implementation plan with clear civil penalties, some propose that education and publicity could also be used to enforce the Measures (Liu et al. 2024).[52] If the public are aware of their rights to informed consent, this could put pressure on research organisations to comply with this component of the Measures. In this way, the public and scientific community can hold human embryology research and researchers to account. Li et al. (2004) propose enabling this through a public reporting platform.

Involvement of the public and scientific community is also needed to inform future updates to the Measures and avoid loopholes. Although the Measures were updated in consultation with embryologists, some argue that expert input was not heeded fully, meaning that several gaps in oversight remain (Lloyd et al. 2023). This is particularly relevant regarding the scope of the previous 2003 Ethical Guidelines and 2016 Ethical Review Measures, which

50 Chapter IV (Articles 33 to 39).
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only applied to research institutions. While the 2023 Measures extend the scope of organisations covered, private entities, industry and companies are still excluded in an effort to continue promoting innovation within China and avoid 'red tape' (Gang and Peng 2023).[53] This is particularly concerning given the increase in academia–business collaborations being encouraged nationally in China, and therefore remains a potential loophole that could be exploited in future (Zhang and Lei 2023). In response, experts have noted that the extended scope of the 2023 Measures is not enough (Normile 2023; Lloyd at al. 2023; Gang and Peng 2023), with some saying that it renders the Measures' aims moot and leaves China open to a new scandal.[54]

For example, in a 2023 update following the release of the Measures, MoST solicited feedback from the public and experts on the *Trial Measures for Ethical Review of Science and Technology* (Interesse 2023). The activities covered by this latest set of Measures include those relating to human embryos and genes, as well as ethical review processes for science and technology research more broadly.[55] The updated Measures came into effect in October 2023 and now extend to private organisations (Gu et al. 2023).

The Measures may need further amendments or clarifications given upcoming changes to international guidance. With any revisions regarding extending the ISSCR's 14-day rule, some researchers argue that 'to secure a higher level of regulation of scientific research, the formulation of clear rules comparable to those supplied by the NHC may be expanded and elaborated further if the 14-day rules were to be extended' (Xue and Shang 2022). Such rules could be similar to the criteria already within the Measures, which state what kinds of research are permissible. While the Measures are at a lower priority level than formal legislation within the Chinese regulatory system, existing 'laws authorized the use of ethical principles as a basis for [legal] judgments…fostering a conducive environment for future modifications to the 14-day rule' (Xue and Shang 2022).

Existing and new oversight mechanisms could complement the Measures, closing loopholes that would perpetuate if the Measures were implemented in isolation. One source indicates that regulations are already in place that could mitigate this risk, such as stipulations in the Measures (regarding exemptions for research that does not harm humans or involve commercial interests or personal information) that mean much fundamental research will not need to go through the review process (Gang and Peng 2023). Others counter this argument, highlighting that the language used in the Measures is too open to varying interpretations of the concept of 'public good' and 'harm'.[56]

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Researchers and experts in the field have highlighted some key learnings from China's race to review its ethical oversight of human embryology research:

- **Incorporating scientific consensus and expert opinion to close loopholes.** Many believe that China has progressed significantly since the original 2003 Ethical Guidelines were developed, with

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current regulations and the Measures going through rigorous consultation processes prior to publication of the final Measures (Interesse 2023).[57] However, evidence from the review process of the 2023 Measures shows that there is still potential for expert inputs to be ignored. For example, the scientific community previously called for the reviewed Measures to consider private entities as well as universities and research and medical institutions, and there was concern regarding the omission of these entities from the final published Measures.

Incorporating the scientific community's voice through public consultations, and avoiding political will or wider influences, could avoid multiple iterations of the Measures that may not blend well with previous Measures or other regulations (Wu and Kong 2023; Gang and Peng 2023). The inclusion of public and expert consultations is also vital to include not only the technical language, but also the legal, ethical and social perspectives necessary to avoid confusion at a later stage.[58]

- **Regularly updating oversight and interfacing with other regulations and regions.** Ethical oversight in China has highlighted the need for collaboration between regions and institutions. The disparate policy landscape in China, where oversight is often at the regional level and includes multiple institutions with blurred responsibilities, has contributed to gaps in oversight that have allowed loopholes in previous Measures to be exploited. Updates to any oversight mechanisms must therefore interface with existing policies and regulations. Regular review processes and public and expert consultations (described above) are two ways to incorporate expert legal input and ensure that regulations are complementary (Peng et al. 2020).[59] This was undertaken to some extent in the 2023 Measures, although the initial exclusion of private entities shows how vital it is to incorporate expert recommendations into any new oversight mechanism.

The addition of specific articles within the measures to incorporate international ethics principles or guidelines can streamline the Measures and avoid confusion or conflicting interpretations between national and international oversight mechanisms. Article 17 in the 2023 Measures, for example, requires research to adhere to international guidelines (Gang and Peng 2023; WMA 2022).

- **The use of penalties or sanctions to comply with rules and regulations, and levels of enforcement.** In China, monitoring and enforcement mechanisms were historically not in place in the original version of the ethical measures, leading to low compliance with rules and regulations that culminated in the CRISPR-modified babies scandal (Wang et al. 2023; Lei and Qiu 2020). In the regulatory review process, several stakeholders welcomed the penalties added into new legislation, which include fines and research licence bans following compliance failures. The Measures have no such penalties beyond specifying that responsibility for penalties lies with other authorities (Articles 44–46).

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Case study 2:
Germany – Changes proposed to legislation to create a more permissive research environment

Table 5. Germany's Embryo Protection Act

Technology area:	Human embryology
Oversight example:	Embryo Protection Act (ESchG)
Type(s) of oversight mechanism(s):	Amendment to existing legislation
Jurisdiction:	Germany
Timescale:	Amendments proposed in 2019

Why is the oversight required?

Currently, the use of human embryos in research and clinical care in Germany is governed by the **Embryo Protection Act** (Embryonenschutzgesetz, ESchG), which came into force in 1991 (German Federal Ministry of Justice 1990). The act outlines strict restrictions on the use of embryos in research and medicine, prohibiting the production of an embryo 'for any purpose other than the bringing about of a pregnancy' and banning the use of embryos 'for a purpose not serving its preservation' (University of Bonn 2024). The positions adopted in the act arose from a view that early human embryos should be afforded the same rights and protections as born humans, resulting in wholesale prohibition against their use in research while allowing avenues to pursue assisted reproduction (e.g. via IVF) in clinical settings (Leopoldina and Union of Academies 2021).

Prohibitions under the act have limited scientific progress in Germany, restricting lines of inquiry in academia and industry, stifling innovation and commercial activity, and limiting access to research funding (Leopoldina and Union of Academies 2021). Proponents of updating the act, such as the Leopoldina working group, state that the act's prohibitions have stifled progress across fields including regenerative and personalised medicine, and have limited scientific understanding of developmental processes unique to humans (Leopoldina and Union of Academies 2021). One interviewee[60] noted that such restrictions on scientific inquiry also affect industry and innovation in Germany around human embryo and reproductive medicine, which limits private investment and commercialisation opportunities. Furthermore, the restrictions under the act limit German scientists' access to research funding. For example, the EU's major research and innovation initiative, Horizon Europe, is generally not available to German scientists due to the restrictions in place (European Union 2021b).

The act's position on embryos is out of step with the perspective of some German scientists and citizens. There is growing evidence that the German public is generally more accepting of reproductive medicine and research involving human embryos today than in the 1990s when the original Embryo Protection Act was developed (Leopoldina and Union of Academies 2021; GSCN 2023). While the majority of the public view the act as outdated, there remains a minority that support wholesale restrictions on research involving human embryos (GSCN 2023).

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The severity of restrictions under the act are out of alignment with international norms in human embryology research and reproductive medicine. The Leopoldina and the German Academies of Sciences and Humanities (Union of Academies) indicate that updates to the Embryo Protection Act are appropriate given relatively broad support for this kind of research among the wider human embryology research community. Notably, research with surplus embryos[61] is permitted in many peer countries, including Denmark, Japan, Sweden, the United Kingdom and the United States (Leopoldina 2013). Furthermore, the International Commission on the Clinical Use of Human Germline Genome Editing recommends intensifying basic research into developing functional germ cells from human stem cells (Leopoldina and Union of Academies 2021), suggesting that updating German legislation to be more permissive of the uses of embryos and stem cells in research is largely in line with international consensus. The creation of embryos for research purposes is much more controversial, although the practice is supported internationally, including by the ISSCR and the American Society for Reproductive Medicine (Leopoldina and Union of Academies 2021).

Differential legal treatment of hESCs in the Embryo Protection Act and the Stem Cell Act (Stammzellgesetz) is seen by some as a double standard. The Embryo Protection Act prohibits harvesting hESCs; however, the Stem Cell Act permits the importation of hESCs for research purposes under some circumstances, implying that embryos, and the stem cells derived from them, have different rights and legal status based on their geographic origin (Leopoldina and Union of Academies 2021). This differential treatment between the two acts is seen by some legal experts as a double standard that can be solved through an update to either or both acts (Leopoldina and Union of Academies 2021).

Recent scientific and technical developments have challenged the logic, relevance and applicability of the Embryo Protection Act. The Leopoldina and the Union of Academies cite many recent advances in biological and medical research that prompt an update to the Embryo Protection Act. Notably, high-profile cases in the United Kingdom have shown that researchers can now sustain human embryos *in vitro* up to the 12- and 13-day mark (Deglincerti et al. 2016; Shahbazi et al. 2016). This advancement has sparked international discourse about the need to update human embryology research oversight mechanisms to account for scientific and technological advancements (Appleby and Bredenoord 2018; Hyun et al. 2016). The recommendations put forward by the Leopoldina and the Union of Academies also note new developments in research techniques including cell-based embryos and the creation of SCBEMs that prompt the need to update the Embryo Protection Act to sufficiently address present-day capabilities (Leopoldina and Union of Academies 2021). The recommendations also highlight the growing potential for advances in the creation of artificial human germ cells and embryos, noting that the act lacks clarity for such developments and thus needs updating (Leopoldina and Union of Academies 2021).

What is the oversight mechanism proposed?

The Embryo Protection Act prohibits the extraction of stem cells from human embryos, as well as interventions in the germ line (Leopoldina and Union of Academies 2021), and lay the foundations

61 Surplus embryos refer to those generated during reproductive therapies (e.g. IVF) that are not used to initiate a pregnancy. Surplus embryos from reproductive medicine procedures in Germany are instead cryo-preserved.

for the 2002 **Stem Cell Act** (German Federal Ministry of Justice 2002). The Stem Cell Act put in place further restrictions on deriving and using stem cells from human embryos in research; however, it allows the importation of stem cells for research purposes under certain conditions. Together, these two acts form the basis for human embryo and hESC research in Germany. At present, the acts pose the following restrictions on the use of human embryos and hESC in research and clinical medicine in Germany:

- Prohibitions on the use of embryos for any purpose other than bringing about pregnancy and hence on the use of **'surplus' embryos** in research.
- Prohibitions on **embryo selection** during assisted reproduction therapies, preventing the selection of embryos judged as having the best chance of initiating a successful pregnancy, inclusive of prohibiting single embryo transfer to prevent multiple pregnancies (Maheshwari et al. 2011). Some exceptions were made to this prohibition in 2011 with the Preimplantation Diagnostics Act (Präimplantationsdiagnostikgesetz), which allows for preimplantation diagnostics in cases where there is a high risk of severe hereditary diseases (Bundestag 2011).
- **Importation of hESC** is allowed for research purposes, but only if the line was generated before 1 May 2007. Approvals for hESC importation are granted by the Central Ethics Committee for Stem Cell Research based on a criteria assessing research objectives (Robert Koch Institute 2023).
- It is a **criminal offence** for German scientists to participate in international research projects involving human embryos, either through counsel or physical participation, even in cases where the research is legal where it is taking place (Leopoldina and Union of Academies 2021).

In 2013, the Leopoldina and the Union Academies established a working group to inform the regulation of reproductive medicine, including the Embryo Protection Act (Leopoldina 2013). In 2019, the group published a summary statement on an updated legal framework for reproductive medicine (Leopoldina and Union of Academies 2019). In this statement, members of the two organisations claimed that updates to the Embryo Protection Act are necessary given rapid advancements in science and medicine, changing social and cultural values, and aspects of the legislation that are ambiguous or contradictory (Leopoldina and Union of Academies 2019). In 2021, the Leopoldina and the Union of Academies produced another statement on **Re-evaluating the protection of in vitro embryos in Germany** (Leopoldina and Union of Academies 2021). The document contains four central recommendations for updating the Embryo Protection Act:

- **Permitting the use of surplus embryos for research in line with international standards and with appropriate informed consent processes:** The Leopoldina and the Union of Academies recommend that surplus embryos from reproductive medicine procedures, including their stem cells, should be permitted to be used for research in line with international standards.
- **Expanding choices for couples receiving IVF treatment:** The Leopoldina and the Union of Academies recommend that the decision as to whether surplus embryos are used for research should be made by the couple or individual from whom they originate, following counselling to support informed decision making.
- **Creating a legal framework that establishes a federal authority and ethics committee to review applications for research involving human embryos:** The Leopoldina and the Union of Academies recommend that a federal authority and

central ethics committee should be established to review proposals for research undertaken using surplus embryos. The recommendations note, in alignment with the current version of the Embryo Protection Act, that human embryos should be reserved for research with 'objectives of outstanding interest, where fundamental research is used to gain scientific knowledge and to expand medical knowledge for the purpose of developing diagnostic, preventative or therapeutic procedures'. The recommendations highlight the United Kingdom's HFEA as an exemplar.

- **Instituting statutory reviews and reporting guidelines for responding to new development is embryo research:** The Leopoldina and the Union of Academies recommend establishing statutory review and reporting periods to consider responses to new developments in the field.

What is the future trajectory for the oversight mechanism?

The use of embryos in research and medicine remains a controversial and divisive topic, both in Germany and across the world, as questions around their use are related to individuals' ethical and often religious views on the beginning of life (Leopoldina and Union of Academies 2021). As such, legislators, policymakers and politicians are often reticent to address this topic, which poses challenges to amassing sufficient political will and backing to support legislative reform. Nevertheless, **there are indications that the present social and political circumstances in Germany may be supportive of changes to the Embryo Protection Act.**

The Leopoldina and the Union of Academies working group recommendations indicate a **high level of willingness to donate surplus embryos for research among German couples undergoing reproductive therapies**, indicating that the proposed amendments are broadly acceptable to many who would have responsibility for deciding whether and how embryos are used for research (Leopoldina and Union of Academies 2021). A survey recently conducted by the German Stem Cell Network found that among 2,500 people surveyed, a majority were in favour of research with human embryos and embryonic stem cells; 44 per cent supported amendments to the Embryo Protection Act, and 49 per cent supported changes to the Stem Cell Act (GSCN 2023).

One interviewee[62] noted recent efforts among the German scientific community to promote discourse around human embryo research, including a recent symposium following the publication of the working group recommendations (German Federal Ministry of Education and Research 2023). However, much now rests on the will of key ministers to take up the cause, which, despite interest from the 2024 presiding Minister of Health, may not necessarily be a political priority given the long list of competing concerns.

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

The Leopoldina and Union of Academies recommendations frequently note the importance of **considering pluralism in ethical views when** discussing avenues for oversight in controversial areas of science, such as human embryology (Leopoldina and Union of Academies 2021). One interviewee[63] also acknowledged the

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importance of considering the full spectrum of views in such cases, as consideration of governing mechanisms should acknowledge the breadth of perspectives present within the society. Hearing all perspectives is a means of recognising, considering and respecting the diversity of viewpoints in a pluralistic society and provides an avenue for considering potential impacts and reactions to new or amended governance mechanisms. While the Leopoldina emphasises the importance of such considerations, it also takes the position that the most restrictive viewpoint should not form the basis for standards in a pluralistic society. Instead, it suggests that liberal societies should afford more decision-making power to those affected by the governance mechanism (couples or individuals undergoing IVF in this case), affording them greater freedoms to make restrictive or permissive decisions based on personal values.

Case study 3:
International proposed guidelines for aligning data standards when using AI in IVF

Table 6. An international data solidarity agreement

Technology area:	Human embryology
Oversight example:	Data solidarity agreement
Type(s) of oversight mechanism(s):	Standards/guidelines
Jurisdiction:	International
Timescale:	Proposed in 2022

Why is the oversight required?

This case study highlights the increasing complexity and challenge of applying AI to the domain of human embryology, specifically in the context of IVF and embryo selection. Challenges in embryo data and IVF can be significantly aggravated when AI is applied to embryo ranking and selection processes, as highlighted below.

Privacy and safety concerns. The personal and identifying nature of the data collected for IVF (e.g. embryo data, patient data on infertility and family life, IVF outcomes) has historically required stricter protections and limitations to data sharing and access, with associated safety concerns for the individuals concerned. Given that AI capabilities centre on the use of data for training, privacy and safety are of particular concern when AI is applied (van Panhuis et al. 2014; Carson et al. 2019).

Access to and interoperability between datasets. IVF data, like many data-heavy fields, faces challenges of aggregation and interoperability

of datasets, as well as diffiulties gathering sufficient quantities of accurate, usable and representative data. This is due to variations in, for example, definitions and the collection of patient demographic information, as well as differences in clinical and laboratory processes between clinics. These interoperability challenges threatens the reliability of AI training data (Hickman et al. 2020). In addition, most routinely collected IVF data is collected for regulatory purposes and aggregated at the national scale in summary form, limiting its potential utility for AI training and validation (Hickman et al. 2020). Furthermore, most IVF clinics around the globe still rely on paper records, meaning that a mass digitisation effort would be necessary to create the large, comprehensive global datasets needed for reliable and generalisable results from AI models (Hickman et al. 2020). As such, data access, sharing and aggregation are formidable hurdles to the continued development and improvement of AI models for embryo selection. Access to diverse, 'real' datasets is also necessary for the training of AI models; while synthetic data can be used to tackle privacy and safety concerns, bias can perpetuate through unverifiable predictions and analysis (Curchoe et al. 2020; Dimitriadis et al. 2022).

Interpretability, explainability and bias of AI models. Key challenges persist regarding the oversight of AI models for applications such as embryo ranking and selection for IVF, including why certain selection decisions are made by the algorithm, what the underpinning analysis represents, and bias within AI models. Human embryology researchers have been calling to move away from 'black box' AI models, where the model workings are obscured, to interpretable and transparent AI (Afnan et al. 2021; Lee et al. 2024). Researchers have noted that using interpretable ML models (constrained models that humans can decipher and interact with) in embryo ranking and selection could improve the transparency and explainability of the AI-driven analysis. Afnan et al. (2021) have noted that 'developers should aim to build interpretable ML models where biologically meaningful parameters guide embryo assessment, reducing the risk of hidden biases in algorithms causing unintended harms to society, permitting better troubleshooting, and better enabling clinicians to counsel their patients on the thinking underlying their treatment'. However, access to sufficient and diverse data is necessary to avoid bias; if the AI is trained on a limited dataset, the analysis of new data could become biased towards specific characteristics of the data the model was trained on (Kragh and Karstoft 2021; Afnan et al. 2022). Training and testing data is vital to improve and validate AI models, including those for embryo selection, and oversight mechanisms are needed to ensure consistency in the field (Afnan et al. 2022; Hickman et al. 2020).

What is the oversight mechanism proposed?

To support IVF research, including the development of AI models for embryo ranking, there are growing calls from the scientific community for an open access and comprehensive data repository of embryo images and data to train AI models (Afnan et al. 2022). Such a repository would enable data aggregation at the scale necessary to develop AI models that are trained and validated on sufficiently diverse datasets. The establishment of such a data repository would require governance mechanisms that appropriately protect the privacy of patients and promote inclusive practices with transparency. To this end, **data solidarity principles**[64] have been

64 Data solidarity is defined as 'an approach to the collection, use, and sharing of health data and data for health that safeguards individual human rights while building a culture of data justice and equity, and ensuring that the value of data is harnessed for public good' (Kickbusch et al. 2021).

suggested as a means of governance (Afnan et al. 2022). These principles look at health data governance through the lens of a social contract, where there is a balance of personal and collective needs and responsibilities, and an interest in where these overlap (Kickbusch et al. 2021). The approach emphasises a non-extractive approach to data analysis (collection, use and sharing), defined as a 'research method and philosophy that recognises, respects, consults and integrates community of practice' based on principles including intent, integrity and process to promote trustworthiness and harness the value of the data for public good (Igwe et al. 2022).

This proposed oversight mechanism represents a bottom-up approach to oversight, where standards and practices are encouraged through infrastructure and research systems, providing principles that researchers must abide by, rather than legislative acts or regulations. The proposed oversight focusses on data sharing that considers necessary safeguards to ensure justice and equity – otherwise known as data solidarity. This feeds into on the ideals of ensuring scientific rigour, transparency and consistency which – as demonstrated by the application of AI/ML to embryo ranking and selection processes – is needed in emerging technology areas.

The approach has considered a number of principles to ensure transparency and reproducibility within AI/ML for IVF. It primarily specifies developing a comprehensive and open access repository of human embryology data, including embryo images used in ranking and selection processes, to ensure that AI/ML algorithms can be effectively trained on a breadth of diverse 'real' data to address the challenges noted above. Some experts caution against prematurely implementing algorithms before they have been properly validated with verifiable datasets and algorithms; an open access repository can support this effort. The proposal also notes the need for 'a minimum predetermined safety standard' for AI algorithms, and 'post-implementation surveillance is essential to ensure the safety of this intervention for embryo selection'.

Given the nascent nature of this call to action, the proposed 'agreement document' does not outline a clear and actionable implementation strategy. Instead, it suggests oversight can be delegated to national, research or clinical organisations, with Afnan et al (2022) stating that 'Data repositories could be achieved under the auspices of government (e.g. the HFEA, although this would be UK only), professional bodies, such as Academy of Clinical Embryologists, or academic institutions, who would oversee the repository, evaluate proposals to access the data, allow access to researchers under licence, and ensure that the data are used ethically, and studies ultimately published.'

There is no evidence of such a repository on an international scale specific to human embryology. Nevertheless, several examples of similar demands exist in the broader health space, including the Health Data Governance Principles[65] and discussions at WHO's Health Data Governance Summit (WHO 2021c; Health Data Governance Principles 2024).

What is the future trajectory for the oversight mechanism?

Interoperability challenges are a persistent gap, even within the call to action for an open access dataset. The key issue of data interoperability was not addressed in the proposed agreement document. However, if multiple open access databases are

65 Which include 'establish[ing] transparent and accessible processes and systems' and 'promot[ing] data sharing and interoperability'.

established across the globe, interoperability will become increasingly important, and questions such as 'how can these databases work together when data is collected in heterogeneous ways?' and 'is there a need for further principles to establish consistent data collection and management strategies?' will need to be answered. Federated approaches, such as those reported by the United Kingdom in the Genome Strategy and via Genome UK (UK Government 2022a; 2022b), have the potential to balance privacy, security and interoperability concerns with progress in research. The features of federated learning, which uses a decentralised AI model, provide a possible solution to these challenges, and the ability of federated learning to work with heterogeneous datasets may be helpful for the aggregation of data from various databases. There needs to be clarification within the principles of whether such an approach is necessary, or new standards for data collection need to be outlined.

Implementation of open access repositories needs high levels of cooperation between actors at every level, from governments to researchers and research centres. According to the original call for data solidarity through an open access repository, this can only be achieved through a cohesive, concerted effort involving not only the researchers themselves, but also trade bodies and academies, clinicians, and computational scientists (Afnan et al. 2022). Developing these principles of data solidarity requires the engagement and input from all affected groups. Public funders and private investors also need to contribute (Lancet Digital Health 2021). Inter- and intra-research centre reliability in embryo ranking is also needed to increase transparency and consistency (Cimadomo et al. 2022), which is currently undertaken through external quality assessment services such as UK NEQAS. A similar mechanism may also be needed to ensure interoperability between data repositories.

Progress in this space has been limited, with a distinct lack of incentives in place to enable implementation. Since the call was published, the study team has found no evidence of progress being made on implementation, with no new centralised, open access repositories launched anywhere in the globe. The requirements to build open access repositories are vast, needing collaboration between actors, potentially internationally if interoperability is to be addressed. Financial support is also notably lacking from the wider public sector to incentivise the development of such repositories. As yet, it is too early to determine if implementation would be better enabled with an alternative oversight mechanism.

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

While data solidarity through open access repositories is suggested as a potential solution to oversee AI in human embryology research, principles, incentives and monitoring of progress are needed for implementation. As the call for action is still in its infancy, there is no evidence of any data-sharing spaces being implemented as a result of the proposal. The call for action does not outline how the data sharing platform will be monitored and enforced, and there are no guidelines for who will have overall responsibility in the event of multiple repositories. If indeed there are multiple repositories operated by various national and professional bodies (as suggested in the call), the question becomes: how will these different bodies ensure transparency and interoperability between platforms to allow for data sharing and reliable, valid training of AI models? While an open access database does address some of the issues brought up by AI-trained embryo selection and ranking, these key challenges may still perpetuate. A set of clear data solidarity principles, such as those defined for health data, may be necessary to guide organisations in actioning open data platforms.

Chapter 5
Current engineering biology oversight developments

To guide the reader, this chapter is structured as follows.

Box 3. Current engineering biology oversight developments: Key takeaways

Engineering biology advancements, especially in AI-enabled biotechnologies, can increase the potential for biosecurity threats. Current oversight mechanisms (e.g. the BWC) are insufficient to assess and manage these risks, particularly the potential for malicious use. Strengthening biosecurity measures through international collaboration, such as the International Biosecurity and Biosafety Initiative for Science, could address gaps in risk management and better monitor the evolving threats posed by engineered pathogens.

AI integration in engineering biology poses challenges to data privacy, accuracy and ownership. Existing frameworks such as GDPR are not designed for the nuanced requirements of AI-driven biological research.

Engineering biology spans multiple sectors, leading to fragmented oversight with long approval timelines. For instance, in the EU, regulations such as REACH apply inconsistently across industries, creating confusion and conflicting incentives for research and commercialisation. Implementing cross-sector collaboration through initiatives such as the UK's Regulatory Horizons Council and Engineering Biology Sandbox Fund can potentially streamline oversight, accelerate approvals, and improve dialogue between regulators and innovators.

Disparate oversight mechanisms globally are creating obstacles for international collaboration in engineering biology, which is compounded by the vast number of sectors involved. International mechanisms such as the Cartagena Protocol could be adapted to ensure alignment across diverse applications and jurisdictions.

Source: RAND Europe analysis.

5.1. Introduction

Engineering biology applies the tools and techniques of engineering to biology, enabling novel biological system design or the redesign of existing systems. There has been a rapid growth of engineering biology infrastructure, research and applications that span biomanufacturing, net-zero and climate mitigation, and agriculture security. Innovations in healthcare, agriculture and industrial biotechnology are leading to sustainable solutions and new bio-based products. However, there are significant safety and security concerns given the dual-use nature of biological tools and outputs, the ethical implications of synthetic organisms, and public acceptance. Given the varied applications of the technology, diverse policies, laws and frameworks govern this field, and convergence with technologies such as AI are adding further complexity to the oversight landscape.

AI-enabled advancements are seen by scientists and policymakers to be increasing biosecurity threats. The integration of AI is also posing further challenges for data privacy and ownership given the need for AI models to be trained on vast quantities of data. Disparate oversight mechanisms globally are creating obstacles for international collaboration in engineering biology, which is compounded by the vast number of sectors involved. There have been proposals for international mechanisms such as the Cartagena Protocol to be adapted to ensure alignment across diverse applications and jurisdictions.

A detailed assessment of the trends, challenges and opportunities associated with engineering biology R&I is provided in the accompanying global technology landscape review report.

The first section of this chapter summarises the strengths and limitations of the emergent engineering biology oversight landscape, alongside some key considerations for addressing the current gaps and bottlenecks. The subsequent sections present the evidence underpinning this assessment, outlining key oversight mechanisms across the United Kingdom, United States, EU and international forums, followed by oversight case studies from the United Kingdom, United States and South Africa that provide more detailed examples of how oversight in this area could be progressed.

5.2. Strengths and weaknesses of the engineering biology research and innovation oversight landscape

Strengths of engineering biology research and innovation oversight

There are many existing biotechnology governance mechanisms that apply to engineering biology by extension. Regulations in the United Kingdom extend from broad conservation regulations to security acts (section 5.3). In the United States, regulation focuses on biosecurity and engineering-biology-derived products, rather than on the technology itself (section 5.4). In the EU, food and food safety is regulated through GMO legislations, which impact engineering biology (section 5.5). In South Africa, a Code of Conduct provides protection for personal information, specifically including genetic data and genomics research (section 5.7, Case Study 3). These regulations are already in place and either implicitly link to engineering biology, or explicitly mention where engineering biology is covered.

For more targeted oversight, international forums provide guidance and recommendations to national governments. Global forums, such as the International Summit on Human Genome Editing, serve as platforms for discussions across scientific developments, including ethics, social and accessibility issues, and are an important mechanism for discussing governance mechanisms, needs and

best practices. International frameworks also guide and provide recommendations on global, national, regional and governance mechanisms for genome editing, including the WHO's Human Genome Editing: A Framework for Governance, the African Union Convention on Cybersecurity and Personal Data Protection, and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (hereafter referred to as 'Nagoya Protocol') (section 5.6).

National and subnational governments and organisations are trying to keep up with the rapid pace of developments in engineering biology. For example, the United Kingdom's National Physical Laboratory (NPL) is working to establish standards in engineering biology (section 5.3). The United Kingdom also has several regulatory networks and councils that include engineering biology in their scope. Research councils and foundations are already calling for more work on the topic, highlighting concerns regarding research risk and providing national recommendations (e.g. the 2018 recommendations by the Nuffield Council on Bioethics, section 5.3). From a new-technology standpoint, multiple AI-genomics-focused advisory boards and consortia are generating insights on non-legislative mechanisms of oversight, with the National Security Commission on Emerging Biotechnology (NSCEB) and the Federation of American Scientists (FAS) in the United States having proposed several policy options in this area (section 5.4).

Due to the risks that unsupervised engineering biology can pose, the sector has been a testbed for novel or rarely used oversight mechanisms. Ethical, Legal and Social Implications (ELSI) advisory boards are being piloted by the Human Genome Project, while regulatory sandboxes are emerging as an experimental approach to the governance of engineering biology, such as the UK Engineering Biology Sandbox Fund (sections 5.3 and section 5.7, Case Study 1). One expert noted that these sandboxes will be particularly important due to the unpredictable nature of regulatory challenges, which will 'require innovative responses'.[66]

Opportunities in engineering biology research and innovation oversight

Engineering biology has seen some movement towards inclusive conversations with the wider sector and stakeholders. Conversations on oversight are increasingly including proposals from academic and third sector researchers. These provide opportunities to catalyse biomanufacturing, synthetic trials and drug development, and environmental risk mitigations in a transparent and measured manner. Engagement with the wider community and considerations of equity and diversity in these conversations (discussed below) is still needed to maximise trust and communicate the benefits of engineering biology.[67]

Some experts are calling for a new global (non-regulatory) mechanism to enable active and ongoing reflections by scientists about their own work. This dialogue should happen with scholars from diverse disciplines and with representatives of the public who come from different social, political and religious backgrounds. Input from experts during the focus group warned that such a mechanism would need careful planning to balance multidisciplinary expert representation and diversity, mediating opinions to prioritise actions. There would also need to be considerations on scope, as well as

66 Expert focus group input.
67 Expert focus group input.

an implementation strategy to appropriately leverage and integrate expert opinion. As such, expert opinion may be better incorporated through national or regional networks that engage with researchers on the ground, enabling access to less represented groups (e.g. indigenous and tribal groups).[68]

As the fields of AI and engineering biology have converged, opportunities are appearing that explore the associated benefits and risks, and governance required. Notable AI governance mechanisms such as the US AI Executive Order (section 5.4) provide new policy windows for considering the oversight and progress of engineering biology where it intersects with AI. The structured access approach, where AI tools/data are restricted to specific users, and users are prevented from acquiring the tools themselves, is another suggested way to govern AI-enabled engineering biology.

However, some focus group experts emphasised that as AI regulations are still relatively nascent, they do not always extend to engineering biology.[69] For example, the EU AI Act (section 5.5) does not explicitly cover engineering biology and its particular risks, such as biological weapons. With regards to the structured access approach, there are increased risks to equity, potentially 'reinforcing inequitable access' by limiting access to certain groups.

Tangential mechanisms and tools could further benefit the oversight of engineering biology. For AI-enabled engineering biology, experts noted an opportunity to use flexible tools alongside non-specific regulations.[70] Other tools can also support advances in engineering biology, such as those providing 'new forms of biocontainment, enhanced microbial forensics, and threat agnostic surveillance capabilities'.[71] Intellectual property rights prizes, such as the United States Patent and Trademark Office's Patents for Humanity project, could be useful mechanisms to address the societal challenges pervasive in engineering biology research, although it was acknowledged that enforcement might be challenging.[72]

Threats and weaknesses of engineering biology research and innovation oversight

The overlap of existing regulations, guidance and advice needs to be clarified. The overlap of many regulations due to the hybrid nature of engineering biology means that there is often already oversight in place. Challenges can arise when these overlapping regulations are in conflict, or if they are confusing to navigate. Some examples include how intellectual property rights apply to engineering biology, engineering biology's position regarding public health research and emergencies, and access to genetic resources for engineering biology research.[73] Challenges for coherent oversight apply also to engineering biology and its convergence with technologies such AI, which has applications in multiple sectors such as climate and the environment, agriculture, human health and defence.

68 Expert focus group input.
69 Expert focus group input.
70 Expert focus group input.
71 Expert focus group input.
72 Expert focus group input.
73 Expert focus group input.

There is a notable lack of clarity around where engineering biology sits within these regulations. Reviews and clarifications may therefore be more productive than new mechanisms, while review mechanisms (not yet used throughout scientific research) could identify emerging oversight needs and how to adapt to them.[74] The United Kingdom's National Securities and Investments Act, which specifies how it applies to synthetic biology, is a successful example in this regard.[75]

Existing mechanisms are not always coherent or effective for when AI converges with engineering biology. Transparency, reproducibility and interoperability are necessary for the successful integration of AI into engineering biology, which could have implications on intellectual property law (e.g. trade secrets). Engineering biology research is currently limited by the reliability and quality of open-source data, which spans borders, and there are challenges due to the lack of standards and interoperability of datasets. Oversight in this regard can be complex and convoluted, potentially creating systemic barriers to progress.

Insights from advisory boards and consortia alone may not lead to effective regulatory responses in such complex cases, and appropriate follow-up and monitoring is also needed. Some mechanisms have started to consider the convergence of these sectors or AI/ML opportunities (e.g. federated learning) to address data-sharing challenges,[76] but this is a rapidly changing space that must be further considered.

Data consent is also an issue within data sharing, particularly in human genomic data. Several consent models have attempted to address this by including processes of re-consent. However, these processes are generally insufficiently comprehensive to address all ethical concerns on consent, particularly given the lack of clear boundaries around what is considered a new technological development.

Some existing mechanisms face implementation challenges, as well as gaps that limit proper and fair deployment. Experts observed that biosafety practices are being implemented inadequately, creating new risks.[77] These practices also often incorporate risk assessment procedures that compare with 'risk-free scenarios', and do not consider engineering biology free (but still risk-heavy) scenarios – some note that this is an important method to properly highlight the value of engineering biology.[78] Equity and accessibility are also left out of considerations for successful implementation at both the national and international level, with a notable lack of support for capacity building in developing nations. The risk of poor, inconsiderate implementation could aggravate inequalities, particularly with regards to biomedical devices that benefit public health.[79]

There are long time-lags to obtain regulatory approval for engineering biology-based products. Engineering biology is a hybrid discipline, falling under multiple regulatory mechanisms at the national and international levels. This creates two issues. First, engineering biology-based products in the EU may fall under multiple

74 Expert focus group input.
75 Expert focus group input.
76 For example, the work of the Spiez Laboratories in Switzerland (expert focus group input).
77 Expert focus group input.
78 Expert focus group input.
79 Expert focus group input.

directives that could be conflicting or confusing to navigate (section 5.5). Second, heavily regulated systems are usually accompanied by long delays and complex approval processes. This places cumbersome administrative and financial burdens on innovators, regulators and governmental staff. In addition, processes to update regulations are cumbersome and not conducive to keeping up with the fast-paced changes in engineering biology.[80] While sandboxes have been proposed to overcome these challenges (section 5.7, Case Study 1), they are not widespread.

Finding a balance between existing general regulations and oversight bespoke to engineering biology is challenging. Current oversight mechanisms are not bespoke to engineering biology and could potentially expose gaps in oversight or make existing regulations obsolete, such as in the case of new gene editing technologies. However, developing reactive regulations for novel engineering biology technologies and products – particularly before the risks and public perceptions are fully understood – poses additional risks and complications. Alternative mechanisms are possible and have yet to be considered. For example, one expert suggested that 'building reflective practices into scientific design, so that scientists are better equipped to engage with early discussions about the risks and benefits of their work' could prevent reactivity and miscommunications about the threat and risk level of technologies before they have matured fully.[81]

As seen with other technologies in this report, bespoke oversight comes with other challenges, such as incorporating inflexible, specific definitions of engineering biology[82] that could create loopholes or become rapidly obsolete as new technologies mature. The slow-moving processes to update regulations means that bespoke oversight may struggle to keep up with a rapidly changing technology.

The benefits of process-driven vs. product-driven approaches to monitoring engineering biology have not been fully explored. Differences across the globe in terms of how to regulate engineering biology may cause further confusion, with some oversight being product-focused (e.g. in the United States, section 5.4) and some focused on the technology or the process. The latter necessitates revisions as the process evolves, rather than product-driven regulations, which focus on the end properties of the product. One expert highlighted the United Kingdom's food crops, which must now accommodate multiple regulations on multiple different processes.[83]

Without due consideration of their composition and remit, advisory boards could end up providing narrow, non-diverse oversight with significant gaps. Without a diverse panel, advisory boards (e.g. ELSI, institutional review boards, ethics review committees) are at risk of providing uninformed or unformulated recommendations. This is particularly true for projects working with low/middle-income countries (LMICs). Experts noted that a diverse and representative panel is an opportunity to have ELSI boards which could be useful mechanisms for reflexive engagement with the issues raised.[84]

80 Expert focus group input.
81 Expert focus group input.
82 There has been some confusion regarding the interchangeability and scope of 'synthetic biology', 'engineering biology' and 'genetic engineering', for example (expert focus group input).
83 Expert focus group input.
84 Expert focus group input.

Equity, diversity and inclusion (EDI) is a crucial topic that is routinely absent from most oversight discussions. Existing oversight mechanisms and discussions focus on risks related to, for example, privacy, security and data protection, but many note that the social aspect is missing. Many global genomics datasets are not representative of African and Asian genetic diversity. This is due to a lack of inclusion of these communities in research and a lack of trust on the communities' part in enrolling into research, leading to an increase in health inequalities. International forums (e.g. the International Summit on Human Genome Editing) have historically failed to properly integrate voices outside of powerful countries with strong research ecosystems. This is a fundamental problem with the convergence of AI and engineering biology, where access to diverse data is vital.

EDI also extends to sex, specifically 'the lack of data on women and the female body', which is vital for research in this space. Experts warned that 'this potentially risks exacerbating an already dangerous situation where women are routinely harmed and killed by structural and systemic assumptions about the average human being male'.[85]

85 Expert focus group input.

To progress safe and innovative research and application of engineering biology, this study proposes two **key considerations** with regards to oversight developments:

Develop a nested network of oversight:

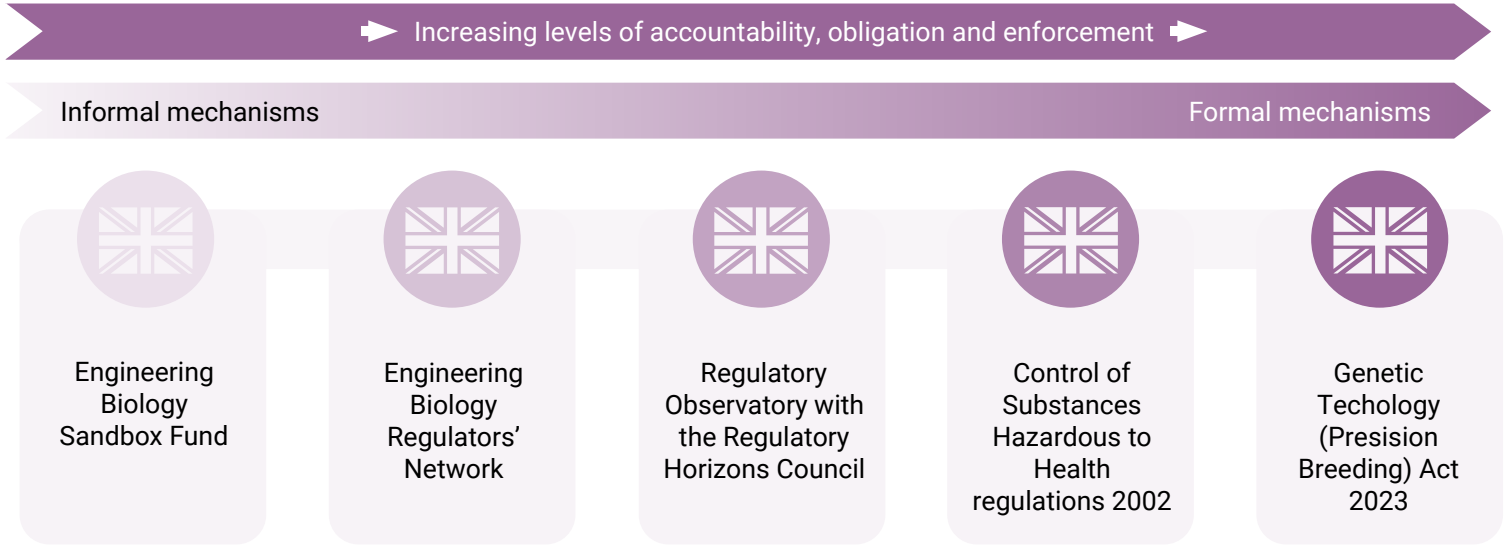
Existing informal mechanisms of oversight are often not effectively implemented. More effort is needed to contextualise informal oversight against formal oversight to develop an 'oversight network for engineering biology' as a whole, and to assess where the lack of implementation is a bottleneck to progress, or even a risk.

Holistic overview and demarcation of oversight for techniques and products is needed:

The benefits of process-driven versus product-driven approaches to monitoring engineering biology have not been fully explored. There are various schools of thought on whether products or processes should have bespoke oversight; however, evidence from this study suggests that processes will require oversight in the realm of research, whereas products will require oversight in the realm of application across many sectors (e.g. food, environment, health). Therefore, it is necessary to take a more holistic view of oversight and demarcate what is the appropriate level of oversight for research versus applications and products.

5.3. Oversight of engineering biology in the United Kingdom

Figure 13. Illustrative oversight examples of engineering biology in the United Kingdom



Source: RAND Europe analysis.

Current oversight mechanisms in the United Kingdom

Given the wide scope of engineering biology and its applications across many diverse sectors, there are several oversight mechanisms in the United Kingdom that are partially relevant for engineering biology:

- The **Genetic Technology (Precision Breeding) Act 2023** is a new law that the Department for Environment, Food and Rural Affairs (DEFRA) is tasked with overseeing. The act, which only applies in England, facilitates the use of new gene editing techniques for increased food resilience and food security (UK Government 2023b; UK Parliament 2023a). The Food Standards Agency (FSA) is currently establishing a regulatory framework for precision bred food and feed in England as part of associated secondary legislation (FSA 2023).
- The **Control of Substances Hazardous to Health (COSHH)** regulations of 2002 are enforced and monitored by the Health and Safety Executive (HSE). They concern controlling hazardous substances (including biological agents) in workplaces to ensure they do not cause ill health among employees (HSE 2024a). These regulations are relevant for engineering biology

laboratories and companies given the potential for hazardous biological agents.

- The **National Security and Investment Act** came into force in January 2022 and is enforced by the Investment Security Unit within the Cabinet Office. It is relevant to engineering biology as it mentions protecting synthetic biology and gives the government a means to screen investments and corporate takeovers that might raise national security concerns. Moreover, the UK's export control regime protects listed items such as dual-use items which could potentially encompass certain synthetic biology tools and products (Legislation.gov.uk 2021).
- The **Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Act** by the HSE passed into law in January 2021. It regulates materials and chemicals that are manufactured in or imported into the United Kingdom (HSE 2024b). It only applies to engineering biology in terms of the production of materials and chemicals through engineering biology techniques.
- **Medicines for Human Use (Clinical Trials) Act 2004** overseen by the MHRA covers all aspects of clinical trials, from safety to access. It applies to engineering biology when new drugs and therapeutics are derived from engineering biology techniques and tested through clinical trials.[86]
- The **Human Fertilisation and Embryology (HFE) Act 1990** is relevant to human genome editing and the use of embryos in research (see also section 4.3), and applies to engineering biology given the novel precision medicine technologies being developed, such as genome-guided medicine (e.g. pharmacogenomics) (Ho et al. 2020). The HFEA is responsible for overseeing and implementing the act.
- The **Human Tissue Act 2004** regulates activities that involve tissue taken directly from the human body, transfers of human remains from certain museum collections and other related activities. It is relevant to engineering biology (and to organoids, as mentioned above) because it governs the removal, storage and use of human tissue for research, medical treatment, post-mortem examination, education and training, and display in public (UK Government 2004). The HTA is responsible for overseeing and implementing the act.
- **Genetically Modified Organisms (Deliberate Release) Regulations 2002.** These regulations are overseen by DEFRA and concern the control of genetically modified organisms developed through engineering biology and other techniques that are deliberately released into the environment. They apply in England and Wales (UK Government 2002).
- **Genetically Modified Organisms (Contained Use) Regulations 2014.** As above, DEFRA is responsible for implementing and enforcing these regulations, which pertain to work with GMOs in contained facilities (HSE 2014).
- The **Natural Environment & Rural Communities Act (2006)** and **Conservation of Habitats and Species Regulations 2010** cover the designation and protection of European sites and protected species with the aim of diversity conservation (Wildlife Trusts 2024). Aspects of this are relevant to engineering biology as its applications can impact the environment, for example climate

86 In March 2023, the MHRA announced plans to reform the national clinical trials regulatory framework following a nationwide consultation in early 2022 (Medicines and Healthcare products Regulatory Agency 2004)

change and bioremediation experiments to help mitigate the negative effects of pollution or climate on the environment and to maintain biodiversity.

- The 2004 amendments to the **Environment Act** apply in England, Wales and Scotland, and are overseen by the Environment Agency and the Scottish Environment Protection Agency. The act is concerned with the major aspects of the natural environment and biodiversity. It is relevant to aspects of engineering biology's application in the environment, for example the modification of hazardous waste into other compounds and changes introduced in biodiversity due to bioremediation measures (UK Government 2021a).
- The **Anti-Terrorism, Crime and Security Act** of 2001 (last amended in 2014) applies across the UK. Because of its broad scope, several government departments are responsible for implementing different parts of the act. Aspects relevant to engineering biology concern weapons of mass destruction, and the control and security of pathogens and toxins. Part 6 makes it illegal to transfer biological agents or toxins outside the United Kingdom, or to assist another person to do so, or to set off a nuclear explosion (UK Government 2001).
- The **UK Biological Security Strategy 2023** was led by the Cabinet Office and updates the United Kingdom's first strategy in this field, published in 2018. Although not an oversight mechanism, it is particularly relevant to engineering biology given its focus on resilience against biological threats (including biological weapons) and the ambitions to make the United Kingdom a world leader in responsible innovation using critical technologies such as engineering biology (UK Government 2023c).
- The **Nagoya Protocol** is an international agreement under the CBD that aims to ensure fair and equitable sharing of benefits arising from the use of genetic resources. It establishes rules for access to these resources and promotes the protection of indigenous knowledge and biodiversity.

Emerging oversight mechanisms in the United Kingdom

- The NPL is leading on developing **standardised, reproducible and scalable methods** to keep pace with the rapid advancements in engineering biology. Suitable standards do not yet exist for engineering biology in the United Kingdom; however, they are important to ensure harmonisation across the sector and to help build the trust and confidence of the scientific community, industry and wider population in the performance of the novel products developed (NPL 2024).
- The UK government announced an **Engineering Biology Sandbox Fund** in March 2024,[87] overseen by the Department for Science, Innovation and Technology (DSIT). The sandboxes[88] are designed to be an experimental space where the engineering biology industry and regulators can exchange information on helpful and hindering innovation regulations (UK Government 2024a).
- The **Engineering Biology Regulators' Network (EBRN)** was launched by DSIT in 2023 and is expected to offer training to people in engineering biology industries to increase knowledge about regulations. The training will complement existing

87 The sandbox fund will allocate £5 million in two competitive rounds, the first of which closed to bids on 19 April 2024.

88 A regulatory sandbox is a contained environment that enables the live testing of regulatory innovations, tools and mechanisms, with interaction and supervision from regulatory bodies.

training courses offered by, for example, the NPL and the British Standards Institute. The EBRN will also help DSIT implement regulatory sandboxes, with members expected to apply for the sandbox fund grants.

- The co-chairs of the Council for Science and Technology wrote a letter to the UK prime minister in March 2023 recommending that DSIT and the Office for Science and Technology Strategy set up a **Regulatory Observatory** with the Regulatory Horizons Council (RHC). The observatory would bring together insights on engineering biology applications for regulators across sectors, advise on improvements to support the sector, and provide consumer engagement and reassurance (Council for Science and Technology 2023).[89]
- The RHC, an independent expert committee, recently recommended **regulating the product** rather than the second generation of genetic technologies themselves (i.e. synthetic biology, engineering biology, genome editing) (RHC 2022). The RHC proposes that regulation should focus on the nature of the products ready for market and the associated benefits and risks, rather than on the technologies used to make these products. It also proposed that standards, guidelines, policy and technology initiatives should be used as alternatives to formal legislation as they take less time but can still enable careful product development (RHC 2022).
- The MHRA is leading a **proposed regulatory framework on manufacturing medicine at the point of care (POC),** drawing on a 2022 public consultation.[90] The new regulations would apply to all POC products manufactured in the United Kingdom, such as personalised medicines and ATMPs (e.g. cell therapy, gene therapy and tissue-engineered products, 3D printed products, blood products). The role of engineering biology and biofoundries could be critical in the development of these products and would fall under the purview of the proposed framework (MHRA 2023).
- The **Engineering and Physical Sciences Research Council (EPSRC)** developed voluntary **guidelines in 2023** to help UK researchers and academics adopt principles of responsible research and innovation in their work. The EPSRC encourages all publicly funded researchers in engineering and physical sciences to use the guidelines and related tools to ensure that responsible research is embedded in their work (EPSRC 2023).

Other mechanisms of relevance in the United Kingdom

- **GDPR** remains in effect in the United Kingdom (UK GDPR), as per section 3 of the European Union (Withdrawal) Act 2018. Following its initialisation legislation, the Data Protection Act of 2018, it is the central oversight mechanism for data handling in the United Kingdom, including data generated by engineering biology.
- The **Common Law Duty of Confidentiality** is a critical part of the regulatory framework on managing patients' health data in the United Kingdom (NHS England 2024), and is therefore relevant to engineering biology.

89 It does not appear that this recommendation has been implemented.

90 This new framework would mean that POC products would have the same level of safety, quality and effectiveness as conventional medicinal products.

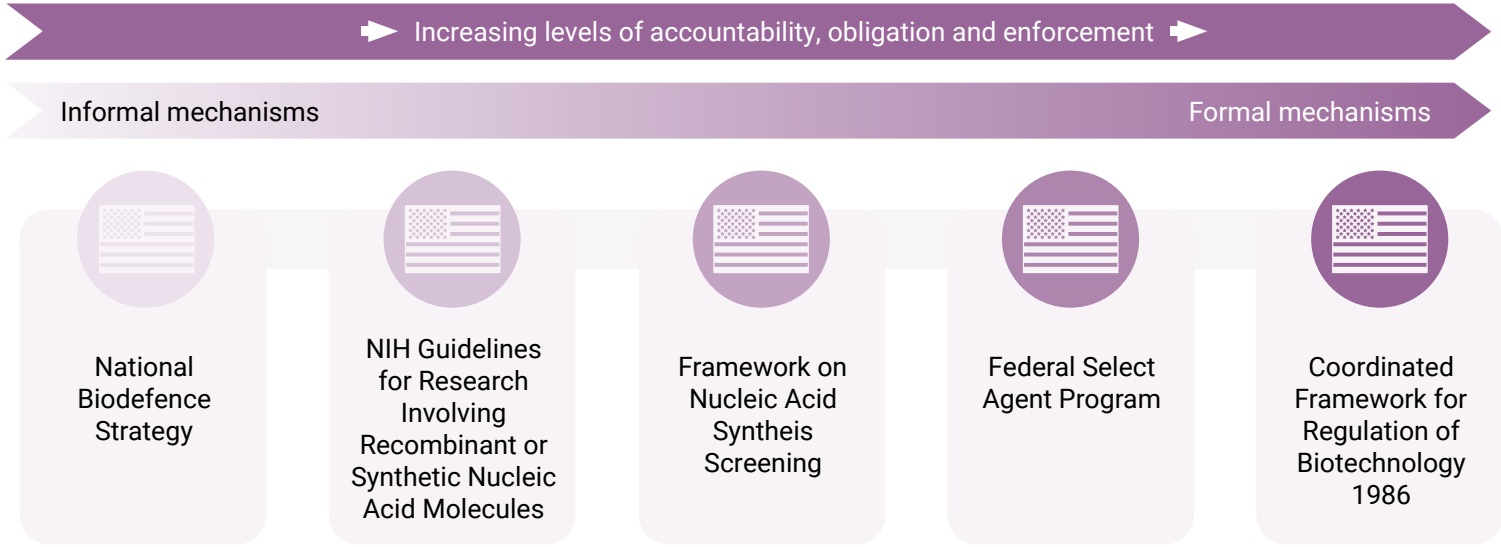
Uncertainties associated with the oversight of engineering biology in the United Kingdom

Uncertainties associated with the oversight of engineering biology in the United Kingdom include:

- Engineering biology developments represent heightened **biosecurity threats**, and current oversight mechanisms do not explicitly provide an adequate framework for risk assessment and management.
- Given the maturity and appetite for the use of AI in healthcare and life sciences, where engineering biology tools and techniques are widely applied, more specific risks have emerged related to **patient safety and privacy, liability, data accuracy and ownership** (Caudai et al. 2021; Holland et al. 2024; Dias and Torkamani 2019). These issues are not comprehensively addressed in the acts and frameworks relevant to biotechnologies and AI.
- **AI-enabled developments pose a security concern.** AI can lower the technical and knowledge barriers relating to genomics research, informing the public on materials and targets, and synthesis methods (Moon and Ghionis 2024). As a result, access to technologies such as ChatGPT is enabling public understanding of bioweapons, providing information on suitable viruses that could lead to a pandemic (Moon and Ghionis 2024). Although previous RAND research has shown that this information is limited, and step-by-step instructions are not provided to the user (Mouton et al. 2023), without proper oversight this open access format could lead to unintended consequences (Egan and Rosenbach 2023; Kuilken 2023).
- Oversight mechanisms on **building trust** and **accountability** in engineering biology are insufficient in the United Kingdom (Sciencewise 2024). It is important to engage society in dialogue on the potential benefits and risks of the rapidly developing field of engineering biology, and the related field of synthetic biology. Recent research has shown that **sceptical public attitudes** towards genetically modified foods in the past may make government, research and civil society stakeholders assume that people will be similarly mistrustful of newer biotechnologies (Sciencewise 2024).

5.4. Oversight of engineering biology in the United States

Figure 14. Illustrative oversight examples of engineering biology in the United States



Source: RAND Europe analysis.

Current oversight mechanisms in the United States

Given the wide scope of engineering biology and its applications in multiple and diverse sectors (such as chemicals, textiles, food, medicine, plant-related applications), there are several oversight mechanisms in the United States that are partially relevant to engineering biology. For instance, in 2012 alone there were 13 US federal government departments and agencies that supported biological research, ranging from the Department for Agriculture to the Space Administration (The White House 2012). Overall, the United States tends to take a **product-based approach to the regulation of biotechnology** (Li et al. 2021).[91] The key oversight mechanisms in the United States include:

91 Product-based regulation means regulation focusing on the nature of the products ready for market and the associated benefits and risks, and less on the technologies used to make these products. As (Li et al. 2021) write: 'The United States government has promulgated policies, regulations, and laws governing different biological products.'

- The National Biodefense Strategy and Implementation Plan for Countering Biological Threats, Enhancing Pandemic Preparedness and Achieving Global Health Security (known as the **National Biodefense Strategy**, issued in 2018 and updated in 2022 in response to the Covid-19 pandemic) outlines a national vision for addressing challenges from naturally occurring, deliberate or accidental biological threats. The strategy sets the course for the United States to combat real, serious and evolving 21st century biothreats (US Government 2022a). Alongside the associated **Implementation Plan and National Security Memorandum 15**, the strategy establishes a leadership structure and approach to coordinate the full range of biodefense activities carried out across the US government to protect the population from bioincidents (White House 2022a). It covers biosecurity concerns, as well as biosafety, public health and environmental protection. It describes how various agencies should coordinate when responding to bioincidents and directs the actions they should take regarding, for example, preparation and assessment. Annex IV lists all federal legislation and policy relevant to biodefense. The act is relevant to engineering biology given the technology's potential uses in the biodefense and security context, such as the development of new or more lethal strains of toxins/pathogens.
- The 2003 **Federal Select Agent Program (FSAP)** is managed by the Division of Regulatory Science and Compliance at the CDC, part of the US Department of Health and Human Services (HHS), and the Division of Agricultural Select Agents and Toxins at the Animal and Plant Health Inspection Service (APHIS), part of the USDA. The FSAP regulates the possession, use and transfer of biological select agents and toxins (e.g. anthrax and smallpox) that have the potential to pose a severe threat to public, animal or plant health, or to animal or plant products. FSAP currently regulates 68 select agents and toxins, and this list is regularly updated (US Government 2023). This mechanism is a potential avenue for mitigating the risk of engineering biology advances, combined with computational maturity, meaning that agents of concern could be generated for nefarious purposes.
- The **Coordinated Framework for Regulation of Biotechnology 1986** (updated in 1992 and 2017) is a foundational piece of legislation that forms the basis of many subsequent legislative acts (US EPA 2017a). It covers diverse fields to ensure a robust regulatory system for genetically engineered products, including human health, medicine, plants, animals, agriculture, food, chemicals, toxic substances and the environment. The 2017 update clarified for the first time the roles and responsibilities of the three regulatory agencies charged with the oversight of biotechnology products: the EPA, FDA and USDA (US EPA 2017a; 2024).
- A set of nine broad **Principles for Regulation and Oversight of Emerging Technologies** were published in March 2011 by the Executive Office of the President of the USA (White House 2011a). This directive included the emerging technologies of nanotechnology, synthetic biology and genetic engineering. It also stressed the need for coordinated research and development, as well as 'appropriate and balanced oversight'. The directive followed on from and emphasised the need to adhere to President Obama's Executive Order No. 13563, **Improving Regulation and Regulatory Review**, of January 2011 (White House 2011a).
- The **National Bioeconomy Blueprint (2012)** by the White House under President Obama recognised the great potential of biological sciences (the bioeconomy) for economic growth and society, specifically citing its potential in agriculture and

industry (fuels, materials, chemicals, and industrial enzymes derived from genetically modified systems), while also noting the significant associated security and safety risks. The blueprint recommended regulatory reforms to help fulfil the potential of the US bioeconomy, including lowering barriers to innovation, speeding up regulatory processes and making them more predictable, and reducing costs of regulatory processes (White House 2012).

- The 2019 Executive Order**, Modernizing the Regulatory Framework for Agricultural Biotechnology Products,** recognises the potential of biotechnology advances in revolutionising agriculture, enhancing rural prosperity and improving quality of life. It refers to biotechnology products for both plants and animals, and calls on regulatory agencies to streamline their work and modernise the regulatory framework (The American Presidency Project 2019).
- **Executive Order on Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy** (September 2022). This presidential executive order includes a specific focus on regulation to 'clarify and streamline regulations in service of a science- and risk-based, predictable, efficient, and transparent system to support the safe use of products of biotechnology'. It takes a product-based approach to regulation (White House 2022b).
- The US Senate (legislative upper house) passed the **United States Innovation and Competition Act of 2021** (previously known as the Endless Frontier Act) on 6 August 2021 (Library of Congress 2021). The overall aim of this act is to strengthen US global leadership in critical technologies through basic research in key focal technologies (artificial intelligence, high-performance computing and advanced manufacturing) and the commercialisation of those technologies to US businesses. The act addresses US technology and communications, foreign relations and national security, domestic manufacturing, education, and trade, which also pertain to engineering biology.
- **The CHIPS and Science Act 2022** is a US federal statute enacted by the US Congress and signed into law in August 2022. It combines two bipartisan bills: the **United States Innovation and Competition Act of 2021** (see above) and the **CHIPS for America Act**, which is focused on reshoring semiconductor manufacturing as a way of competing with China. The act authorises roughly US$280 billion in new funding to boost domestic research and manufacturing of semiconductors in the United States, and invests US$174 billion in the overall ecosystem of public sector research in science and technology, including biotechnology.
- **The National Engineering Biology Research and Development Initiative** was launched in 2019 to provide sustained financial support for engineering biology research and development, and for the establishment, curation and maintenance of curated genomics, epigenomics and other relevant omics databases (US Government 2022b).The cross-government initiative has made progress in coordinating research efforts across federal agencies and fostering collaboration with academic institutions, industry and international partners. Its current focus is on the use of engineering biology in biomanufacturing and sustainable agriculture.
- **The America COMPETES Act of 2022** focuses on strengthening US scientific and technological innovation. It also mandates the HHS to consider national security risks associated with sensitive genetic information. The act is expected to bring together – and subsequently distribute – access to data used in biotechnology discovery applications for investigators and biotechnology start-ups (Fedasiuk 2022).

- The NIH first issued its **Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules** in 1976, and they have been continuously updated since, most recently in 2024. The guidelines specify for researchers working on recombinant or synthetic nucleic acid molecules the level of physical containment or biological containment that needs to be in place.[92] While no legislation has resulted from these guidelines, they are considered essential by funders and universities conducting recombinant DNA research (both NIH-funded and funded by other sources). Federal agencies have also adopted the guidelines (Talbot 1983; NIH 2024).
- The CDC and the NIH first published a **manual on recommendations for the physical containment of pathogens**, Biosafety in Microbiology and Biomedical Laboratories, in 1984 (Li et al. 2021). It has since been updated six times, most recently in 2020, and continues to be a central and authoritative advisory document in the field of biosafety practice in the United States (CDC 2024).The manual covers pathogens that could be derived from engineering biology techniques.
- Medicines in the United States are governed by a set of laws known collectively as the **Federal Food, Drug, and Cosmetic Act (FD&C Act)** of 1938 (last amended in 2023) (National Archives Catalog 1938). The FDA is responsible for implementing this act to oversee the safety of food, drugs, medical devices and cosmetics. The FD&C Act outlines the regulatory approval and testing of pharmaceuticals, including specifications, labelling, safe handling and directions for the safe use of such drugs, as well as requirements for clinical trials (FDA 2022). Any drugs, devices and food derived from engineering biology tools and platforms are covered. Under section 408 of the FD&C Act, the EPA establishes the amount of pesticide chemical residues that may be present in food.
- The FDA regulates to protect and promote public health under the FD&C Act and the **Public Health Service Act** (last amended in March 2024). Its responsibilities include: governing the safety of most foods for humans and animals, including those produced using biotechnology; the safety and effectiveness of intentional genomic alterations in animals produced using biotechnology; the safety and effectiveness of human and animal drugs; and the safety, purity and potency of human biologics, including drugs and human biologics from plants and animals produced using biotechnology (US Government 2024).
- **The Toxic Substances Control Act (TCSA)** of 1976 is the main federal law on chemicals management and gives EPA various authorities to regulate chemical substances and/or mixtures, excluding certain categories such as food, drugs, pesticides, cosmetics and medical devices. The TCSA was updated and amended in June 2016 when President Obama signed the **Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg Chemical Safety Act).** The key elements of the 2016 act are a mandatory requirement for EPA to evaluate existing chemicals with clear and enforceable deadlines, risk-based

92 Recombinant and synthetic deoxyribonucleic acid nucleic acid molecules are defined by the NIH as: (1) molecules that a) are constructed by joining nucleic acid molecules and b) can replicate in a living cell, i.e. recombinant nucleic acids; or (2) nucleic acid molecules that are chemically or by other means synthesised or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e. synthetic nucleic acids; or (3) molecules that result from the replication of those described in (1) or (2) (NIH 2024). The NIH guidelines apply to all research projects (irrespective of whether they are NIH-funded) that involve recombinant or synthetic nucleic acid molecules and are conducted at or sponsored by an organisation that receives NIH support for recombinant or synthetic nucleic acid molecules (NIH 2024).

chemical assessments, greater public transparency for chemical information, and a consistent source of funding for EPA to carry out its responsibilities under the new law (US EPA 2013a; 2024).

- **Biotechnology regulations as pertaining to plants** were comprehensively revised for the first time in May 2020 by APHIS. APHIS coordinates responsibility for regulating genetically engineering organisms with other designated federal agencies as part of the Federal **Coordinated Framework for the Regulation of Biotechnology of 1986** (see above). The ambition of the 2020 revisions is to enable APHIS to regulate with more precision and to lessen the regulatory burdens for developers of organisms less likely to have plant pest risks (USDA 2020).
- Under the 2002 **Animal Health Protection Act** and the 2020 **Plant Protection Act**, the USDA regulates biotechnology products that may pose a risk to agricultural plant and animal health (USDA 2020; US Government 2000).
- Under the **Virus-Serum-Toxin Act**, amended in 1985, the USDA has regulatory oversight over products of biotechnology included in veterinary biologics and ensures that veterinary biologics are pure, safe, potent and effective (US Government 1985).
- Under the **Federal Meat Inspection Act,** the **Poultry Products Inspection Act** and the **Egg Products Inspection Act**, the Food Safety and Inspection Service (FSIS) – a public health agency in the USDA – inspects all meat, poultry and processed egg products in interstate commerce. The FSIS uses these acts to regulate products under its jurisdiction, including those derived using genetic engineering.
- Under the **Federal Insecticide, Fungicide and Rodenticide Act** enacted in 1947 (and amended in 1972 and 2003), the EPA regulates pesticides (US EPA 2013b).
- In line with President Biden's Executive Order on the Safe, Secure, and Trustworthy Development of Artificial Intelligence (AI) (see section 5.7, Case Study 2), in April 2024 a **Framework on Nucleic Acid Synthesis Screening** was issued by the White House Office of Science and Technology Policy.[93] This framework aims to encourage synthetic nucleic acid providers to implement comprehensive, scalable and verifiable screening mechanisms, and assist in mitigating the risks of applying AI to synthetic biology (White House 2024b).
- The 2002 **US Farm Bill** created the **BioPreferred Program,** led by the USDA. The programme has two main components: 1) a federal procurement mandate for bio-based products that means federal agencies buy bio-based products from categories the USDA has identified as having bio-based content minimum levels; and 2) a voluntary labelling initiative for bio-based products that uses third-party testing to quantify how much 'new carbon' (i.e. derived from plants and other renewable agricultural, marine, and forestry materials) is in the products (OECD 2021).

93 Nucleic acids are 'the critical building blocks for life science research and development (R&D) —including the development of new biomedical products, novel strategies for recycling and energy production, and the creation of new classes of materials.... Nucleic acid synthesis screening is an effective, targeted measure to mitigate the potential for misuse of AI-enabled biotechnologies.' (The White House 2024b).

Emerging oversight mechanisms in the United States

- The **National Security Commission on Emerging Biotechnology (NSCEB)** is a legislative branch advisory entity requested by Congress to conduct a thorough review of how advancements in emerging biotechnology and related technologies will shape current and future activities of the Department of Defense (NSCEB 2024a). **Since December 2023, it has produced more than 30 reports, press releases and public letters of support** on diverse topics, including on the risks of AIxBio (the convergence of AI and biotechnology), policy options for AIxBio, support for the **Biosecure Act** (see end of this section), bioliteracy (i.e. public awareness and education about biotechnology), biomanufacturing, biological data as a strategic resource, gene synthesis security, and the impacts of biotechnology on agriculture and the environment. It produced an interim report to the president and the Armed Services Committees in December 2023. It is due to submit a final, unclassified report in December 2024, including recommendations for action by Congress and the federal government (NSCEB 2024a). In addition, the commission has **developed its first three legislative proposals**: the **Agriculture and National Security Act**, the **Agricultural Biotechnology Coordination Act**, and the **Biotechnology Oversight Coordination Act**. These bills direct the USDA and other agencies to consider emerging technology in multiple ways. Each bill would aim to strengthen the government's abilities at the intersection of national security and emerging biotechnology (NSCEB 2024b).
- FAS is leading on efforts to find creative policy **recommendations for the oversight of biosecurity risks from AI**. It organised a 'Bio x AI Policy Development Sprint' in 2023 that enabled leading scientists to generate – through a bottom-up approach – some innovative ideas for the oversight of biodesign tools (FAS 2023).
- Seven leading large language model-based chatbot developers recently signed up to a **voluntary commitment** to follow certain security measures proposed by the White House in July 2023, including internal and external security testing to guard against AI-based biosecurity risks and help achieve responsible AI (White House 2023).
- The **Artificial Intelligence and Biosecurity Risk Assessment Act** and the **Strategy for Public Health Preparedness and Response to Artificial Intelligence Threats Act** are in the process of being discussed (in July 2023, they were at the committee stage in the US Senate) (Markey 2023; Library of Congress 2023a; 2023b). If enacted into law, the acts would give the US federal government a mandate to understand the public health security risks of AI from engineered and accidental biothreats, and naturally occurring bioincidents. The Artificial Intelligence and Biosecurity Risk Assessment Act would also mandate the Assistant Secretary for Preparedness and Response to research how AI tools could be used to generate biological weapons.
- The United States government has implemented the **Policy for Oversight of Life Sciences Dual Use Research of Concern 2012** (US EPA 2017b), which establishes review processes for research projects that may pose dual-use threats.
- If the **Biosecure Act**, introduced in the House of Congress in January 2024, becomes law, it would prohibit federal contracting with certain biotechnology providers 'of concern' connected to foreign adversaries. A list of providers is specified in the bill and includes BGI, MGI, Complete Genomics and WuXi AppTec, as well as any subsidiary, parent affiliate or successor of such entities,

and any entity that poses a risk to US national security based on specified activities, with exceptions. The bill prohibits executive agencies from: 1) procuring or obtaining any biotechnology equipment or service produced or provided by a biotechnology company of concern; or 2) entering into a contract or extending or renewing a contract that uses such equipment or service or that will require the direct use of such equipment or services. Those agencies may not obligate or expend loan or grant funds for such purposes (Library of Congress 2024).

Other mechanisms of relevance in the United States

- The **Executive Order on Safe, Secure, and Trustworthy Artificial Intelligence** (October 2023) is an important broad-scope presidential oversight mechanism that aims to help the United States be a global frontrunner in reaping the benefits from and managing the risks of AI. The executive order creates new standards for AI safety and security, protects the privacy of American citizens, advances equity and civil rights, stands up for consumers and workers, promotes innovation and competition, and advances American leadership around the world (White House 2023). Many of its components refer to risks posed by the combination of AI and biotechnologies such as engineering biology. For further information see section 5.7, Case Study 2.
- The **Executive Order on Preventing Access to Americans' Bulk Sensitive Personal Data and United States Government-Related Data by Countries of Concern** (February 2024) is another significant presidential oversight mechanism that protects US citizens' sensitive personal health data and human genomic data, which is relevant to engineering biology as it relies on health and genomic datasets in its activities (White House 2024a).

Uncertainties associated with engineering biology oversight in the United States

Uncertainties associated with engineering biology oversight in the United States include:

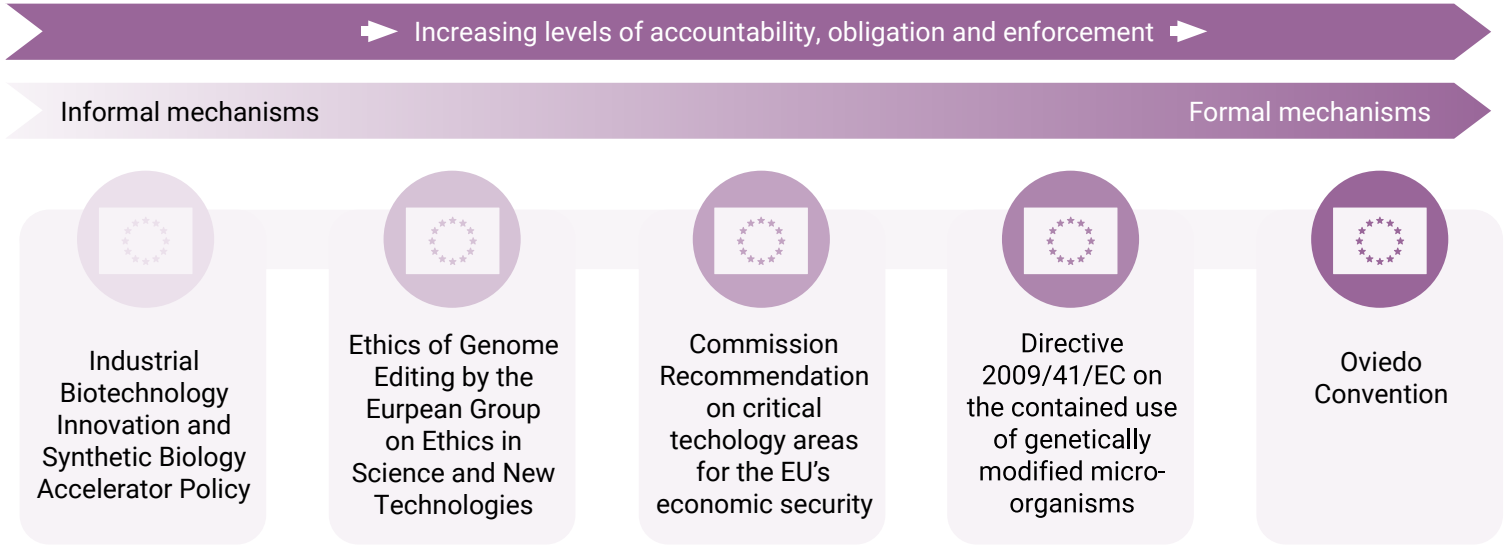
- **The potential risks** of technological advances in engineering biology create novel security threats (Li et al. 2021) that current oversight mechanisms are not yet agile enough to address.
- Given the maturity and appetite for the use of AI in healthcare and life sciences, which are areas where engineering biology tools and techniques are widely applied, specific risks have emerged related to **patient safety and privacy, liability, data accuracy** and **ownership** (Caudai et al. 2021; Holland et al. 2024; Dias and Torkamani 2019). These issues are not comprehensively addressed in the acts and frameworks for biotechnologies, nor for AI.
- **AI-enabled developments pose a security concern.** AI can lower the technical and knowledge barriers to genomics research, providing information to the public on materials and targets, and synthesis methods (Moon and Ghionis 2024). As a result, access to technologies such as ChatGPT are enabling public understanding of bioweapons, for example providing information on suitable viruses that could lead to a pandemic. Although previous RAND research has shown that this information is limited, and step-by-step instructions are not provided to the user (Mouton et al. 2023), this open access format could lead to unintended consequences without proper oversight (Egan and Rosenbach 2023; Kuilken 2023).
- Members of the US AI community, including those signed up to the voluntary commitments issued by the White House in 2023), have issued **calls to ensure that governance mechanisms**

recognise the difference between general AI tools such as chatbots and more biology-specific biological design tools (BDTs). BDTs are AI models that have been trained on biological data (specifically on the amino acid sequences of proteins or other biological sequences) to be able to produce biological sequences as outputs rather than natural language. BDTs are meant to help solve biological engineering tasks by, for example, predicting sequences or protein structures. They are therefore more specific than large language model-powered chatbots (Walsh 2023) and require oversight.

- There are **long and complex processes to get regulatory approval for engineering biology based bioeconomy products.** This is because approval is needed from several different agencies, given the number of sectors involved, and there are various safety requirements that need to be met from the perspective of each of these sectors/agencies (Hodgson et al. 2022).
- There is **low societal trust and acceptance of applications of engineering biology** based on worries about the impacts on the environment and natural world and unintended consequences of the technologies. Financial or geographic inequalities (i.e. because of the cost of treatment or location of treatment centres) in accessing medical applications developed due to engineering biology also hinder societal trust and acceptance (US Government Accountability Office 2023).

5.5. Oversight of engineering biology in the European Union

Figure 15. Illustrative oversight examples of engineering biology in the European Union



Source: RAND Europe analysis.

Current oversight mechanisms in the European Union

The oversight of engineering biology in the EU largely concerns the regulation of GMOs. In this regard, the EU has adopted a **precautionary approach**, focusing on the **contained use** of GMOs and, in some cases, their carefully considered and **deliberate release** into the environment (Sundaram et al. 2023). This approach prioritises the protection of human and environmental health. Aspects of human genome editing are similarly considered with a precautionary approach, with relevant governance mechanisms existing in biomedicine and health. Relevant engineering biology oversight mechanisms in the EU include:

- **Directive 2001/18/EC on the deliberate release of GMOs into the environment** establishes a prior authorisation system for GMO release, rules for experimental release, labelling and monitoring requirements, and an opt-out system for member states (European Union 2001).
- **Directive 2009/41/EC on the contained use of genetically modified micro-organisms** establishes rules for the contained use of GMOs, namely a notification process based on the GMO's

class designation. The directive also requires an emergency plan for potential failures in containment (European Union 2009).

- **Regulation (EC) 1946/2003 on transboundary movements of GMOs** implements the Cartagena Protocol to the Convention on Biological Diversity (CBD) within the EU, providing export rules that include notification processes for GMOs (European Union 2003).
- **Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions** harmonised national patent law and established ethical criteria for patenting new biotechnology inventions (European Union 1998).
- The **Oviedo Convention**, referred to previously in the context of organoids and embryology, established by the Council of Europe in 1997, is the only international legally binding instrument for the protection of human rights in biomedicine. It is regarded as the European treaty on patient rights. A report published in 2022 by the Council of Europe Steering Committee for Human Rights in the fields of Biomedicine and Health, **Intervention on the Human Genome: Re-examination Process of Article 13 of the Oviedo Convention: Conclusions and Clarifications** (Council of Europe 2022), clarifies the convention's implications for human genome modification in research and clinical practice.
- The **Nagoya Protocol** is an international agreement under the CBD that aims to ensure fair and equitable sharing of benefits arising from the use of genetic resources. It establishes rules for access to these resources and promotes the protection of indigenous knowledge and biodiversity.

Emerging oversight mechanisms in the European Union

- **Proposal for a regulation of the European Parliament and of the Council on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625**, published in 2023, modified and updated regulation 2017/625 to include greater specificity and applicability to new genomic techniques and their use in the production of food and feed. Compared to other legislation regarding genetic modification, which focus on containment, the proposal also focuses on creating an enabling environment for research and innovation (European Union 2023a).
- **Commission Recommendation (EU) 2023/2113 of 3 October 2023 on critical technology areas for the EU's economic security for further risk assessment with member states** identified biotechnologies (specifically genetic modifications, new genomic techniques, gene drives and synthetic biology) as a critical technology for economic security in the EU and acknowledged their potential for dual use. The recommendation indicates further risk assessments that may inform changes to EU or member state enforcement instruments or contribute to the design of future national or EU policy actions (European Union 2023b).
- In March 2024, the European Commission issued a **Communication to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Building the future with nature: Boosting Biotechnology and Biomanufacturing in the EU** (European Union 2024a), which indicates forthcoming efforts to streamline regulatory pathways for biotech innovations. As part of this, a study is expected to lay the foundations for a possible EU Biotech Act and the establishment of an EU Biotech Hub. The communication also indicates that the European Commission will

support regulatory sandboxes to facilitate the supervised testing of novel innovations.

- In 2023, the **Industrial Biotechnology Innovation and Synthetic Biology Accelerator** issued a policy note that discussed the need for dedicated European policy to support the international competitiveness of the European industrial biotechnology and biomanufacturing sectors. The note called for members states to undertake strategic planning and for EU institutions to develop supportive legal, logistic and financial mechanisms (Industrial Biotechnology Innovation and Synthetic Biology Accelerator 2023).
- The European Group on Ethics in Science and New Technologies' opinion on the **Ethics of Genome Editing**, published in 2021, discusses ethical questions related to the use of next generation genome editing tools such as CRISPR-Cas9 in humans, animals and plants. It recommends that the European Commission, WHO, the Food and Agriculture Organization, and the International Organisation for Standardization (ISO) develop international guidelines and standards for the ethical and safe use of genomes across applications (European Union 2021a).

Other mechanisms of relevance in the European Union

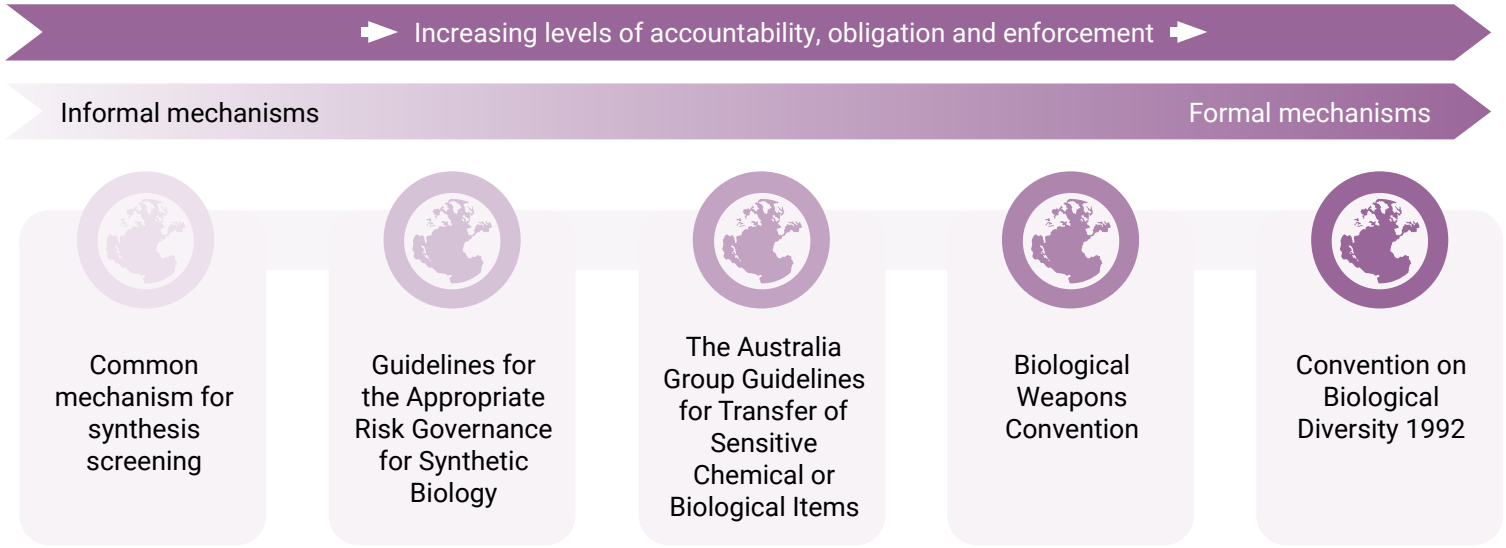
- The **European Health Data Space** supports the safety and quality of SoHO. It includes EU-supported national-level oversight of health data (e.g. training and IT) and allows patients access to their health data throughout the EU.
- **EU GDPR** set the framework for handling and protecting personal data in the EU, including genetic information.
- The **EU AI Act** takes a risk-based approach to AI governance, where the regulatory approach varies based on the perceived risk of the AI use. The act also indicates that **regulatory sandboxes** will be used to test novel applications of AI-enabled technologies under controlled conditions.

Uncertainties associated with engineering biology oversight in the European Union

- **Dedicated oversight mechanisms outside of food and feed products:** As current oversight mechanisms focus on GMOs, particularly those used for food and feed, they lack applicability and specificity to other applications of engineering biology, notably health and medicine, environmental biotechnology (climate change, bioremediation), energy, industrial biotechnology (e.g. materials, chemicals), and national security (RHC 2022; Sheets et al. 2023).
- **Some products are borderline technologies, straddling contained use or deliberate release**. Developments in engineering biology have resulted in products that blur the boundaries of whether they fall under contained use or deliberate release directives (i.e. products that may undergo 'contained release', e.g. whole-cell biosensors), highlighting that this dichotomous categorisation is increasingly tested by advancements in the field, and the desire and potential need to test novel products (Sundaram et al. 2023). This also highlights a lack of clarity regarding the responsible EU body in such cases, which is another gap.

5.6. Oversight of engineering biology in international forums

Figure 16. Illustrative oversight examples of engineering biology in international forums



Source: RAND Europe analysis.

Current oversight mechanisms in international forums

There are numerous WHO and UN frameworks and guidelines relevant to engineering biology oversight that span laboratory safety and biosecurity guidelines, responsible life sciences, and the safe transport of infectious substances, among others. The list below is therefore far from exhaustive, and provides a selection of directly relevant and more notable mechanisms:

- The **Convention on Biological Diversity (CBD) 1992**, adopted by 196 parties (with the notable exception of the United States), governs conservation and the sustainable use of biological resources, including genetic resources (Secretariat for the Convention on Biological Diversity 1992). The convention sets national and global targets, the latest of which are included in the Kunming-Montreal Global Biodiversity Framework (Convention on Biological Diversity 2024). **Decision 14/19 Synthetic biology**, adopted by the Conference of Parties in 2018, explicitly states an agreement to conduct multidisciplinary assessments of synthetic biology advancements within the context of the CBD (Convention on Biological Diversity 2024).

- The **Cartagena Protocol on Biosafety 2003**, a supplementary agreement to the CBD adopted by 173 parties, governs the movements of biotechnology-generated living modified organisms across international borders. It focuses primarily on living modified organisms for intentional release into the environment (United Nations 2000).
- **The Nagoya Protocol** is an international agreement under the CBD that aims to ensure fair and equitable sharing of benefits arising from the use of genetic resources. It establishes rules for access to these resources and promotes the protection of indigenous knowledge and biodiversity.
- **The BWC**, established in 1972 and currently adopted by 187 parties, bans the development, transfer, stockpiling and retention of bioweapons and their associated delivery mechanisms. The text of the convention is understood as prohibiting all hostile uses of biology, extending to novel synthetic agents, in cases where no prophylactic or peaceful use can be found for a given biological agent. Mechanisms to support implementation are the **1540 Committee and the UN Security Council resolutions,** and the UN Secretary General's **Mechanism for Investigation of Alleged Use of Chemical and Biological Weapons** (Hamilton et al. 2021).
- WHO's 2021 **Human Genome Editing: A Framework for Governance** recommends that the international governance of human genome editing includes: international collaboration, human genome editing registries, responsible international research practices, a mechanism for the confidential reporting of illegal or unethical activities, equitable access to opportunities for intellectual property, and the WHO-led development of ethical values and principles. WHO simultaneously published complementary pieces, Human Genome Editing: Position Paper and Human Genome Editing: Recommendations, which address human genome editing as a public health tool (WHO 2021a).
- The **Guidelines for the Appropriate Risk Governance of Synthetic Biology**, developed by the International Risk Governance Council (IRGC) in 2010, aim to help policymakers take an approach that supports innovation, minimises risk to people and the environment, considers interests and values of relevant stakeholders, and adapts to the changing scientific and technical landscape (IRGC 2010). While it is unclear whether the guidelines are active or being updated, the IRGC is actively publishing risk governance approaches in general.
- **The Australia Group Guidelines for Transfer of Sensitive Chemical or Biological Items**, published in 2015, outlines control guidelines aimed at harmonising export controls to prevent the development of chemical and biological weapons. Currently, 42 parties participate in the voluntary, informal group, including the United Kingdom, United States and the EU (Australia Group 2015).

Emerging oversight mechanisms in international forums

- The 2023 **Third International Summit on Human Genome Editing** discussed research and regulation related to human genome editing, including developments in clinical trials and genome editing tools (e.g. CRISPR-Cas9). It also addressed ethical, social and accessibility issues related to new developments in the field. Oversight discussions included presentation of the WHO recommendations on human genome editing, reporting on the state of governance across nations, and considerations of equity and public welfare (Royal Society 2023).

- In 2022, parties to the CBD adopted a proposal **to expand the scope of the Nagoya Protocol to include genomic sequence and related digital data** (Klünker and Richter 2022). The CBD agreed that genetic resources should be shared fairly and equitably in the spirit of the protocol but indicated that a specific benefits-sharing agreement is needed (Convention on Biological Diversity 2018). This is expected to be a topic of discussion at the UN Biodiversity Conference 2024.
- In 2022, the **Nuclear Threat Initiative (NTI)** presented on **DNA Synthesis Screening & the International Common Mechanism** at the G7 Global Partnerships Conference on Current Biosecurity Challenges (NTI 2022). The presentation highlighted the risks and benefits of existing and emerging gene synthesis technologies, and outlined a common mechanism for screening customers that would be housed at the **International Biosecurity and Biosafety Initiative for Science** (NTI 2024).
- In late 2023, the **Engineering Biology Research Consortium**, a US-based consortium with international membership, published a white paper on **Security Considerations at the Intersection of Engineering Biology and Artificial Intelligence** (Johnson et al. 2023). The paper recommends establishing an international stakeholder forum to identity and address security concerns at the intersection of engineering biology and AI.
- In March 2024, the CBD's Ad Hoc Technical Group on Risk Assessment published **Additional Voluntary Guidance Materials to Support Case-by-Case Risk Assessments of Living Modified Organisms Containing Gene Drives**[94] (Convention on Biological Diversity 2024). The publication provides guidance on safety considerations associated with the rapidly developing area of gene drives, responding to a lack of processes specific to gene drives within the current CBD and associated protocols.
- In 2021 the OECD published an implementation report related to the **Recommendation of the Council on Assessing the Sustainability of Bio-Based Products** (OECD 2021). The report contains recommendations to develop and implement national frameworks for assessing the sustainability of bio-based products, considering their environmental, economic and social impacts throughout the life cycles of bio-based products.
- The Global Alliance for Genomics and Health (GA4GH) **sets standards** and **provides guidelines** to facilitate and expand genomic data use within a **human rights framework**. In September 2024 it published a brief on the recent changes to the EU Health Data Space regulation to catalyse thinking on genomic data use (GA4GH 2024).

Other mechanisms of relevance in international forums

The development of new international oversight mechanisms for engineering biology is an ongoing discussion across various forums. Although regional or national developments do not constrain the development of new international oversight mechanisms, they do influence them, and vice versa. For example, the **EU AI Act**, as a prominent first mover in AI regulation, largely takes a supportive stance on AI in biotechnologies, with the aim of facilitating generative AI uptake in the sector through the EU's **GENAI4EU** initiative (European Union 2024a). As with other areas where the EU was a first mover (e.g. GDPR for data privacy regulation), early EU legislation

94 A gene drive is a 'system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced' (National Academies Press 2021).

may set the tone for subsequent mechanisms developed nationally and internationally. The not-for-profit GA4GH also sets **standards and frameworks** to facilitate genomic data use globally in the context of human rights.

Uncertainties associated with engineering biology oversight in international forums

- **AI-enabled engineering biology:** Current developments and capabilities in AI-enabled engineering biology are not captured in existing formal international oversight mechanisms. Oversight gaps include: 1) the use of and products resulting from AI integration; 2) the use and governance of data in the training and deployment of AI-enabled engineering biology models; and 3) dual-use capabilities of AI-enabled engineering biology (Undheim 2024).
- **Dual-use capabilities:** Formal international oversight mechanisms regulating the malicious use of biotechnologies, including the BWC, have general weaknesses in remaining relevant in the face of rapid advancements at the intersection of AI integration, automation, additive manufacturing and cloud computing (Saunders 2021; WEF 2019). There is also ongoing debate as to whether synthetic biological products (e.g. non-biological products that mimic biological effects, such as biomimetics) are encompassed appropriately within existing bioweapon governance (Johnson et al. 2023). Existing formal oversight mechanisms also have gaps related to the increasing ease of access to information enabled by generative AI (Undheim 2024).
- **Heritable genome editing:** There is a lack of existing formal international oversight mechanisms for heritable human genome editing technologies for somatic and germline cells, as it is prohibited in many nations including the United States and several European countries. Multiple stakeholders have acknowledged the need to establish international scientific and ethical standards, with WHO's work actively pursuing efforts in this regard (National Academy of Medicine, National Academy of Sciences, and the Royal Society 2020).
- **DNA synthesis** is a key enabling technology for engineering biology. Democratised access to these technologies raises the risk of deliberate and accidental release of engineered pathogens. **Customer screening** among commercial DNA synthesis providers is currently voluntary, leaving gaps in surveillance that could be exploited by malicious actors (NTI 2022).
- **Engineered gene drives** represent a challenge for current international governance frameworks, notably the CBD and its Cartagena Protocol, due to trade-offs associated with their use outside the laboratory (Reynolds 2020). Depending on how they are used, gene drives can enhance or homogenise genetic diversity. Furthermore, gene drives show potential to address prominent human health issues (e.g. malaria through the use of gene drives in mosquitos), but this may come at a cost to genetic diversity in the species (Hartley et al. 2022). To date, oversight bodies have struggled to balance the potential risks and benefits, particularly as prominent bodies such as the CBD and WHO have differing priorities (biodiversity and health, respectively) (Thizy, Coche, and Vries 2020).

5.7. Case studies of engineering biology oversight mechanisms

Case study 1:
United Kingdom – Regulatory sandbox to support experimentation in oversight mechanisms associated with engineering biology

Table 7. UK regulatory sandbox and experimentation in regulation

Technology area:	Engineering biology
Oversight example:	Engineering Biology Sandbox Fund
Type(s) of oversight mechanism(s):	Regulatory sandbox and experimentation in regulation
Jurisdiction:	United Kingdom
Timescale:	Launched early 2024 with plans to run the sandboxes until 2027

Why is the oversight required?

In the United Kingdom, engineering biology is a critical technology, with multiple efforts focused on progressing discovery research, and on implementation and commercialisation. There are a vast number of regulations that cover engineering biology in some way (as demonstrated by the sections above in this chapter); however, one interviewee noted that many of these relevant **regulations are not designed with biology in mind**, exposing the need for a nuanced approach to catalyse innovation in engineering biology.[95]

There also appears to be limited **dialogue between the engineering biology industry and regulators**, with one interviewee stating that industry members (many of whom are at an early stage of developing engineering biology applications) find it hard to reach out to regulators, and regulators struggle to devote time to reaching out to related industry.[96] The regulators also have limited forums for interacting with each other to discuss how engineering biology touches upon their areas of oversight, and whether there are areas of growth that warrant a review of current oversight. Following a 2023 review by the Government Chief Scientific Adviser (UK Government 2023d), DSIT set up the Engineering Biology Regulators Network (EBRN) in 2023 to address the lack of dialogue between the diverse regulatory bodies. However, mechanisms are needed to **upskill UK regulators** regarding engineering biology applications so that they can anticipate and develop future-focused oversight.

There is a developing need to get **more clarity** in this complex and evolving ecosystem so that innovation can be encouraged and SMEs incentivised to invest in the sector. For example, one interviewee noted that it is likely more SMEs will work on precision breeding once DEFRA implements all aspects of the 2023 Genetic Technology Act.[97]

What oversight is being proposed?

Regulatory sandboxes have existed for several years in diverse sectors. The UK's Financial Conduct Authority (FCA) first trialled the

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use of regulatory sandboxes in the financial services sector in 2015. A detailed case study on the use of these sandboxes is provided by Gunashekar et al. (2019). In a report published in November 2015, the FCA defined a regulatory sandbox as a 'safe space' in which businesses can test innovative products, services, business models and delivery mechanisms without immediately incurring all the normal regulatory consequences of engaging in the activity in question (FCA 2015).

The UK government announced an Engineering Biology Sandbox Fund (EBSF), overseen by DSIT, in February 2024. It is designed to be an experimental space where the engineering biology industry and UK regulators can exchange information on helpful and hindering regulations for innovations relevant for engineering biology (UK Government 2024a). It aims to help UK regulators increase their capacity and adapt their regulations to the transformations enabled by engineering biology. Although not an oversight mechanism, rather an opportunity to develop and experiment with regulatory reform in a contained environment, it is anticipated that some relevant oversight mechanisms may emerge from this fund.

The EBSF comprises a pot of R&D money of up to £5 million that will be allocated on a competitive basis as grants to UK regulators between February 2024 and the end of March 2027. UK regulators can bid for sandbox funds jointly or individually. According to the sandbox fund competition documents available online, projects can run for between 6 and 24 months. This fund will 'sponsor sandboxes led by regulators which aim to accelerate regulatory reform and encourage business innovation and investment.' (UK Government 2024a).

Two or three funding rounds are envisioned, and applicants must be UK regulators.[98] Round 1 is closed for applications, with the winners due to be announced at the time of writing this report. Round 2 is planned to be launched in December 2024, with the DSIT team responsible for overseeing and coordinating the fund anticipating getting more applications given increasing awareness.[99] One interviewee noted that the funding model is unusual, as DSIT is giving R&D grants to other parts of government (i.e. UK regulatory bodies).[100]

DSIT has deliberately kept the scope of the EBSF broad due to the diversity of the many sectors (e.g. health, chemicals, agriculture, fuels, environment) in which engineering biology is forecast to drive transformative change. A sandbox funded through the EBSF could be a physical environment where people go to do work, for example in robotics, or it could be a space for greater dialogue between regulators and businesses that are developing new engineering biology applications (many of which are at an early stage).[101]

What is the future trajectory for the oversight mechanism?

According to an interviewee, DSIT hopes that the sandbox fund will lead to new engineering biology regulations and frameworks being proposed or issued by UK regulators, i.e. new forms of oversight mechanisms that are stronger and more legally enforceable than codes of conduct. Moreover, the same interviewee perceived that the EBSF will help to create new standards on safety and measurement, in conjunction with the NPL and UK National Measurement Laboratory.[102]

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According to an interviewee, the outputs of the EBSF will be welcomed broadly as most experts working in engineering biology in the United Kingdom agree that there is insufficient regulation for engineering biology.[103]

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

While it is premature to evaluate the effectiveness of the EBSF given its recent launch, it signifies the UK government's appetite for experimental and agile regulation, with the fund providing room for UK regulators to use their topical expertise through the lens of engineering biology applications.

The sandbox idea drew on an earlier Regulators' Pioneer Fund (run by the former Department for Business, Energy & Industrial Strategy and the Department for Business & Trade), which launched in 2021 to support UK regulators keen to experiment and try something different (UK Government 2022c). Similar in structure and process to the EBSF, the Regulators' Pioneer Fund was not for a particular technology (although often the fund supported a particular technology, e.g. a sandbox for robotic submarines). One interviewee noted that given the Regulators' Pioneer Fund demonstrated impact, the EBSF has been developed from something that works.[104]

The EBSF embraces communication. Facilitating dialogue between UK regulators and engineering businesses is one of the key aims of the EBSF, although it is too early to assess success in this regard.

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Case study 2:
United States – Executive Order on Safe, Secure, and Trustworthy AI focusing on genomic data and risks from Biological Design Tools (BDTs)

Table 8. The US Executive Order on Safe, Secure, and Trustworthy AI focusing on genomic data and risks with BDTs

Technology area:	Engineering biology
Oversight example:	Executive Order no. 14110 on Safe, Secure, and Trustworthy Artificial Intelligence with a focus on aspects relating to genomic data and risks with BDTs
Type(s) of oversight mechanism(s):	Presidential executive order and associated decrees
Jurisdiction:	United States
Timescale:	October 2023 to present

Why is the oversight required?

Given the speed and scale of technology maturity witnessed in AI, and its application to other technology sectors such as engineering biology, multiple studies have highlighted the need for bespoke mechanisms of oversight that can recognise the risks posed by the developments and provide related transparency and mitigations

(Walsh 2023; Botes 2023; Johns Hopkins Center for Health Security 2023; FAS 2023).

Oversight is specifically needed to mitigate the risks from dual-use research and applications, including the development of bioweapons, when AI advancements are applied to engineering biology tools. DNA-based surveillance is another biosecurity threat posed by AI powered engineering biology technologies: commercial DNA databases have a risk of becoming the next frontier of 'surveillance capitalism' (Kemp 2021; Kemp et al. 2020). To counter the threat of greater surveillance, the US government is taking steps to put in place more restrictions on genomic data being shared outside of the United States, for example the Biosecure Act was introduced to the House of Congress in 2024 (see section 5.4). In a report published in November 2023, the Engineering Biology Research Consortium highlighted three technological areas that need to be monitored due to potential security threats if used by actors with malicious intents: 1) *de novo* biological design[105]; 2) closed-loop autonomous labs[106]; and 3) large language models.[107] The report also noted that it is hard to assess how much of a risk these technologies pose and difficult to reach agreement on how to stop or mitigate the risks (Johnson et al. 2023).

While it is important to mitigate against the risks of these developments, the United States remains at the forefront of international efforts in reaping the benefits from AI and tangential developments in biology, which requires novel mechanisms of oversight.

What oversight is being proposed?

Executive Order (EO) no. 14110 on Safe, Secure, and Trustworthy Artificial Intelligence is an important presidential oversight mechanism that came into effect in October 2023 to create new standards for AI safety and security, protect the privacy of American citizens, advance equity and civil rights, stand up for consumers and workers, promote innovation and competition, and advance American leadership around the world. It establishes a governance framework for the safe and responsible development and use of AI (White House 2023).

In the United States, EOs are a frequently used oversight mechanism at the federal level and have long been used by presidents to make significant policy decisions unilaterally (Mayer 1999; Lowande and Rogowski 2021). EOs direct policy and guidelines that are subsequently developed and implemented by various federal and state agencies and government departments. The EO on Safe, Secure, and Trustworthy Artificial Intelligence aims to enable the United States to become one of the frontrunners globally in reaping the benefits from and managing the risks of AI and its applications to engineering biology tools.

Within this broad EO, several clauses are relevant to engineering biology, including developing strong **new biological synthesis standards**. Noting the aim to protect the country from potential risks of using AI to engineer dangerous biological materials, this clause mandates the creation of robust new standards on biological synthesis screening. Funding agencies for life-science projects

105 *De novo* biological design refers to the process of creating novel biological systems, molecules or organisms from scratch.

106 Closed-loop autonomous labs are advanced laboratory systems that integrate automation, robotics, AI and data analytics.

107 Large language models are advanced AI models that are trained on vast amounts of text data (billions of words) to understand and generate human language.

must develop these standards to be eligible for receiving federal funding in the future. This is a strong incentive to ensure appropriate screening and manage risks potentially made worse by AI (White House 2024c).

The EO states that actions will be taken 'to reduce the risk of misuse of synthetic nucleic acids, which could be substantially increased by AI's capabilities in this area, and improve biosecurity measures for the nucleic acid synthesis industry'. These include establishing criteria for flagging and identifying sequences of concern, as well as customer screening mechanisms (White House 2023).

Another clause in the EO aims to support the **responsible use of AI in healthcare** and in developing **affordable and life-saving drugs**, which is relevant to AI-supported engineering biology in the context of drug screening and drug design. The HHS will establish a safety programme to receive reports of, and try to remedy, harmful or unsafe healthcare practices involving AI. The EO has some specific directives about algorithms used in healthcare settings that are designed to protect patients from harm (Miliard 2023). It also states that a strategic plan for the responsible use of AI in the health and human services sector, including **medical device safety**, should be developed.

The EO required the National Science Foundation (NSF) to fund and launch AI-focused NSF Engines, so-called Regional Innovation Engines (NSF Engines), within 150 days of the EO. One of the NSF Engines, the Piedmont Triad Regenerative Medicine Engine in North and South Carolina states, launched recently with an initial investment of US$15 million over two years and will build on the world's biggest regenerative medicine cluster to create and scale breakthrough clinical therapies, including by leveraging AI (White House 2023; NSF 2024).

In the nine months since the EO was passed, several significant developments have occurred that impact the oversight of engineering biology. The Federal Department of Defense has signed a contract with the National Academies of Sciences, Engineering and Medicine to conduct a consensus study: Assessing and Navigating Biosecurity Concerns and Benefits of Artificial Intelligence Use in the Life Sciences. The topics covered are AI, biological data and biosecurity risks. The aims of this study are to:

- Assess how AI can increase biosecurity risks, including risks from generative AI trained on biological data, and make recommendations on how to mitigate those risks.
- Consider the national security implications of the use of data and datasets, especially those associated with pathogens and omics studies, that the United States government hosts, generates, funds the creation of, or otherwise owns, for the training of generative AI models, and make recommendations on how to mitigate the risks related to the use of these data and datasets.
- Assess how AI applied to biology can be used to reduce biosecurity risks, including recommendations on opportunities to coordinate data and high-performance computing resources (National Academies of Sciences, Engineering, and Medicine 2024).

At the end of April 2024, the Department of Homeland Security published a report for President Biden on the potential of AI to cause or exacerbate chemical, biological, radiological and nuclear (CBRN) threats, as well as its ability to help counter such threats. The report is meant to provide longer-term objectives around how to ensure the safe, secure and trustworthy development and use of AI, and guide potential inter-agency follow-on policy and implementation efforts.

As mandated by the EO, the HHS, in consultation with the Secretary of Defense and the Secretary of Veterans Affairs, has set up an **AI Task**

Force to develop **policies that provide regulatory clarity and catalyse AI innovation in healthcare**. A White House Fact Sheet published in late January 2024 stated that the task force will, for example, 'develop methods of evaluating AI-enabled tools and frameworks for AI's use to advance drug development, bolster public health, and improve health care delivery'. The task force has already coordinated work on publishing guiding principles to address racial biases in healthcare algorithms (White House 2024c; Stanford University 2024a).

Nine federal agencies, including the HHS, Department of Defense, Department of Transportation and Department of the Treasury, have completed and submitted **risk assessments covering AI's use in every critical infrastructure sector** to the Department of Homeland Security. The assessments cover risks related to **dangerous biological materials** and critical infrastructure. These assessments, which will serve as the foundation for future federal actions, help to ensure that the United States is 'ahead of the curve' in integrating AI safely into vital aspects of society, such as the electric grid (White House 2024c).

There has been progress in bringing together the key relevant stakeholders from government, private sector and NGOs to discuss governance and **oversight at the intersection of AI and biotechnology (AIxBio).** The John Hopkins Center for Health Security convened a high-level workshop in late November 2023 to discuss AIxBio risks and possible oversight. Participants came from across the US government and industry.[108]

Representing solely the views of the **Center for Health Security**, the report of the meeting recommends the following policy initiatives:

- The creation of an **ongoing public–private forum** to facilitate the sharing of important information related to biosecurity risks.
- A **regulatory framework** that defines mandatory practices, reporting and oversight of highly capable AI models.
- A **legal accountability framework** to incentivise developers and deployers of models to adequately address emergent risks (Johns Hopkins Center for Health Security 2023).

What is the future trajectory for the oversight mechanism?
An online policy tracker maintained by AI researchers at Stanford University implies that implementation of the EO in the first nine months since it was issued is progressing well (Stanford University 2024a). However, federal authorities will need to be agile and flexible to keep up with rapid technological advances. For example, a 2024 report by the Department of Homeland Security (discussed above) highlights how nucleic acid sequence screening mechanisms need to do better to keep abreast of technological developments in nucleic acid synthesis, such as benchtop synthesisers, that use AI or BDTs to make new kinds of nucleic acid sequences (DHS 2024).

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Although it is too early to identify lessons learned from the EO, it has catalysed widespread action, such as the development of voluntary codes of conduct for AI development and deployment, and nucleic acid synthesis screening recommendations.

108 Officials from the White House National Security Council, White House Office of Science and Technology Policy, Department of Energy, Department of Commerce, Department of Defense, Department of State, and Department of Homeland Security), the UK Cabinet Office (individuals responsible for implementing recommendations from the UK Frontier AI Task Force) and the private sector (AI representatives from companies including Amazon, Anthropic, Google DeepMind, Meta, Microsoft, and OpenAI), Centre for Long-Term Resilience, Gryphon Scientific, MIT, RAND Corporation and Yale Law School.

There remains a need to build consensus and awareness among diverse national security, public health and animal health agencies about the potential risks of using AI tools. Given the pace of technological developments, policy stakeholders find it hard to keep up with AI developments and how they might affect their sectors, as well as how they can counter CBRN threats (DHS 2024).

There does not appear to have been much public engagement or consultation on measures implemented in pursuant of the EO. However, this could strengthen the legitimacy of the EO and foster greater public trust in AI, specifically regarding how it relates to genomic data and risks with BDTs. Sceptical attitudes towards genetically modified foods in the past may make government, research and civil society stakeholders assume that people will be similarly mistrustful of newer biotechnologies (Sciencewise 2024), and can thus be a barrier to widespread adoption.

Case study 3: South Africa – Draft Code of Conduct for Research under the Protection of Personal Information Act (POPIA)

Table 9. South Africa's Code of Conduct for Research under the Protection of Personal Information Act (POPIA)

Technology area:	Engineering biology
Oversight example:	Code of Conduct for Research under the Protection of Personal Information Act (POPIA)
Type(s) of oversight mechanism(s):	Code of conduct
Jurisdiction:	South Africa
Timescale:	2021-present

Why is the oversight required?

In South Africa, the oversight of engineering biology is addressed via multiple mechanisms and sectors due to its widespread applications. However, this case study focuses on the challenges in the domain of genomic datasets underpinning engineering biology progress. In 2013, the South African Parliament introduced its first comprehensive legislation for the protection of personal information, **the Protection of Personal Information Act (POPIA).** The act came into full force in 2021 (Republic of South Africa 2013) and is implemented by the Information Regulator of South Africa. It provides a constitutional right to privacy and seeks to protect individuals' rights to security and privacy while allowing for the free flow of information within and outside of South Africa by setting minimum standards for entities

that 'access' and 'process' personal data (Adams, Veldsman, et al. 2021). As the act provides a general data governance framework, it does not include sector or industry specific provisions for personal information processing; however, bodies 'sufficiently representative' of a sector can propose a sector-specific code of conduct under POPIA (Adams, Veldsman, et al. 2021).

POPIA requires further efforts and consensus building on how it can be applied to the research sector to aid compliance and uniformity. One prominent uncertainty is whether genetic data can ever be fully de-identified,[109] as the act defines de-identified data, partly, as that which cannot be associated with identifiers by a 'reasonably foreseeable method' (Adams, Adeleke, et al. 2021). Recent developments in AI and ML capabilities, and the prominence of open science practices and norms in genomics and adjacent fields, have brought reasonably foreseeable methods to the present, prompting reconsideration of the governance of genetic data in South Africa (Gooden and Thaldar 2024).

The sensitivity of genetic data and the need to carefully consider its potential misuse, particularly in cases that could lead to stigmatisation, discrimination or bias, is crucial in this context due to histories of exploitative and extractive research practices throughout Africa (Adams, Veldsman, et al. 2021; de Vries et al. 2011). Governance mechanisms must align with the nation's constitution, which contains significant rights safeguards (Adams, Veldsman, et al. 2021). Moreover, the stark underrepresentation of African genetic diversity in most international genetic datasets is a critical driver for establishing genetic data governance mechanisms that are permissive of national and international data sharing and re-analysis, in line with existing standards in genomics research and open science principles (Adams, Veldsman, et al. 2021).

What oversight is being proposed?

There has been a call for the development of codes of conduct to support the uniform implementation of POPIA. Once accepted by the Information Regulator, codes of conduct established under POPIA function as a legally binding mechanism for personal information protection specific to the sector (Adams, Veldsman, et al. 2021). They also allow for prior authorisations under the act, enabling organisations that handle personal information to process unique identifiers (e.g. ID numbers) (Adams, Veldsman, et al. 2021). Following two public engagement events, **the Academy of Science of South Africa (ASSAf),** the country's national academy established under the Academy of Science of South Africa Act of 2001, established steering and drafting committees to lead the development of a code of conduct for the research sector (Adams, Veldsman, et al. 2021).

The Code of Conduct for Research under POPIA (henceforth 'the Code') seeks to clarify how aspects of personal information protection specific to the conduct of research are governed under POPIA, including consent, data sharing and secondary use (ASSAf 2023; Adams, Veldsman, et al. 2021; Adams, Adeleke, et al. 2021). The Code includes some provisions specific to biometric and **genetic data**, although this is not a prominent feature. Dialogue in South Africa around the development of the Code has focused extensively on its implications for genetic data and genomics research (Gooden and Thaldar 2024; Adams, Veldsman, et al. 2021).

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The proposed Code of Conduct for Research under POPIA, presently in draft form, includes the following provisions relevant to accessing and processing genetic data for research:

- **What is considered 'research' under the Code:** The Code considers a broad definition of the research sector, including any entity that conducts research, which the Code defines as '…the range of activities that a private or Public Body conduct to extend knowledge through disciplined enquiry or systematic investigation' (ASSAF 2023). This definition therefore encompasses all academic research disciplines and includes public and private entities, as well as industry and academia. Market research, political or public opinion polling, audits, quality assurance, and monitoring and evaluation are not considered research under the Code (ASSAF 2023). The Code, and POPIA more broadly, do not apply to personal information that has been 'de-identified', which is defined as '…any information that – (a) identifies the data subject; (b) can be used or manipulated by a reasonably foreseeable methods to identify the data subject; or (c) can be linked by a reasonably foreseeable method to other information that identifies the data subject' (Republic of South Africa 2013).
- **Consent:** POPIA stipulates that consent for personal information collection, access and processing must be voluntary, specific, informed and explicit, but also indicates there may be circumstances where data reuse would reasonably occur (Adams, Adeleke, et al. 2021). Consequently, the Code considers several research consent models to be permitted under POPIA, including narrow, tiered and broad consent, as defined in the Department of Health guidelines of 2015 (ASSAf 2023). POPIA and other data governance mechanisms such as the Department of Health guidelines (discussed below) do not permit blanket or unrestricted consent, and as such this type of consent is not permitted under the Code (ASSAf 2023).

Drafters of the Code indicate that the sensitivity of genetic data necessitate additional consideration in consent processes (Adams, Veldsman, et al. 2021), suggesting community and individual engagement processes to communicate the risks of genetic data collection and how these would be mitigated (Adams, Veldsman, et al. 2021). They also indicate that for genetic data it may be prudent to provide an option in the consent process for a data subject to indicate that they do not wish to have their genetic data de-identified, as this significantly changes how the data is governed (discussed below) (Adams, Veldsman, et al. 2021).

Data sharing and secondary use: POPIA allows for 'further processing' of personal information under some circumstances (Republic of South Africa 2013). The Code indicates that in conducting research, further processing is permissible when the data used for research purposes is not in an identifiable form, where consent has been obtained for further processing or where the information is already in the public domain (Adams, Veldsman, et al. 2021). Genetic data present an interesting case for data sharing and further processing under POPIA and the Code, as there is ongoing debate regarding the extent to which genetic data is inherently identifiable (Adams, Veldsman, et al. 2021). POPIA allows for the processing of health information containing 'inherited characteristics' where there is a serious medical interest or where the processing is necessary for 'historical, statistical or research activity' (Adams, Veldsman, et al. 2021). The Code contains little mention of genetic data directly; however, drafters acknowledge that some forms of genetic data are inherently identifiable and that recent advances in data processing capabilities (e.g. AI and ML) have increased the potential for reidentification (Adams, Veldsman, et al. 2021). Nevertheless, the drafters of the Code indicate that individual

identification from genetic data is 'highly dependent on the availability of additional identifiers' (Adams, Veldsman, et al. 2021). As such, unless genetic data is associated with other identifiers, it is largely considered de-identified and therefore exempt from governance under the Code and under POPIA more broadly, rendering the data subject unable to access or delete the data (Adams, Veldsman, et al. 2021).

POPIA allows for **cross-border data sharing** in circumstances where the recipient is located in a country with data protection mechanisms comparable to POPIA (Republic of South Africa 2013). Similar to GDPR, POPIA indicates that those responsible for the data must establish a binding, contractual transfer agreement that offers appropriate safeguards (Adams, Veldsman, et al. 2021).

What is the future trajectory for the oversight mechanism?

In February 2024, the Information Regulator declined the latest version of the Code, stating that ASSAf was not an organisation 'sufficiently representative' of the research sector, as defined by the Code, to have the standing necessary to put forward a code of conduct (ASSAf 2024). One interviewee[110] noted that this decision may have been a response to push back from some sectors, for example the banking sector, that objected to the Code's broad definition of the research sector, feeling that their inclusion was inappropriate and would result in significant compliance burden. The Information Regulator indicated that the Code may be reconsidered should ASSAf amend it to apply only to ASSAf members and not to the research sector as a whole (Assaf 2024).

Considering this feedback, **ASSAf subsequently elected to convert the Code to a voluntary POPIA Compliance Framework**, which will serve as a best practice guideline for the research sector (ASSAf 2024). Such frameworks, unlike codes of conduct under POPIA, are not legally binding but are considered by the Information Regulator when assessing compliance with POPIA, thus supporting the sector in risk management and systemic compliance efforts (ASSAf 2024). ASSAf have noted that a framework will have fewer structural constraints than a Code and have indicated an intention for the framework to be accessible and user-friendly for the research community (ASSAf 2024).

The framework drafting process may offer opportunities to address uncertainties not fully clarified in the most recent version of the Code. One interviewee[111] pointed to lingering uncertainties around data sharing in a research context, specifically data processing and analysis capabilities hosted in cloud-based systems. POPIA indicates that South African data should remain in South Africa, with exceptions for research purposes (Republic of South Africa 2013). As such, the framework may offer a mechanism for articulating best practices for such activities in the research sector. Another interviewee[112] indicated a potential need for further clarification on research circumstances that require specific consent, as articulated in POPIA, noting that this may not be desirable nor practical in genomics research given prevailing norms around broad consent processes.

At present, **it is unclear how genetic data will be considered under a POPIA Compliance Framework for research**. Nevertheless, there

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are ongoing debates regarding appropriate governance mechanisms for genetic data in South Africa, including in relation to the Draft National Open Science Policy (Thaldar, Gooden and Steytler 2023) and the Draft National Policy on Data and Cloud (Thaldar, Gooden and Steytler 2023), as well as discussions around a potential open access genetic biobank (Thaldar, Gooden and Donnelly 2023; Gooden and Thaldar 2023; de Vries et al. 2017). Such discourse builds on a significant body of genomics governance and bioethics scholarship in South Africa (for example, Munung et al. 2021; Pepper et al. 2018; de Vries and Munung 2019). Whether the forthcoming Compliance Framework will squarely address genetic data is unclear; however, it is unlikely that this discourse will fade in the near future given the live discussions and legislative opportunities as a result of POPIA and other mechanisms.

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Codes of conduct are a flexible tool for oversight; however, they may face challenges in defining scope. The development of codes of conduct under POPIA provide an interesting example of an adaptable and participatory governance process that allows specific industries and sectors to tailor general legislation to their particular needs. As the Code of Conduct for Research under POPIA demonstrates, sector-based oversight can be challenging, both in defining what constitutes a sector and in assessing whether sector-specific governance is a useful approach. For example, codes of conduct under POPIA can also be organised around the type of information governed. In the context of research, the Code of Conduct for Research could be reimagined as a Code of Conduct for Human Subjects Data or a Code of Conduct for Genetic Data. While this approach may have advantages, including being more precisely tailored to different data types, there are also cross-sector implications, creating coordination challenges within the participatory process. As such, there are inevitable trade-offs in determining the bounds chosen for an oversight mechanism.

Oversight bodies conducting participatory governance approaches such as codes of conduct should consider offering capacity building support to enable broad and effective participation. One interviewee[113] highlighted that challenges with developing codes of conduct under POPIA related to capacity, noting that drafting a code of conduct requires significant legal expertise. However, such expertise is not present in all sectors to which general legislation such as POPIA will inevitably apply. Oversight bodies considering a framework that allows sectoral bodies to propose codes of conduct should evaluate the capacity required to participate and determine whether additional support is necessary to support engagement with the governance process.

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Chapter 6
Current neurotechnology oversight developments

To guide the reader, this chapter is structured as follows.

Box 4. Current neurotechnology oversight developments: Key takeaways

Current regulations in jurisdictions such as the United Kingdom, United States and EU largely depend on broader frameworks for medical devices, data privacy and research ethics. These frameworks do not specifically address the unique challenges posed by neurotechnologies such as brain–computer interfaces and neural implants, which are generating new forms of data and have the potential for cognitive influence.

Neurotechnologies generate sensitive neurodata, raising privacy concerns and issues of consent. Traditional frameworks such as the GDPR in the EU and HIPAA in the United States do not explicitly address the nuances of neurodata, which creates risks for misuse or unauthorised exploitation of this information, such as in a discriminatory fashion by employers or the services sector. Ethical guidelines focused on neurorights, such as Chile's constitutional amendments, offer a proactive model for addressing these challenges.

Neurotechnologies developed for medical purposes (e.g. BCIs for rehabilitation) can also potentially be repurposed for military or surveillance applications, leading to significant ethical and security concerns. Current oversight mechanisms are reactive and do not adequately prevent dual-use scenarios. Developing international guidelines, such as the proposed Neurological Innovation and Defence Act in the United States, could help pre-emptively regulate the dual use of neurotechnologies, ensuring their applications remain ethical and beneficial.

There are limited mechanisms for the post-market surveillance of neurotechnology devices. This can lead to 'device abandonment', where manufacturers fail to maintain or repair devices, creating risks for users, especially those with implanted devices. Strengthening post-market oversight and surveillance systems, particularly for medical devices and consumer neurotechnology, could help manage long-term risks.

Source: RAND Europe analysis.

6.1. Introduction

Neurotechnology is a rapidly evolving field that consists of devices and procedures used to access, monitor, investigate, assess, manipulate and emulate the structure and function of the neural systems of animals or human beings. Progress in BCIs, neural prosthetics and cognitive enhancement technologies is ongoing, with significant investments seen in both the United States and China. The potential to treat neurological disorders, improve mental health and enhance cognitive abilities in a medical setting is being progressed, while non-medical use cases such as immersive gaming and meditation are emerging. Ethical issues related to cognitive enhancement, privacy concerns, agency and autonomy, and the need for long-term safety studies, are some of the many challenges in this complex field.

Neurotechnologies generate sensitive neurodata, raising privacy concerns and issues of consent. Traditional frameworks such as the GDPR in the EU and United Kingdom and HIPAA in the United States do not explicitly address the nuances of neurodata, creating risks that this information will be misused or exploited, potentially in a discriminatory fashion by employers or the services sector. Ethical guidelines focused on neurorights, such as Chile's constitutional amendments, offer a proactive model to address these challenges. Neurotechnologies developed for medical purposes (e.g. BCIs for rehabilitation) can be repurposed for military or surveillance applications, leading to significant ethical and security concerns. Current oversight mechanisms are reactive and do not adequately prevent dual-use scenarios. Moreover, there are limited mechanisms for the post-market surveillance of neurotechnology devices. This can lead to 'device abandonment', where manufacturers fail to maintain or repair devices, creating risks for users, especially those with implanted devices. Strengthening post-market oversight and surveillance systems, particularly for medical devices and consumer neurotechnology, could help manage long-term risks.

A detailed assessment of the trends, challenges and opportunities associated with neurotechnology R&I is provided in the accompanying global technology landscape review report. The first section of this chapter summarises the strengths and limitations of the emergent neurotechnology oversight landscape, alongside some key considerations for addressing the current gaps and bottlenecks. The subsequent sections present the evidence underpinning this assessment, outlining key oversight mechanisms across the United Kingdom, United States, EU and international forums, followed by oversight case studies from Chile, the United States and China that provide more detailed examples of how oversight in this area could be progressed.

6.2. Strengths and weaknesses of the neurotechnology research and innovation oversight landscape

Strengths of neurotechnology research and innovation oversight

Neurotechnology oversight is primarily provided through various frames of reference, ranging from data and privacy to health and consumer protection. In the United Kingdom, United States and EU, there are no regulations specific to neurotechnology and/or neurodata and neurorights (sections 6.3 to 6.5). However, healthcare-focused neurotechnology is covered by multiple mechanisms of legally binding oversight, such as device regulation, clinical trials regulation and clinical research. These enable the management of direct risks from the use of neurotechnologies and BCIs (e.g. through existing consumer protection regimes and healthcare-based consents).

Neurorights, neurodata and neuroprivacy are being discussed globally, with national jurisdictions following suit. International forums have spearheaded efforts to formally oversee neurotechnologies from ethical and data privacy perspectives, with multiple recommendations published by the OECD, UNESCO International Bioethics Committee and UN (section 6.6). National agendas are also following, with various informal mechanisms being developed and trialled, such as guidelines from the Information Commissioner's Office (ICO) on neurodata in the United Kingdom (section 6.3) and the creation of the Neuroscience Information Nondiscrimination Act (NINA) in the United States (section 6.7, Case Study 2). In particular, some developing countries are pushing ahead with legally binding mechanisms of neurorights oversight, paving the way globally for a bespoke regime (sections 6.5 and 6.6).

There appears to be investment and effort emerging in the science and policy community in ensuring that current and emerging mechanisms of oversight are focused on responsible innovation. For example, lab-based research is bound by various ethics and data protection focused mechanisms under the purview of research ethics bodies and funders, such as the Health Research Authority's (HRA) Research Ethics Committee in the United Kingdom (section 6.4). China's ethical guidelines for BCI research incorporate requirements regarding researcher aptitude and risk consideration, and state that research must provide proof of benefit (section 6.7, Case Study 3). The United States has also considered first implementing NINA at an academic level (section 6.5).

Opportunities in neurotechnology research and innovation oversight

The protection of human and digital rights is being proposed by various stakeholders to create an ethics-by-design ecosystem. Ethical guidelines have been proposed to consider all aspects of neurotechnologies in the public domain. If implemented this could improve technology adoption and uptake, and generate societal trust. The OECD's report on BCIs aimed to develop responsible and proactive governance, incorporating ethics early on in the technology development process (García and Winickoff 2022). Alongside other initiatives to develop ethics guidelines, such as those in the United States (section 6.4) or the bespoke dynamic consent mechanisms proposed by international scientists (section 6.6), this could provide a useful frame of reference to all sectors using and developing neurotechnologies. A number of these ethical recommendations have stemmed from the application of AI in neurotechnologies, which aim to ensure research and data integrity (sections 6.5 and 6.6).

There is an increasing demand for experiments in oversight that will anticipate the technology maturity and provide a more nimble and responsive approach to oversight as neurotechnologies evolve. This includes both participatory and regulatory experiments in oversight, increasing involvement from the public and scientific communities, as well as developing new, flexible oversight mechanisms. The NIH's BRAIN Initiative Public Engagement, for example, uses public engagement processes to discuss the ethical, legal and societal implications of brain research (section 6.4). In general, there is an increasing call from scientists for a data governance framework to be put in place, particularly for brain data and AI (section 6.6). Participation from the wider community could help direct oversight of neurotechnologies, highlighting priorities, concerns and potential solutions. In tandem, sandboxes could be used for experimental regulatory mechanisms, such as the AI Airlock sandbox for medical devices (section 6.3).

There is much activity taking place in academia around the development of neurodata governance. Academia is driving research

on governance frameworks and dynamic consent regimes, which could improve transparency and facilitate the better use of neurodata. As such, these institutions are joining public and private companies in drafting guidance on the ethics, legal and societal implications of neurotechnology. For example, several US research groups and institutions are leading research on neuroethics and neurorights practices. These include specific research groups (e.g. MIT Media Lab's Fluid Interface and Synthetic Neurobiology Groups, Columbia University's Neurorights Foundation, section 6.4) and international networks of academics (section 6.6).

The global race to innovate in this space is unlocking further technological maturity and oversight, which could expedite reach to market. For example, the convergence of neurotechnologies with AI is generating novel opportunities to consider the oversight of baseline capabilities, as well as novel capabilities and use cases unlocked through this convergence.

Threats and weaknesses of neurotechnology research and innovation oversight

Most legally binding oversight is not specific to neurotechnologies, which may imply loopholes that could be exploited. Aspects of neurotechnology are included in oversight by virtue of definitions and scope (for example, in GDPR, clinical trials regulation or devices regulation); however, broad brush mechanisms of oversight are not attuned to rapid advancements in technologies, nor the associated uncertainties. For example, within neurotechnologies there may be a lack of clarity in the classification of non-invasive devices (sections 6.4 and 6.5), which could lead to loopholes being exploited. There is also no binding definition of neurodata in data governance oversight, leaving it prone to misuse. Loopholes or lack of clarity on consumer rights could lead to product abandonment, with uncertain liability in case of accidents or harm. However, one expert highlighted that national-level oversight should be mindful of the consequences of introducing specific definitions and protections on particular aspects of technologies, as this could restrict innovation and limit the potential benefits of neurotechnologies.[114]

The globally inconsistent approach to oversight could lead to the misuse of neurotechnologies and neurodata. National and international regulatory frameworks and networks are fragmented across neurotechnology oversight, leading to misuse cases (e.g. use without appropriate consent, use of devices without legitimate consumer protection and gaps in liability). For example, products developed outside of the United Kingdom may not adhere to the same transparency requirements as specified in the UK GDPR. There has been some movement to streamline regulations between the international and national level, such as the RHC's creation of a new category for neurodata to ensure appropriate protection in the United Kingdom (section 6.3), but these are isolated efforts.

The lack of oversight mechanisms specifying standards for neurodata could lead to misuse. The lack of standards on neurodata capture, interpretation and use could produce unreliable information which could be used in a healthcare or social justice setting to make uninformed decisions. This risk increases if there is unethical or uninformed training of AI models for predictive or screening applications. To tackle these risks, the UN has called for such

114 Expert focus group input.

standards to be incorporated in oversight mechanisms to protect data privacy and human rights (section 6.6).

There is an increased risk of data biases and limited data access if equitable governance is not considered. Equity does not appear to be greatly considered in oversight, which has led to biases in the datasets amassed through BCIs and those underpinning BCI development (sections 6.4 and 6.6). This is also an issue in AI-neurotechnology research, where the training of algorithms relies on diverse data to not proliferate biases. Equitable access to neurotechnologies and neurodata may also be at risk if equitable governance is not considered, with underrepresentation in neurotechnology outputs and use cases already seen.

There are limited post-market surveillance and vigilance mechanisms in place, particularly in existing device regulations. The monitoring of medical devices after they are brought to market is therefore limited, making it difficult to identify misuse cases. The lack of economic, market and regulatory incentives for rapid technology uptake could lead to harmful access and applications driven by market signals or geopolitical interests (for example, US vs. China market dominance). Focus group experts[115] were less engaged on the topic of post-market uses of neurotechnologies, suggesting that it was not at the forefront of oversight discussions, despite the additional risks associated with misuse of neurotechnologies, such as military, surveillance and cognitive enhancement applications.

115 Expert focus group input.

Given the current trajectory of the technology, this study identifies the following **priority considerations** to support oversight for safe and innovative deployment of neurotechnology:

Create standards and categorisation for neurodata:

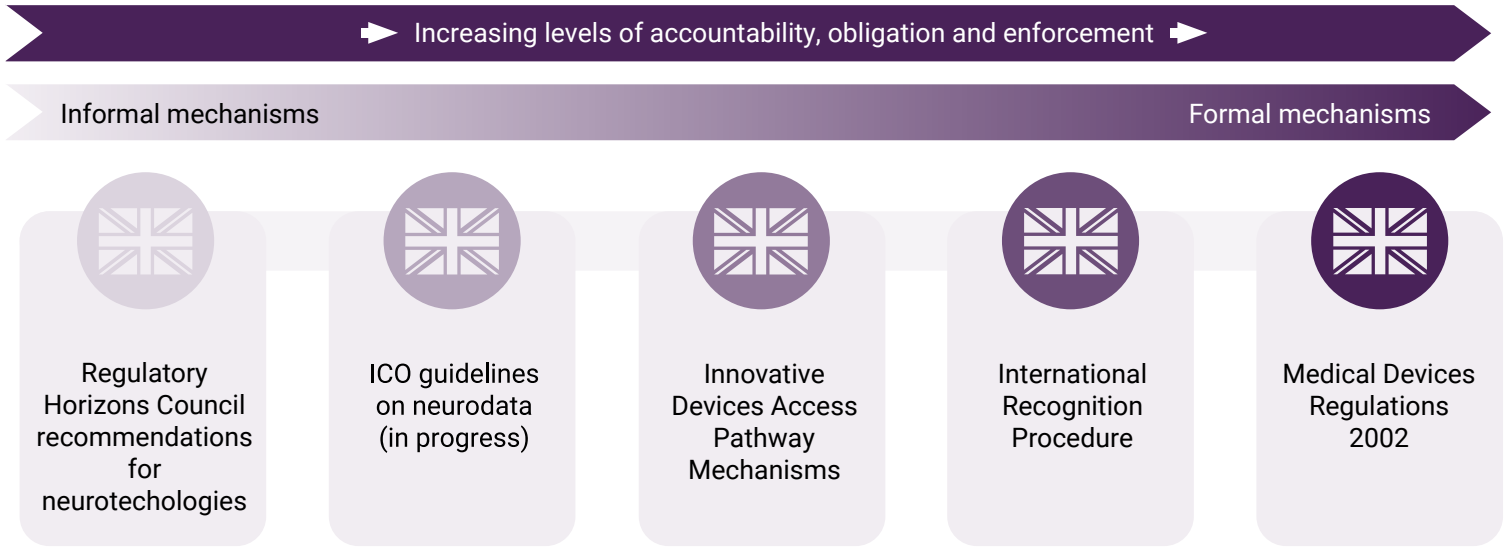
There is a lack of bespoke oversight for neurodata in terms of specifying standards and categorising it as special category data. It is important that this is reviewed and addressed in light of the challenges outlined on oversight loopholes and risk of neurodata misuse, or conversely the underutilisation of datasets.

Fortify post-surveillance mechanisms for products:

There are limited post-market surveillance and vigilance mechanisms in place, particularly in existing neurotechnology device regulations. There is a need to generate appropriate measures to assure the sustainability of devices and to generate accountability for those with both medical and non-medical devices.

6.3. Oversight of neurotechnology in the United Kingdom

Figure 17. Illustrative oversight examples of neurotechnology in the United Kingdom



Source: RAND Europe analysis.

Current oversight mechanisms in the United Kingdom

In the United Kingdom, there are no specific formal oversight mechanisms for neurotechnology such as BCIs, with oversight primarily falling under existing regulatory frameworks governing medical devices, research practice and data protection. These include:

- The **Medical Devices Regulations 2002 (UK MDR),** updated in 2023, is the primary oversight mechanism for medical devices on the UK market, and extends to BCI devices intended for medical use. The UK MDR is overseen by the MHRA and sets out safety, quality and performance standards. These have remained in force following Britain's exit from the EU and allow devices compliant with the EU Medical Devices Directive to be placed on the UK market (MHRA 2024).
- The **Innovative Devices Access Pathway (IDAP)** was introduced in 2024 by the MHRA and provides guidance and mechanisms to integrate innovative medical devices into the UK market. It is being trialled to enable and improve access to innovative and transformative medical devices, including in neurogenerative disease (UK Government 2024b).

- The **Cares Act 2014** is the UK's principal oversight mechanism on health and social care research involving human participants. It is overseen by the HRA, which has oversight authority on all health and social care research involving 'procedures with human participants' (Legislation.gov.uk 2014). Research involving neurotechnology is included within this remit and requires approval from the **HRA's Research Ethics Committee**.
- The **Data Protection Act of 2018** encompasses data generated by neurotechnology in the United Kingdom.
- The **Consumer Rights Act 2015 (CRA)** outlines consumer rights and the responsibilities of businesses in the United Kingdom, including non-medical neurotechnology, such as gaming headsets, stress relief and well-being devices (Legislation.gov.uk 2015).

Emerging oversight mechanisms in the United Kingdom

- The new **Regulatory Framework for Medical Devices**, published by the MHRA in 2020 but updated in February 2024, is a major update that includes strengthening post-market surveillance requirements, improvements in regulations on implantable devices and software as medical devices (SaMD) (UK Government 2024c). **AI Airlock**, a regulatory sandbox, was launched in October 2023 to create novel oversight approaches for the use of AI/software in devices to improve patient outcomes (UK Government 2024c).
- In January 2024, the MHRA introduced the **International Recognition Procedure** for the international recognition of medical devices to address the 'gap' related to international products used within the United Kingdom or by individuals with data rights under UK GDPR (UK Government 2024b). The RHC has recommended the creation of a new **special category for neurodata** to ensure it is captured and appropriately protected under UK GDPR (RHC 2022).
- Based on RHC recommendations, the ICO is working to develop specific **guidelines on neurodata**, including core definitions and approaches, risks, and good practice. These will be published in 2025 (ICO 2023).

Other mechanisms of relevance in the United Kingdom

- The **Equality Act 2010** covers unfair inferences, including discriminatory or biased inferences, drawn from neurodata. However, it is unclear how comprehensively it addresses the challenges of neurodata use in sensitive contexts such as the workplace or education (Legislation.gov.uk 2010).
- The **MHRA** oversees clinical trials in the United Kingdom, including those involving neurotechnology and neurodegenerative disease. The **RHC** recommends that the MHRA consider options for the generation and presentation of clinical evidence related to neurotechnology trials to streamline innovation and avoid unnecessary repetition (RHC 2022)**.**

Uncertainties associated with neurotechnology oversight in the United Kingdom

- There is **no explicit definition of 'neurodata'** as either a form or category of data in formal oversight mechanisms, which has been raised as a concern given its sensitive nature (ICO 2023).
- The **regulatory framework overseeing neurotechnology in the United Kingdom is fragmented** and formed by disparate regulations covering medical devices, consumer protections and safety regulations (RHC 2022, 41).

- Difficulties related to **handling personally identifiable neurodata** have been noted as the lack of a uniform definition, insufficient protection against neuro-discrimination, the lack of an appropriate consent standard for neurodata use, the dangers of closed-loop processing,[116] accuracy and data minimisation concerns, and information rights (ICO 2023).
- **BCIs not intended for medical use by the manufacturer are not captured under the UK MDR**, and there are concerns over aspects that may fall through the gaps between device regulation and consumer protection acts (UK Government 2022d). Particularly of concern are enhancement technologies that do not have a medical purpose. The RHC has recommended that any devices that can regulate neural activity or signals should be classed as medical devices, regardless of purpose.
- Analytical tools involving AI and ML techniques are increasingly used alongside neurotechnology/BCIs in processing and interpreting brain data, leading to active debates on issues such as **algorithmic bias, liability and data reliability**. Given increased AI deployment in healthcare and life sciences, risks related to data accuracy, ownership, safety and privacy have emerged (Taddeo et al. 2021).
- Unlike static data (e.g. date of birth, biometric data), neurodata is in flux and may change with time (ICO 2023). This raises challenges in **retaining accurate information**, specified as necessary in the UK GDPR, and for neuroscience research that requires longitudinal information (ICO 2023).
- As neurotechnology develops across the globe, relevant **technology developed outside the United Kingdom may not adhere to the UK GDPR** standards of fairness and transparency in their use of data. This poses challenges when those devices are used in the United Kingdom or by individuals with data rights under the UK GDPR (ICO 2023).
- There are uncertainties regarding the strength of requirements for **manufacturers to implement post-market surveillance and vigilance systems** in existing medical devices regulations. The government has announced its intent to address this via legislation in 2024 (UK Government 2024d).

116 Closed loop neurotechnologies are those that operate autonomously and use programming or algorithmic processing to react or input data. Open loop technologies allow users to make interventions into this process (ICO 2023).

6.4. Oversight of neurotechnology in the United States

Figure 18. Illustrative oversight examples of neurotechnology in the United States

Source: RAND Europe analysis.

Current oversight mechanisms in the United States

- The United States does not have specific legislation solely dedicated to neurodata governance or neurorights. However, several existing laws, regulations and soft law mechanisms collectively address concerns related to neuro-discrimination and the sensitive handling of neurodata. The **HIPAA Act of 1996** covers data privacy and security provisions for safeguarding medical information that can be linked to an individual (neurodata is not explicitly mentioned, but is included) (HHS 2022).
- The FDA oversees the safety and efficacy of medical devices, including neurotechnologies (ranging from non-invasive brain stimulation tools to invasive BCIs) (FDA 2024). The FDA performs this duty under the provision of the **FD&C Act** of 1938, and its key amendments,[117] as well as key regulations under the act

117 Key amendments include the Medical Device Amendments of 1976, the Safe Medical Devices Act of 1990 and the FDA Modernization Act of 1997.

pertaining to medical devices. It categorises devices into **three classes**[118] based on risk and implements rigorous pre-market approval processes for high-risk devices, including requirements for rigorous testing and clinical trials to be undertaken.

- The FDA, under the FD&C Act, oversees neurotechnology devices through post-market surveillance mechanisms such as mandatory reporting (21 CFR Part 803), medical device tracking (21 CFR Part 821), post-market surveillance studies (21 CFR Part 822) and post-approval studies. It also collaborates with manufacturers and professional societies to develop robust **registries** for monitoring device performance over time (FDA 2024).
- The NIH plays a key role in neurotechnology research by providing research funding and establishing **ethical guidelines** for federally funded research. It monitors compliance with acts and regulations such as the HIPAA, FDA regulations and the Common Rule (45 CFR Part 46)[119] through institutional review boards (independent committees established by research institutions) to ensure that neurotechnology research is ethical and safe for all participants.
- The Federal Trade Commission (FTC) plays a key role in ensuring **consumer protection** for neurotechnology products, particularly those marketed directly to consumers, via the **Federal Trade Commission (FTC) Act** of 1921 and its amendments. The FTC, under various sections of the FTC Act, oversees advertising and marketing practices, claims of health and safety, consumer education, and the increased scrutiny of direct-to-consumer neurotechnology products and devices. It collaborates with the FDA and issues guidelines for the neurotechnology industry (Wexler and Reiner 2019).
- Several US universities are at the forefront of neurotechnology oversight, implementing robust institutional policies and ethical guidelines, and often collaborating with government and industry. These include:
  - **MIT Media Lab's Fluid Interface** (MIT 2024a) and **Synthetic Neurobiology Groups** (MIT 2024b) emphasise user-centred design and ethical considerations in technology development through their work, especially in wearable technologies and BCIs.
  - **Columbia University's Neurorights Foundation** was set up formally in 2019 to tackle ethical concerns around neurotechnology. It has been working on a propounded framework of **Neurorights** and has contributed to advancing neurorights protections in Chile, Spain and the UN (Neurorights Foundation 2024; Khan et al. 2024). Its latest report highlights the emerging privacy concerns associated with consumer neurotechnology companies.

118 Class I neurotechnology devices are low-risk and do not need any pre-market approval. Class II (moderate-risk devices, e.g. neurostimulators, aneurysm clips) typically need a pre-market notification (under regulation 21 CFR Part 807 of the FD&C Act) and are subject to general and special controls such as performance standards and post-market surveillance. Class III devices support or sustain human life or are crucial for preventing impairment, such as deep brain stimulators and devices for brain tumour treatment; they require rigorous testing and clinical trials under premarket approval requirements (under 21 CFR Part 814).

119 The Common Rule is a federal policy regarding human subject protection that applies to 17 federal agencies, including the NIH. It establishes requirements for institutional review board review, informed consent and assurances of compliance by research institutions.

Emerging oversight mechanisms in the United States

- With rapid technological development in neurotechnology, public and private institutes, as well as academic bodies, are routinely producing **neuroethics guidance documents** that emphasise the ethical, legal and societal implications of neurotechnologies. A systematic review of these recent initiatives points to common themes, including the need for global standards, ethical frameworks and public engagement to address challenges such as privacy, autonomy and equity (O'Shaughnessy et al. 2023).
- There have been **calls by science professionals for the Neurological Research and Innovation Act** to streamline the regulatory approval process for neurotechnologies, while ensuring safety and efficacy.
- Proposals have also been made to revise the **FD&C Act** to include specific provisions for emerging neurotechnologies.
- The proposed **Neurological Innovation and Defense Act (NIDA)** aims to establish guidelines for the dual use of neurotechnologies, ensuring that innovations designed for medical purposes are not easily repurposed for harmful or unethical uses.
- Proposed amendments to the **HIPAA Act** would see the expansion of protections for neurological data, requiring more robust consent processes and data security measures. There are also **calls for new legislation** – the **Neuroscience Information Nondiscrimination Act (NINA),** similar to the **Genetic Information Nondiscrimination Act (GINA)** – to prevent discrimination based on neurological data (Kraft and Giordano 2017).
- **The Neurotechnology Public Engagement Act** proposes the creation of a federal advisory committee to facilitate ongoing dialogue between stakeholders.

Other mechanisms of relevance in the United States

- The **ISO** develops and publishes international standards for various technologies, including medical devices and neurotechnologies. This standard is applicable to the manufacture of neurotechnology devices to ensure that they are consistently produced and controlled.
- The NIH initiative, **BRAIN Initiative Public Engagement**, includes public engagement efforts to discuss the ethical, legal and societal implications of brain research.
- US oversight bodies and regulators are keen to establish dynamic and adaptive pathways for neurotechnologies. For example, under the **FDA's Adaptive Regulatory Pathways**, programmes such as the **Breakthrough Devices Program** and the **21st Century Cures Act** allow for accelerated development and approval of innovative neurotechnologies, while ensuring safety and efficacy.

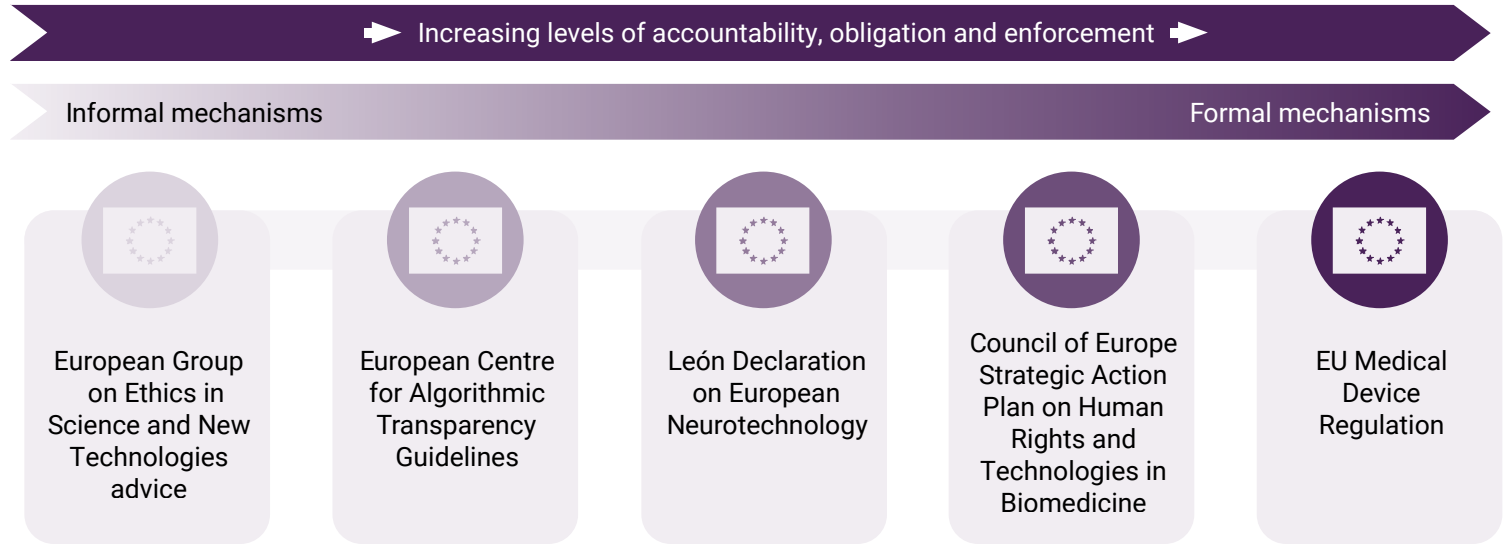
Uncertainties associated with neurotechnology oversight in the United States

- **Dual-use concerns:** Neurotechnologies with potential dual use (civilian and military applications) pose challenges for oversight due to their implications for national security (DeFranco et al. 2020).The proposed act, NIDA, aims to address these concerns, but its implementation and impact are still uncertain.
- **Ethical dilemmas and the debate on neurorights and neuroethics:** The evolving nature of neurotechnologies presents ethical challenges, such as privacy concerns and the potential for cognitive enhancement (Goering et al. 2021). Ethical guidelines for BCIs and neural implants often struggle to keep up with technological advancements, leading to uncertainties in how to apply these principles consistently.

- **Data privacy and security:** Current US regulatory frameworks may not fully cover emerging neurotechnologies, leading to gaps in oversight (O'Shaughnessy et al. 2023). The extension of the HIPAA Act regulations to include neurodata is under discussion, but there is still uncertainty about how to effectively implement these protections and ensure compliance.
- **Long-term effects, risks and the issue of 'abandonment':** There is limited understanding of the long-term effects and risks associated with the use of neurotechnologies, particularly for invasive devices. For example, deep brain stimulators and other implanted devices may have unknown long-term effects on brain health, and require extensive post-market surveillance and studies. Ongoing research is needed to assess these risks, but the current lack of long-term data creates uncertainty.
- **Equity and access:** Ensuring equitable access to neurotechnologies and addressing disparities in their availability and use remain significant challenges, and there are persisting uncertainties about how to create inclusive policies that ensure fair access. Public perception and acceptance of such devices is also likely to emerge as a challenge for oversight (Maddox 2017).

6.5. Oversight of neurotechnology in the European Union

Figure 19. Illustrative oversight examples of neurotechnology in the European Union



Source: RAND Europe analysis.

Current oversight mechanisms in the European Union

There are no bespoke oversight mechanisms for neurotechnology in the EU, and oversight currently falls under existing regulatory frameworks governing data, medical devices, research and scientific development. These include:

- The **EU GDPR 2016** contains several elements pertinent to neurotechnology, particularly regarding the collection, processing and storage of sensitive neurological data, and seeking explicit consent for its use. The regulation extends to technology developers/companies, which must ensure that individual rights can be exercised in relation to neurodata. **Data protection impact assessments** are also recommended for those handling and processing neurodata. Individual data protection authorities within member states are responsible for enforcing the GDPR.
- The **EU Medical Device Regulation (EU MDR)** and the **In Vitro Diagnostics Medical Device Regulation (IVDR),** both adopted in April 2017, are the EU's principal mechanisms for overseeing medical devices, including neurotechnological devices. The regulations came into effect in May 2021 and May 2022,

respectively, and are overseen at the member state level (by 'notified bodies'), with involvement at the EU level through the EMA. The EU MDR/IVDR cover a broad range of devices, including implantable devices (BCIs, neurostimulators, diagnostic tools, etc.) and SaMD. The EU MDR requires that manufacturers establish and maintain a post-market surveillance system and register their devices in the European Database on Medical Devices (EUDAMED) to ensure transparency and regulatory oversight.

- The **European Group on Ethics in Science and New Technologies (EGE)** is an independent advisory body to the European Commission set up in 1991. It issues opinions and recommendations on ethical issues pertaining to novel technologies, including neurotechnologies such as BCIs and neural implants, as well as genomic editing, AI and the future of work (European Union 2021a).
- The **Strategic Action Plan on Human Rights and Technologies in Biomedicine (2020–2025) (SAP)** was issued by the Council of Europe's Committee on Bioethics in 2019. SAP highlights concerns for neurotechnology's impact on, for example, cognitive liberty, mental privacy, mental integrity and psychological continuity (Council of Europe 2019, 9). Although not legally binding, SAP is based on the Council of Europe's **Oviedo Convention,** which is the sole legal instrument for protecting human rights in biomedicine in Europe (Council of Europe 2019).
- **Regulation (EC) No 1394/2007** provides the oversight framework on advanced therapy medical products (ATMPs) in Europe, including neurotechnology based products. It established the Committee for Advanced Therapies, which follows developments, issues recommendations on ATMP classification, and assesses the quality, safety and efficacy of ATMPs (European Parliament, Council of the European Union, and Directorate-General for Health and Food Safety 2007).
- **Regulation EU No 536/2014** specifies 'good clinical practice' that all ATMP developers must ensure are applied when carrying out clinical trials.
- **Commission Directive 2003/94/EC** lays down principles and guidelines for best manufacturing processes with which all ATMP developers must comply throughout the development process.

Emerging oversight mechanisms in the European Union

- In October 2023, 26 European member states signed the **León Declaration on European Neurotechnology**, a voluntary policy statement that defines neurotechnologies, fosters neurotechnological ecosystems within Europe, and emphasises the protection of human and digital rights in the development of neurotechnologies (León Declaration on European Neurotechnology 2023). The declaration advocates for ethical, safe and socially responsible neurotechnology development in Europe, aiming to balance innovation with the protection of individual rights and societal well-being.

Other mechanisms of relevance in the European Union

- **The EU AI Act** has the potential to impact the development and deployment of neurotechnology within the EU (ICO 2023). The act incorporates a risk-based approach to algorithmic technologies. In particular, Article 5.1.a outlines a prohibited use case as one that 'deploys subliminal techniques beyond a person's consciousness or purposefully manipulative or deceptive techniques, with the objective, or the effect of materially distorting the behaviour of a person or a group of persons by appreciably impairing their ability to make an informed decision, thereby causing them to take a decision that they would not have otherwise taken in a manner that causes or is reasonably likely to cause that person, another person or group of persons significant

harm'. This provision may potentially be applied to the use of neurotechnology in non-medical contexts (ICO 2023).

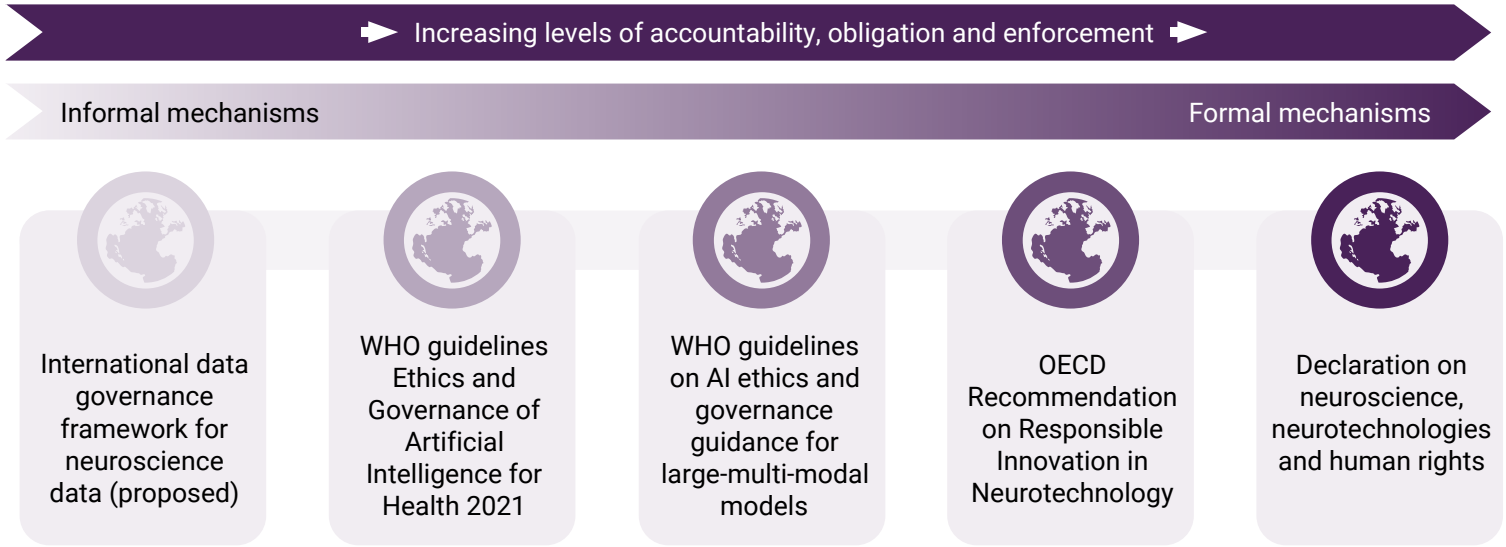
- **The EU Charter of Fundamental Rights (CFREU)** came into force in December 2009. Its central task is to outline the rights and freedoms that must be respected by the EU and its member states. The **EU Agency for Fundamental Rights (FRA)** has been charged with monitoring and advising on the fundamental rights noted in the CFREU, such as data protection, privacy and new technologies, including neurodata. The European Convention on Human Rights also has relevance in this regard, for instance in terms of protections around freedom of thought.
- The **European Centre for Algorithmic Transparency (ECAT)** assists the European Commission in a supervisory role to ensure transparency and accountability among algorithmic systems. While ECAT's primary focus is online platforms and search engines, its principles and methods are relevant to neurotechnology because they deploy algorithmic technologies such as BCIs and AI-driven diagnostic tools (European Commission 2024).
- **Commission Directive 2009/120/EC** covers gene therapy and somatic cell therapy products; however, it has also established scientific and technical requirements for devices containing ATMPs and products used in tandem with ATMPs, extending the directive to cover neurotechnology devices (Commission of the European Communities 2009).
- The **EU Directorate General for Justice and Consumers** coordinates consumer protection rights across all member states, which all have national consumer protection agencies. Commercial BCIs that fall out of the scope of medical devices must comply with consumer protection laws at the member state level.

Uncertainties associated with neurotechnology oversight in the European Union

- **Neurorights** are not defined nor recognised within the CFREU and are not a part of the EU Declaration on Digital Rights and Principles.
- The **legal statuses of 'brain' and 'neural data' are not clarified** under EU GDPR.
- Existing human rights frameworks relevant to neurotechnology (e.g. Oviedo Convention) may not be fit to protect **human rights**, dignity and individual freedoms against developments in neurotechnology (Council of Europe 2019, 8).
- The CFREU includes rights to non-discrimination, equality and justice, but **does not address how brain or neural data may be used to discriminate** (e.g. employment, insurance, the justice system), **may threaten equality** (e.g. neuroenhancement) or **may interfere with justice** (e.g. protection of right to a fair trial, presumption of innocence, or right not to self-incriminate) (TechEthos 2023).
- Niche or emerging applications of neurotechnology may need to be monitored as innovation and development occurs. This is particularly true of **'dual-use' technologies**, such as BCIs used in non-medical applications (e.g. gaming, commercial, cosmetic) (TechEthos 2023).
- There is a potential gap in **oversight of direct-to-consumer, non-invasive products** that collect and process brain/other neural data for health-related (but not medical) reasons, for example well-being apps (TechEthos 2023).
- As the EU AI Act is nascent, its **scope and specificity on matters related to neurotechnology may need further clarification** (TechEthos 2023).

6.6. Oversight of neurotechnology in international forums

Figure 20. Illustrative oversight examples of neurotechnology in international forums



Source: RAND Europe analysis.

Current oversight mechanisms in international forums

International oversight mechanisms for neurotechnology research and innovation involve a mix of global guidelines, country-specific mechanisms, and emerging initiatives focused on ethical conduct, data privacy and adaptive regulatory frameworks. These include:

- The **OECD Recommendation on Responsible Innovation in Neurotechnology** was adopted by the OECD Council in 2019 and is a soft law instrument to govern the sector (OECD 2019a). These guidelines address the ethical, legal and social implications of neurotechnology research and applications, aiming to ensure that advancements in this field are conducted responsibly and ethically. In April 2024, the OECD published its **Neurotechnology Toolkit** to support policymakers in implementing these recommendations (OECD 2024b).
- UNESCO has spearheaded developments to address the human rights perspective of neurotechnologies. The 2021 report by its **International Bioethics Committee** on the ethical issues related to neurotechnologies (UNESCO 2019) and the 2023 International Conference on the Ethics of Neurotechnology

called for the development of a global normative instrument and ethical framework similar to UNESCO's recommendation on the Ethics of Artificial Intelligence (UNESCO 2022). The committee has published its first set of draft guidelines on the ethics of neurotechnology (UNESCO 2024), with a global consultation ongoing.

- The human rights approach is mirrored in the Council of Europe's **Strategic Action Plan on Human Rights and Technologies in Biomedicine (2020–2025),** which stresses the need to protect human dignity, privacy and autonomy in the development and application of neurotechnological innovations (Council of Europe 2019).
- The **UN Report on Neurotechnology and Human Rights (2021)** focuses on the human rights implications of neurotechnologies, with a strong emphasis on privacy. It highlights the need for international standards on protecting neural data privacy in order to create legal frameworks to prevent the misuse of neural data (UNESCO 2021)
- In 2021, the Inter-American Juridical Committee of the Organisation of American States (OAS) issued a **declaration on neuroscience and neurotechnologies and human rights** that highlighted ethical and legal concerns, including the potential impacts on human dignity, personal autonomy, privacy, freedom of thought, and mental health arising from advancements in the field. It called for regulatory frameworks to address these risks and urged the private sector and scientific community to come together in this regard. In 2023, the OAS adopted a set of principles for the ethical development and application of neurotechnologies, emphasising the protection of human rights (Inter-American Juridical Committee 2023).

Emerging oversight mechanisms in international forums

- An international group of academics proposed an international **data governance framework** for neuroscience data in 2022, calling for organisations such as the International Brain Initiative to develop and formalise such a framework and facilitate international governance and the open sharing of neuroscience data (Eke et al. 2022). In November 2023, GA4GH and the International Neuroinformatics Coordinating Facility launched a Neuroscience Community to connect neuroscience and genomic data on a global stage (GA4GH 2023).
- A **multi-level governance framework** for capturing and processing brain data, especially in the context of applying AI to the datasets, has been proposed by a group of internationally diverse academics. The framework aims to establish standards for data capture and processing to ensure transparency and increase the utility of data in progressing medicine and science (Ienca 2021).
- Given the rapidity with which the field is progressing, consent and the reuse of data can be challenging, as technologies evolve based on original consent. **Bespoke dynamic and continuous consent mechanisms** for neurotechnologies have been put forward by scientists in response to this issue (O'Shaughnessy et al. 2023).

Other mechanisms of relevance in international forums

- **WHO guidelines on AI ethics and governance guidance for large-multi-modal models** were released in January 2024 (WHO 2024b) with over 40 recommendations for policymakers and technology developers to enable the appropriate use of AI models in a health context. This has implications for neurotechnology and BCIs, and their use.
- WHO's 2021 guidance, **Ethics and Governance of Artificial Intelligence for Health**, focuses on the handling of neural data

collected by AI-driven health technologies. It emphasises the protection and secure handling of neurodata and calls for robust data governance frameworks to ensure data integrity and security (WHO 2021d).

- **ISSCR Guidelines for Stem Cell Research and Clinical Translation** (2021) focus on the use of neural stem cell data in research and therapy, stipulating rigorous ethical standards for collecting and using neurodata derived from stem cell research, and encouraging data sharing to promote scientific progress while safeguarding patient privacy

Uncertainties associated with neurotechnology oversight in international forums

- **Risk of fragmentation and lack of a consistent approach globally:** While there are a range of oversight mechanisms in place or being proposed across different forums globally, the lack of harmonised international regulations creates inconsistencies and gaps in oversight, complicating the enforcement of ethical standards and safety protocols across borders, especially in the context of commercially available BCI devices.
- **Complexities around informed consent:** While most guidelines and frameworks focused on neurotechnologies stress the importance of informed consent, traditional informed consent processes may not adequately address the evolving nature of neurotechnologies, where ongoing data collection and new applications can emerge after the initial consent (Kwiatkowska 2023). Neurotechnologies by their very nature may also alter the decision-making abilities of the consenter later down the line.
- **Lack of specificity around neurodata:** While data protection laws such as the EU GDPR and the HIPAA Act in the United States provide a framework for safeguarding personal data, including neural data, they often do not explicitly address the unique nature and sensitivity of neural data. This lack of specificity can lead to gaps in protections, as neural data may be more susceptible to misuse and breaches than other types of personal data. Recent developments in Latin America aim to include specificity in data laws regarding neurodata and could lead to new precedents in this area.
- **Abandonment:** This concept deals with the legal and ethical ramifications that arise when makers of neural implants 'abandon' their projects, whether due to commercial or regulatory bottlenecks. A leading example is the closure of ATI (a company treating cluster headaches through their implants) after failing to get FDA approval in the United States (Drew 2022). Abandonment is related to congruent debates on the **sustainability** of neural devices, as well as patients' **right to repair.** Current oversight mechanisms focusing on neurotechnologies do not adequately cover the risk of abandonment, and legacy customer protection laws may not be enough to safeguard against the unique and serious threats posed by such devices.
- **Dual-use concerns:** Neurotechnologies developed for medical or commercial purposes can be repurposed for military or surveillance applications, raising significant ethical and security concerns. Current measures are often reactive rather than proactive, leading to gaps in the prevention of misuse.
- **Ensuring global equity:** With greater generation and use of neurodata, the issue is emerging of to what degree this data is representative and inclusive. Neurorights advocates and data ethicists from the developing world have steadily pointed out how current developments in the field are reliant on the use of global population datasets, with a glaring lack of local datasets and brain-imaging data from LMICs (Ricard et al. 2023). This has potential ramifications for the inclusivity of neurotechnology and leads to biases in insights generated.

6.7. Case studies of neurotechnology oversight mechanisms

Case study 1:
Chile – Constitutional change to protect neurorights

Table 10. Chile's constitutional change to protect neurorights

Technology area:	Neurotechnology
Oversight example:	Chilean constitutional change to protect neurorights
Type(s) of oversight mechanism(s):	Law
Jurisdiction:	Chile
Timescale:	Bill to amend constitution approved in 2021

Why is the oversight required?

Chile's Law No. 19.628 on the Protection of Private Life, similar to the EU GDPR, addresses the protection of personal data. However, there are many oversight gaps regarding challenging aspects of neurodata. First, while neurodata can be categorised under personal, and thus identifiable, data, **neurotechnology is an evolving field, meaning that even data not currently identifiable could become so in the future** (Cornejo-Plaza et al. 2024). Second, under Law No. 19.628, sensitive data includes information related to physical or moral characteristics, racial origin, and other personal attributes that cannot be processed. However, **neurodata is not recognised as sensitive data, despite its potential to reveal sensitive information about an individual** (Cornejo-Plaza et al. 2024). Lastly, due to the novelty and 'specialness' that neurodata presents, regulating it under Law No. 19.628 or even GDPR-like legislation may be challenging. **Neurodata, similar to genetic data, possesses a special status because it can provide a wide range of information about an individual** (Cornejo-Plaza et al. 2024). For instance, while other sensitive data such as religious belief typically provides information only about a person's faith, neurodata can reveal information about a person's health, origins, physical characteristics and potentially much more in the future. Therefore, the level of protection and regulation provided by Law No. 19.628 may be insufficient.

The idea of neurorights, proposed in 2017 (Ienca and Andorno 2017) as a new advancement in basic human rights (Macpherson et al. 2021; Mostajo-Radji 2023), identifies key areas upon which to build a framework:

- **Cognitive liberty:** The ability and right of an individual to protect their mental information and prevent unauthorised intrusion into their cognitive space (European Union 2024c). In brief, cognitive liberty grants individuals the right to reject the coercive application of such technologies (Hertz 2023).
- **Mental privacy:** Several international conventions recognise the right to privacy; however, they do not adequately address the privacy of mental or thought processes. An individual's neurodata, such as brain waves, can be identifying and acquired without their knowledge (Hertz 2023).
- **Mental integrity:** The ban on the non-consensual and harmful manipulation of a person's neural activity safeguards individuals

from intrusions such as malicious brain hacking (Hertz 2023; European Union 2024c).

- **Psychological continuity:** The right to psychological continuity is designed to prevent alterations in neural functioning that extend beyond protecting access to brain data. Alternations to the mind might not all violate mental privacy or/and integrity but may be more subtle, such as marketing techniques used to influence behaviour (Hertz 2023).
- **Fair access:** The right to cognitive liberty should, in theory, encompass positive aspects such as ensuring equal access to neurotechnology, provided the technology is considered ethical (European Union 2024b).

What oversight is being proposed?

In 2021, the Chilean Senate (Senado de la Republica de Chile) approved a bill to amend the constitution to protect brain rights (neurorights) and neurodata (Guzmán 2022.; Do et al. 2024). The amendment states that 'the law shall regulate the requirements, conditions, and restrictions for [neurodata], and shall especially protect brain activity, as well as the information derived from it'. Furthermore, scientific and technological developments are to be conducted with 'respect for […] physical and mental integrity' (Do et al. 2024). The amendment places Chile as the world's first country to have legislation to protect 'neurorights' such as mental privacy, free will and non-discrimination in citizens' access to neurotechnology (Guzmán 2022). The anticipated value of the amendment and neuroprotection bill lies in the establishment of mental identity as an inviolable right that is safeguarded from manipulation due to advancements in neuroscience and AI. It also sets out to protect mental privacy, personal identity, free will and equitable access to human-enhancing technologies, and guard against discrimination.

The idea of neurorights was introduced into the Chilean context in 2017 by the director of the Neurorights Initiative, Rafael Yuste, Professor of Neuroscience and initiator of the BRAIN Initiative, who highlighted their importance now and in the future. Yuste formed a partnership with Chilean Senator Guido Girardi to explore a pilot constitutional amendment in Chile (Neurorights Foundation 2024) that would recognise brain data and activity as protected under neurorights. This activity was facilitated by three key aspects: 1) a significant social awareness of human rights, resulting from Chile's history (Einhorn and Yuste 2022); 2) the presence of a specific committee within the Chilean senate focused on launching legislative initiatives driven by science and medicines, the *Comision del Futuro* (The Future's Commission) (Einhorn and Yuste 2022); and 3) Chile's strong reputation and track record in the field of neuroscience (Einhorn and Yuste 2022), which acted as an enabler for the legislation's development. Senator Girardi worked with a team of lawyers and several academics to produce a constitutional amendment bill (Boletín 13.827-19) and a bill of law (Boletín 13.828-19), with the amendment providing the constitutional base for the bill (Senate of the Republic of Chile 2020a; 2020b).

The change to the Chilean constitution to protect neurorights is an example of a hard law approach to governance. The neuroprotection bill outlines three main areas for the implementation of neuroprotection (Einhorn and Yuste 2022):

- **Preservation of neurorights and mental integrity:** The bill establishes that neurodata is a special form of sensitive health data that has the same restrictions human organs receive under Chilean law, meaning it cannot be sold or bought commercially (Einhorn and Yuste 2022). In practice, any neurotechnology wishing to be deployed needs to undergo a registration pipeline adjacent to that required for medical devices, thus the same

level of compliance and rules apply to neurotechnologies as to therapeutics instruments so that their quality and safety can be thoroughly evaluated (Perelló 2022).

- **Informed consent:** The bill states that anyone who receives any neurotechnological intervention must understand and consent to the potential short- and long-term effect the applied neurotechnology might have on their physical, cognitive and emotional state, especially for commercial applications (Einhorn and Yuste 2022). In practice this means that when registering the neurotechnology its intended application must be stated (Perelló 2022). The use of any neurotechnology must also be reversible (i.e. the use can be terminated without any negative effects) (Perelló 2022).
- **Benefits to society:** The bill states that all research within the field of neurotechnology should be conducted for the benefit of society while preserving the user's mental integrity and continuity applications (Einhorn and Yuste 2022). Thus, certain uses are defined as definitively prohibited, including influencing human conduct without consent, exploiting weaknesses of vulnerable populations and affecting the neuroplasticity of vulnerable populations (Perelló 2022).

What is the future trajectory for the oversight mechanism?

The constitutional amendment has already been applied during a landmark ruling, where the Chilean Supreme Court upheld the principles of neurorights in the case of neurotechnology company Emotiv Inc. v. Guido Girardi. The plaintiff, Guido Girardi, claimed that his brain data was inadequately protected by Emotiv's device, Insight, which records detailed brain electrical activity. Emotiv responded that the harms were hypothetical, and that the data was collected and stored in an anonymous, encrypted manner. The court judged that Emotiv did not uphold the plaintiff's constitutional rights to privacy and physical and psychological integrity (Do et al. 2024), with the sentence stating that as technology advances, user identification may become possible even with anonymised data (Cornejo-Plaza et al. 2024). Emotiv's reliance on user consent as a safeguard was therefore misleading, as even with consent users remain vulnerable to the exposure of their personal data as they are not aware of potential future threats (Cornejo-Plaza et al. 2024). **This judgement by the Chilean Supreme Court was the first in the world to rule on a neurorights/neuroethics case** and, unsurprisingly, **created significant momentum in the rest of Latin America regarding neurorights.** For example, in 2022 in Brazil, Bill 522/2022 was introduced, amending the General Data Protection Law (LGPD), to regulate neurodata as sensitive data (Câmara Dos Deputados 2022), and in 2023, Bill 29/2023 was proposed to include protections for mental integrity and algorithmic transparency in the constitution (Federal Senate of Brazil 2023). The Parlatino (Latin American and Caribbean Parliament) introduced the Neurorights Model Law in 2022 to regulate neurotechnology, establish an independent oversight authority and provide redress mechanisms (Muñoz and Borbón 2023). In Mexico, two pending neuroprivacy bills seek to amend the constitution to protect individual identity, physical and psychological integrity, and provide congressional authority to pass federal legislation on AI, cybersecurity and neurorights (Do et al. 2024). Further efforts in the region include the proposed data protection amendments in Costa Rica and Colombia, pending bills in Argentina, and Uruguay's intention to regulate neurotechnologies in a similar way to Chile (Do et al. 2024).

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Chile's constitutional amendment and subsequent ruling has received some criticism that it addresses threats that do not yet exist or that

may be very distant, with critics labelling this as 'legal fiction' (Cornejo-Plaza 2023) and a 'precipitous advancement of the Chilean neurorights movement, predicated upon the false premise of worries about cognitive liberty' (Fins 2022). Other criticisms are based on the idea that premature neurorights agendas could undermine the potential of neurotechnology, and legislation must be sufficiently framed and nuanced when implemented. The proposal for the strict regulation of neurodata could hinder research for beneficial purposes and obstruct legitimate public interests in law enforcement and justice by limiting evidence acquisition (Bublitz 2022). For example, the identification of covert consciousness – patients who appear to be unresponsive but who are conscious when checking with electroencephalography (EEG) studies – could potentially be hindered (Fins 2022). DerechosDigitales, a Latin American advocacy group for individual digital rights, has strongly criticised the Chilean initiatives, arguing that they misinterpret and undermine the human rights and individual liberties of those they aim to protect (Rommelfanger et al. 2022).

As with most changes of this magnitude, there are both supporters and critics of the implementation. Chile's constitutional amendment is spearheading neuroethics legislation, and valuable lessons can be learned and applied broadly. Several potential issues with the latest bill have been noted by Rommelfanger et al. (2022):

- **Conceptual ambiguities:** Terms often used in relation to neuroethics, such as 'mental integrity', can be interpreted as vague concepts and pose challenges for judicial interpretation. Definitional issues and terminological imprecisions regarding what constitutes neurodata and neurotechnology can arise if not sufficiently nuanced; for example, defining neurotechnologies as only involving the central nervous system and excluding those interacting with the peripheral nervous system. Erroneous interpretation could have a negative impact on research and medical care.
- **Private sector involvement:** Technologies often migrate from healthcare to other domains, as seen with smartphones and the Internet, so consideration of commercial risks such as harmful inferences from neurodata is important to ensure that significant threats are not left unregulated. Private sector involvement in a neurorights framework could ensure ethical innovation in non-medical contexts.
- **Public engagement:** Currently, policymakers and academics have been involved in the design and implementation of the bill; however, the role of patients and other consumers is not clearly defined. The involvement of diverse communities can shape the criteria for evaluating the potential risks and benefits of establishing additional neurorights.

Beyond Chile, most current health information laws do not protect neurotechnology derived data specifically. For example, the HIPAA Act in the United States primarily regulates specific data-holding entities such as hospitals but does not cover device makers or consumer neurodata (Rommelfanger et al. 2022). Other regulations are more comprehensive. For example, the EU GDPR includes provisions for biometric data, which could arguably encompass neurodata if it can identify individuals. However, even such comprehensive frameworks have gaps as they focus on identification rather than inferences about an individual's interests, preferences or psychological state derived from neurodata (Rommelfanger et al. 2022). Chile is currently at the forefront of the discourse on the practical implementation of neurorights, offering valuable insights into effective strategies and broader considerations. By examining Chile's approach, areas requiring further attention can be identified, discussions on these topics can be stimulated, and the most suitable and valuable mechanisms and frameworks for neurorights can be explored.

Case study 2:
United States – Proposed legislation to prevent discrimination on the basis of neurodata

Table 11. The US Neuroscience Information Nondiscrimination Act (NINA)

Technology area:	Neurotechnology
Oversight example:	Neuroscience Information Nondiscrimination Act (NINA)
Type(s) of oversight mechanism(s):	Proposed legislation
Jurisdiction:	United States
Timescale:	First proposed in 2012

Why is the oversight required?

Just as the Human Genome Project[120] raised concerns about genetic data safety, similar issues are emerging with the completion of initiatives such as the Human Brain Project or the Human Connectome Project, highlighting the need for safeguards around neuroscience data. Following the introduction of GINA, some US scholars have proposed the creation of the Neuroscience Information Nondiscrimination Act (NINA) to address potential discrimination based on predictive neuroimaging and neuroscience data (Kostiuk 2012).

Similar to GINA, **a case needs to be made as to why neuroscience data needs to be protected and why it is distinct from other types of sensitive data.** The main rationales supporting the special nature of neuroscience data are the intimate characteristics of the data (personhood and potential identification), its direct correlation to a person's mental state, invasiveness, and societal impacts such as surveillance (Jwa and Martinez-Martin 2023). The field of neuroscience has been rapidly advancing in recent years as fundamental research has been supported and catalysed by developments in AI/ML and big data analytics (and vice versa). Examples of this include ML algorithms that enable and facilitate the complex analysis of functional magnetic resonance imaging (fMRI), BCI and electroretinogram (ERG) data to understand specific cognitive processes, or the ability to identify and sometimes predict mental states for digital phenotyping (Jwa and Martinez-Martin 2023). Neuroscience data, shadowing the trajectory of genetic technology, is also becoming increasingly accessible outside of the clinic and research labs and is used in direct-to-consumer applications such as EEG (electroencephalographic), BCI and transcranial electrical stimulation (tES) devices, which has led to the commercial use and sharing of neuroscience data within a context where data brokerage is a very lucrative business, accentuating concerns for the reidentification and misuse of personal data (Jwa and Poldrack 2022; Jwa and Martinez-Martin 2023).

Currently, US federal laws are not suitable for specifically protecting against the acquisition and misuse of neuroscience information by employers (Kostiuk 2012). The Americans with Disabilities Act Amendments Act protects employees who have developed neurological or psychological conditions but does not clarify whether

120 Since the Human Genome Project first successfully sequenced 92% of the human genome in 2003 and made the information freely available in public databases, genomics has transformed healthcare through numerous applications such as non-invasive prenatal genetic testing, DNA-based forensics, genetic disease diagnostics, personalised healthcare treatments and Covid-19 surveillance (UK Parliament 2023b).

their neurological information (which could suggest potential future conditions) counts as a significant impairment. It is also not clear whether, if an employee is fired due to a potential future condition, they could claim that their employer perceived them as having an impairment (Kostiuk 2012). Attempts to pass a general data protection regulation in the United States (American Data Privacy and Protection Act), similar to the EU GDPR, to provide some degree of protection to sensitive data have failed to go through (Bailey 2024).

What oversight is being proposed?

NINA is a proposed legislation that would prevent the misuse of information inferred from neuroscience data. It is based on GINA, which was signed into US law in 2008.

To better understand NINA as a proposed governance framework, it is necessary to understand how GINA was implemented and what gaps in the law it aims to address. GINA was implemented following the completion of the Human Genome Project in 2003, and the associated leaps in genomics R&D that enabled a better understanding of, among other things, the genetic basis of illnesses (Kostiuk 2012). It prohibits health insurers (Title I) and employers (Title II) from discriminating based on genetic information (EEOC 2024). The regulatory model was a significant step in recognising the specific need for the governance of genetic information, which is inherently identifying, rather than relying on existing general data protection laws in specific states (Jwa and Poldrack 2022). Although other laws offer protection against genetic discrimination, GINA was the first to establish a federal standard that prevents the discrimination of individuals based on genetic information and the characteristics of their relatives (Jwa and Poldrack 2022). It is relevant to note that unlike the Americans with Disabilities Act (ADA), GINA does not prevent the discrimination of individuals already affected by a genetic condition (Joly et al. 2020). Proponents of GINA demonstrated that the ADA was inadequate in stopping employers from using genetic information, once they had access to it, from discriminating. Title I of the ADA, which guards individuals seeking employment or working in the private sector against discrimination due to disability, does not specifically address genetic information (Kostiuk 2012).

The implementation of NINA has only been discussed at an academic level, and it is far from enactment. The motivation behind the proposal is to establish a new regulatory framework that enhances the protection of data subjects in the realms of data sharing and privacy. As data privacy becomes a global imperative, numerous regulatory proposals have emerged. Most of these focus on obtaining more specific consent for the use of research data or imposing stricter access controls. While these measures have their advantages, they also risk hindering open science practices and curtailing the benefits of data sharing. **One interviewee stated that they believe it crucial to address not only the risk of reidentification, but also to minimise potential harm resulting from the misuse of data.**[121] By focusing on harm, NINA would fundamentally support data sharing and research, balancing a data protection regime with research interests. This could be achieved through an empirical assessment of privacy risks to develop appropriate privacy protection levels.

What is the future trajectory for the oversight mechanism?

GINA's implementation was facilitated by various factors, including the widespread adoption and commercialisation of genetic testing

121 Interview_07.

technologies. According to an interviewee, the growing demand for genetic testing, whether voluntary or requested, helped build momentum for GINA's cause, and although neurotechnology and neuroscience information are currently attracting attention, they may not yet be perceived as pressing real-world concerns in the same way as genetic information. Therefore, even if NINA were to be implemented now, it might serve more as a symbolic gesture. Nevertheless, attention is growing. A systematic literature review examining approaches to brain data regulation over the last 20 years shows a trend has emerged in articles advocating for increased brain data protection. More recent publications tend to support a wider scope of brain data, likely due to the recognition that recent advancements in computational behavioural technologies have improved the capacity to derive significant behavioural and health insights from diverse personal data (Jwa and Martinez-Martin 2023). In April 2024, a new bill was passed in Colorado (US) that amends the state's privacy law to include the privacy of neural data (Stevens 2024). This means that such data will be protected in the same way as fingerprints and facial images under the Colorado Privacy Act. Other states including California and Minnesota are likely to follow a similar approach (Samuel 2024). As the neurotechnology market grows (it is projected to grow to US$15.28 billion in 2024) (Yahoo! Finance 2024) and neuroscience technologies advance, there will likely be increasing support for the implementation of governance mechanisms such as NINA. It is therefore important to consider the potential challenges that may arise.

Similar barriers and limitations to those identified for GINA are likely to affect NINA. NINA covers an area of science and technology that is nascent and will rapidly evolve in the future. This **rapid advancement could lead to new forms of unforeseen discrimination** that will need to be addressed by more adaptable policy frameworks (Joly et al. 2020). **GINA focuses solely on private sector discrimination, whereas public agencies also show interest in genetic information** (Joly et al. 2020). Organisations that provide life, long-term care and disability insurance are not covered by GINA (Prince 2018). According to one interviewee, this was a balance that had to be struck to enable the bill to be successfully passed. Despite these barriers, most legal scholars would agree that GINA has been a valuable milestone in recognising the power of genetics and injustice of discrimination based on that data (Kostiuk 2012). GINA has also helped ease people's fear and scepticism and allowed individuals to make the most of genetic testing and novel technologies and therapies, leading to the facilitation of research (Jwa and Poldrack 2022). So far there have not been many cases filed under GINA. It is unclear whether this is because the legislation is effectively discouraging genetic data malpractice or because the need for such legal action is not yet significant.

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

Although recent movements in the United States and Chile show progress in this field, the practical implementation of such legislation remains challenging, requiring continuous input to balance effective regulation with the maintenance of open science. By examining issues from other governance frameworks, such as the EU GDPR and GINA, proponents of NINA have identified some considerations for NINA that could be implemented more broadly. First, efforts should focus on regulation that supports and enhances data sharing, research and innovation. **While other legislations and proposals emphasise reducing sharing or controlling access, NINA considers other aspects of privacy risk, such as harm, rather than just the risk of data disclosure.** According to one interviewee, focusing on harm reduction rather than only reidentification is a fundamentally pro-research approach; however, it does not negate the necessity of rigorous data protection regimes, and a balance needs to be

found. he interviewee noted that focusing on harm should involve conducting empirical assessments of privacy risks to develop best practices for research. Specifically, an appropriate level of privacy protection should be established, and harm prevention regulations should be accompanied by a tiered approach to data sharing and use. This means that the openness or sharing of data should depend on its level of sensitivity.[100] The interviewee suggested that a mechanism to evaluate the level of risk should be developed and updated in response to advancements in reidentification threats or technology. Second, according to another interviewee, and emphasised in literature (Jwa and Poldrack 2022), while **GINA only focuses on employment and health insurance, NINA would expand this scope into education, housing and legal settings.**

Case study 3:
China – Non-binding ethics guidelines for brain–computer interface research

Table 12. China's ethics guidelines for BCI research

Technology area:	Neurotechnology
Oversight example:	Ethics guidelines for BCI research
Type(s) of oversight mechanism(s):	Guidelines
Jurisdiction:	China
Timescale:	February 2024 – present

Why is the oversight required?

In China, neurotechnology oversight is split across many mechanisms and sectors, ranging from medical devices and clinical trials regulation to consumer protection laws; however, there is vast geographical variation in its oversight. There are also complexities that accompany the neurodata captured from BCIs in neurotechnology research and implementation due to the plasticity of the brain and the sensitivity of the data captured, which warrants special protections.

In China, neurotechnology has been deployed in some controversial contexts that have given rise to concern.[122] In 2019, an electroencephalogram (EEG) was used at the Xiaoshun Central Primary School in Jinhua City to monitor students' concentration.

122 INT_01, INT_02.

The devices, developed in conjunction with US-based BrainCo and Chinese partner company Zhejiang Brainco, were placed on children for 30 minutes while the research collected data (Standaert 2019). The trial was halted amid parents' concerns that devices could be used to control their children.[123] As a result, there have been increasing calls for discussion on a rights framework and a review of the application of neurotechnology (Li Xueyao 2023). Although China's government apparatus has major influence over the trajectory of BCI and neurotechnology development, it nevertheless is reactive to people's concerns.

Commentators have noted that neurotechnology, particularly when combined with AI, can pose a serious threat to human rights and freedoms, including cognitive liberty, personality integrity and psychiatric privacy (Li Xueyao 2023). Considering this, many in China believe that a set of rights – 'neurorights' – have become a practical necessity. These rights draw on a variety of disciplines, including philosophy, ethics, jurisprudence, neuroscience, cognitive science and medicine (Li Xueyao 2023). Interviewees mentioned concerns within China about the values that guide neurotechnology research and its intersection with AI. These concerns are underscored by questions such as who will control the values that will characterise AI and its use in BCIs, especially artificial general intelligence, which is big priority for China.[124]

In response to growing concerns over personal data and its collection, storage and use, Chinese authorities have been prompted to adopt similar regulations to countries that have recently developed legislation (e.g. EU/UK GDPR) (Calais et al. 2023). Furthermore, substantial investment in neurotechnology and brain research in the United States has prompted Chinese authorities to make similar investments in recognition of the implications of neurotechnology development for society, public health and national security (Putney 2021).

China has a relatively light touch set of restrictions for neurotechnology research, including animal research, which alongside the drive from the government suggests that research in China will continue to grow.[125]

What oversight is being proposed?

Regulation in China, like in many countries, is comprised of both voluntary, informal oversight (implicit regulations or norms that are not codified but guide acceptable behaviour) and formal oversight (explicit regulation, law) (Fedaseyeu and Yu 2022). Informal oversight is not codified, but is communicated by administrators or government officials via the press, public addresses and other modes of communication. It often precedes formal or binding regulation, which is put into place after the government detects fraud or abuse. Interviewees noted that this appears also to be true for neurotechnology and BCI research.[126]

The Ethics Guidelines for Brain–Computer Interface Research, authored by the Artificial Intelligence Ethics Subcommittee of the National Science and Technology Ethics Commission, part of the Chinese Communist Party Central Science and Technology Commission, offers non-binding principles for researchers and

123 INT_01, INT_02.
124 INT_01, INT_02.
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126 INT_01, INT_02.

research institutions for the ethical conduct of BCI research in China to prevent risk and promote the development of the technology (Center for Security and Emerging Technology 2024).[127] Its basic principles include:

- **Ensure health, enhance well-being:** BCI research must be harmless and must assist, enhance and repair sensory-motor functions or improve human–computer interaction.
- **Respect participants, apply technology in moderation:** BCI research must ensure the consciousness, function and structure of the human brain and should fully consider the risks/benefits; augmentative BCIs should follow principles of moderation; applications should be cautious; and studies involving children should adopt stricter ethical evaluations, review and risk prevention.
- **Adhere to justice, ensure fairness:** BCI research should be transparent and fair when applied in competitive social environments (medical, educational, employment, etc.) wherein human cognition is paramount and fairness in social competition is valued; research should prevent bias against the non-target audience and assure fairness between the target and non-target audience.
- **Control risks, ensure safety:** BCI research should adhere to high scientific standards, professional norms and ethical principles. High-quality research design should control research risks, and ethical and data security reviews should be conducted. Risk monitoring should be dynamically adjusted throughout the research process to control risk and management, and to protect physical safety, privacy, data security and the legitimate rights of participants.
- **Information disclosure, assurance of the right to know:** Researchers should actively share information with relevant stakeholders, ensure openness and transparency, and safeguard the right to know. There should be accurate and timely disclosure of information and research results, new and controversial technologies should be fully discussed, and stakeholders and the wider public should be heard.
- **Support innovation, strictly regulate:** Clinical trials of BCIs may be conducted with fully informed consent in cases of rare disease or if the life of the patient is seriously endangered and no alternative treatment exists. Trials should remain in strict compliance with national regulations on medical devices, clinical research and related stipulations.

The guidelines categorise BCI technologies and differentiate between BCIs designed to enhance human cognition (**augmentative**) and those designed to help people with neurological disabilities (**therapeutic**). Further differentiations are drawn between **non-invasive restorative** research, **invasive restorative** research, and **interventional, enhanced** and **animal research** (Center for Security and Emerging Technology 2024).

The guidelines stipulate that research that replaces or weakens human judgement/decision making, interferes with human autonomy and self-awareness, or that may cause addiction or affect behaviour

127 The information in this case study is based on an English translation of the official guidelines issued by the Artificial Intelligence Ethics Subcommittee of the National Science and Technology Ethics Commission in China (Center for Security and Emerging Technology 2024). The original source text, which served as the basis for this translation, can be accessed here: https://most.gov.cn/kjbgz/202402/W020240202808384301641.docx

should be avoided until BCI technologies prove to be superior to human capabilities and garner societal consensus.

The guidelines propose specific recommendations, including:

- **Legality and compliance:** BCI research should comply with national laws and regulations, including the Ethical Review Measures for Life Science and Medical Research Involving Humans, and pass ethical review (Center for Security and Emerging Technology 2024). Invasive BCI research should be conducted with evidence of safety and benefit, and medical staff must adopt a patient-centred approach, ensure quality and safety, and maximally avoid or minimise tissues damage or infection.
- **Social and scientific values:** BCI research much have social value and focus on restorative technologies; non-medical purposes can be pursued with strict regulation and clear benefit.
- **Informed consent:** BCI researchers must obtain written informed consent from participants or their legal representatives/guardian; participants must be fully informed of risks and benefits; the consent form should be standardised and approved by the ethics review committee; the discovery of a new risk requires a renewal of consent; and participants must be allowed to withdraw.
- **Privacy protection and personal information protection:** Data collected during BCI research constitutes private data; the scope of data collection and access permissions are to be approved by the ethics committee; the handling and management plan should be established; and data should be protected throughout the research process in accordance with laws, regulations and standards, such as the Personal Information Protection Law of the People's Republic of China (Webster 2021) and the Data Security Law of the People's Republic of China (DigiChina 2021) .
- **Risk prevention and control:** Risk control mechanisms should be established, including operating procedures, correction mechanisms, emergency plans, suspension procedures and remedial response guidelines to ensure safety; continuous attention security risks are required, including long-term security evaluations and validations; device and equipment identification, information encryption, system protection mechanisms and emergency handling mechanisms must be in place.
- **Aptitude requirements:** BCI researchers should be at the appropriate professional level and ability; they must undergo specialised skill and ethics training; clinical research involving patients must involve clinicians; research teams and institutions must have necessary key technologies, research prerequisites and infrastructure. Invasive BCI should use professionally certified equipment; drug and device safety should comply with the Drug Administration Law of the People's Republic of China (National Medical Products Administration 2019) and the Regulations on the Supervision and Administration of Medical Devices (National Medical Products Administration 2022).
- **Responsibility mechanisms:** BCI research should enhance transparency, explainability, reliability and controllability; ensure accountability at technology design, R&D, use and deployment; obey national laws, regulations and standards, and clearly define the responsibility mechanism.

What is the future trajectory for the oversight mechanism?

The **Brain Science and Brain-like Intelligence Technology Development Plan**, launched by China's Ministry of Science and Technology in 2021, outlines China's strategy for neuroscience development to 2030. The regulatory landscape will likely continue to evolve with the growth of these research efforts, including informal

oversight mechanisms such as the Ethics Guidelines for Brain–Computer Interface (BCI) Research. One of the most significant developments is the **China Brain Project**, approved in 2016 and launched in 2021, which targets the neural basis of cognition, diagnosing and treating brain diseases, and brain-inspired computing (Normile 2022).

Ethical guidelines, including the Ethics Guidelines for BCI Research, are discretionary, and variations in their application may prolong uncertainty and informality within the regulatory landscape governing neurotechnology research (Calais et al. 2023). The Chinese state perceives AI as an enabler of cognitive neuroscience – i.e. it can be used to better understand how knowledge is represented in the brain – as evidenced by large research budgets in China.[128] One interviewee noted that one of the concerns of many academics outside China is that 'China's pursuit of BCI will continue to the point that the divergence between human cognitions and artificial intelligence is no longer distinguishable; that there is no distinction between one and the other. At this point, ethical concern for neurotech development becomes huge.'[129] While the principles represented within the Ethics Guidelines for BCI Research go far in addressing some ethical concerns, they are discretionary and therefore it remains unclear how and to what degree they will be realised in future BCI research in China.

As AI capabilities develop and Chinese authorities show continued interest in related regulation, including the **Interim Measures for the Administration of Generative Artificial Intelligence Services** (Office of the Central Cyberspace Affairs Commission 2023), it is expected that the regulatory landscape, including ethical guidelines for research practices, will continue to evolve in response to technological developments (Calais et al. 2023).

What lessons can be learnt from this example regarding the effectiveness of the oversight mechanism(s)?

In putting forward the Ethics Guidelines for BCI Research, China has demonstrated a willingness and adaptability to play by international norms and rules – even adopting variations of them – to gain recognition of Chinese achievements and collaborate with the international community of scientists (Mallapaty 2018). This has also been seen with China's 2021 data protection regulation, the Personal Information Protection Law, which appears in part modelled on the EU GDPR.

The 'mixed' regulatory environment of informal and formal regulatory measures, although integral to innovation in China, is difficult to navigate, particularly for international firms, which has emerged as a key insight through the process. While the Ethics Guidelines for BCI Research puts forward noteworthy principles in ethical BCI research, they are nevertheless discretionary, and it is unclear to what degree they affect research practice. There are few reasons to believe this model may not be future proof (Fedaseyeu and Yu 2022).

Chinese authorities, including those overseeing neurotechnology and research involving neurotechnology, appear to be responsive to views of the public. This was seen in the Xiaoshun Central Primary School example, where research involving BCIs was halted following a negative public response.[130] The Ethical Guidelines for BCI Research may similarly be a response to public sentiment regarding the need for oversight of BCI research.

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Chapter 7

Concluding remarks and priority considerations for effective technology oversight in the future

Box 5. Priority considerations for effective oversight of emerging technologies in the future: Key takeaways

Priority consideration 1: Develop comprehensive process maps and establish networks of interconnected oversight mechanisms to support stakeholders in effectively navigating the labyrinth of relevant mechanisms in the technology oversight landscape.

Priority consideration 2: Ensure that equity considerations are prioritised and integrated into all aspects of technology oversight to promote fairness and inclusivity.

Priority consideration 3: Identify and establish common ground for practical and actionable international alignment to harmonise governance practices across borders.

Priority consideration 4: Intensify efforts to develop internationally coordinated risk mitigation strategies as part of implementing oversight mechanisms to address global challenges posed by emerging technologies.

Priority consideration 5: Support the implementation and scaling of innovative oversight mechanisms to effectively manage the complexities and dynamics of emerging technologies.

Priority consideration 6: Facilitate proactive public involvement in the development of oversight frameworks to ensure transparency and accountability.

Priority consideration 7: Incorporate adaptive practices into oversight processes to foster continuous learning, flexibility and agility in response to technological advancements.

Priority consideration 8: Integrate anticipatory strategies into oversight frameworks to prepare for and address future developments in emerging technologies.

Source: RAND Europe analysis.

7.1. Introduction

As technologies become more pervasive and form a critical aspect of our societal infrastructure, governance and wider oversight mechanisms have a key role to play in ensuring that benefits from technology are maximised and risks are managed proactively.

The goal of technology oversight is to ensure that technology is developed, deployed and used in a responsible and ethical manner, and that it does not pose undue risks or harm to individuals or society as a whole. The effective oversight of technology is a crucial factor underpinning the impact of an array of new and emerging technologies on research and innovation systems, health, and the

environment. This chapter presents concluding remarks on the findings of the study and reflects on the potential future directions of oversight in the four technology areas. It also considers broader technology and policy developments occurring globally.

This report adopts a hybrid approach by examining a series of overview and detailed vignettes designed to present an evidence-based snapshot of critical technology oversight developments occurring in key global jurisdictions of interest to Wellcome. The overviews provide a holistic view of oversight occurring in four globally influential jurisdictions that are often at the leading edge of both technology developments and governance debates. The more detailed case studies offer evidence from a diverse selection of specific use cases of both emerging and established technology oversight in different cultural and social contexts. Collectively, these vignettes provide a deeper insight into the key oversight conversations occurring and pinpoint areas where Wellcome and other stakeholders might effectively contribute. This understanding will also aid in identifying learning opportunities and evaluating prospects for further actions and initiatives, potentially influencing change in these areas over time.

7.2. Priority considerations for effective technology oversight in the future

This study has synthesised a vast body of evidence. Although the oversight mechanisms, along with their associated challenges and opportunities, differ to varying degrees across the technology areas, several common themes have emerged. Addressing the challenge of balancing risks and innovation through oversight, and future-proofing oversight mechanisms against technological progress, are critical and common challenges encountered across various technologies.

The eight main common themes are highlighted below, alongside a series of priority considerations for stakeholders engaged in technology R&I, to support the development of the broader R&I and technology oversight ecosystem. These priority considerations – as a set of cross-cutting actions – will also be relevant for a broader audience, including individuals and groups with a vested interest in the oversight of emerging technologies, such as policymakers, industry professionals, funders, researchers and the general public. High-level stakeholders that could potentially play a role in developing some of the proposed actions are also highlighted.

Priority consideration 1: Develop comprehensive process maps and establish networks of interconnected oversight mechanisms to support stakeholders in effectively navigating the labyrinth of relevant mechanisms in the technology oversight landscape.

Context: The development and adoption of informal oversight mechanisms and the use of boards, taskforces or review committees is gaining popularity. Their timeliness and flexibility are key for keeping pace with fast-evolving technological developments and for adapting specific implementation strategies associated with the technology governance. However, the increasing commonality of informal oversight mechanisms (sometimes driven by the ambiguity of pertinent overarching regulations) can also lead to a complex and intertwined ecosystem of formal oversight mechanisms, informal guidelines and codes of practice, and numerous review committees and boards. This complexity and patchwork nature of the technology governance ecosystem can be difficult for researchers and industry stakeholders to navigate. For example, the SCBEM code of practice, ethical review processes, the HFE Act, ISSCR guidelines and the German Embryo Act would make for a very complex and potentially

contradictory oversight landscape for an international researcher in the United Kingdom working on a Horizon Europe grant and collaborating with German academics.

Proposed action: Stakeholders involved in oversight should ensure that any implementation-focused informal oversight mechanisms developed, including those involving committees and guidelines, offer clear guidance and delineation regarding their position within and relationship to the broader technology oversight landscape. Developing such technology oversight 'process maps', and outlining and mapping the network of linked and nested oversight mechanisms at national and international levels, could prove valuable to researchers, industry professionals and regulators. For example, the OECD AI Policy Observatory serves as an international hub for AI policy, providing a comprehensive online platform that continuously monitors and analyses AI policies (and a range of other data) worldwide (OECD 2024c). In conjunction with this, the OECD AI Network of Experts assembles a diverse group of AI specialists from various sectors and backgrounds to inform policy responses on critical emerging topics related to AI (OECD 2024d). Likewise, the AI Index from Stanford University serves as an authoritative recurring source of data and insights concerning global developments in AI, including policy and governance (Stanford University 2024b). The UK government launched the Engineering Biology Regulators' Network (EBRN) in 2023 to enhance collaboration among regulators, promote the sharing of knowledge and best practices, and engage in horizon scanning (UK Government 2023e). These represent a selection of niche examples. The core idea is to establish concrete cross-cutting tools that are designed to help stakeholders effectively navigate and manage the complex array of mechanisms with the broader technology oversight landscape.

Example actors to involve: Supranational/inter-governmental organisations involved in technology oversight; national funding organisations; regulators; academia.

Priority consideration 2: Ensure that equity considerations are prioritised and integrated into all aspects of technology oversight to promote fairness and inclusivity.

Context: Disparities in access to, representation in and benefits from emerging technologies – and their oversight mechanisms – can lead to unequal societal and economic outcomes, undermining the potential for inclusive growth and innovation. Often, equity does not seem to receive the same level of attention as other critical aspects such as privacy and safety in the context of technology oversight. For instance, proposals for the oversight of neurodata and neural organoids are primarily focused on agency, autonomy, privacy and protection, and do not explicitly feature equity. Furthermore, technology oversight, especially regulatory measures, can occasionally favour large organisations that possess the resources necessary to meet compliance requirements. Therefore, there is a growing recognition of the importance of incorporating equity considerations into discussions on technology oversight.

Proposed action: There is a need to actively support and refine technology oversight mechanisms to place greater emphasis on equity considerations. This is crucial for fostering an inclusive and fair technological landscape, and can help reduce barriers to entry for researchers, innovators and wider stakeholders involved in oversight mechanisms, including those from LMICs. Ensuring diverse and equitable representation in decision-making processes will help address the needs and concerns of marginalised or underrepresented communities, promoting fairness and reducing biases in

technological development. In the context of neurotechnology, GINA in the US serves as a specific example of a formal technology oversight instrument designed to prioritise social equity and prevent potential discrimination (EEOC 2008). Regarding AI, several high-level guidelines over the years have explicitly integrated dimensions of equity into their principles, to varying extents. Notable examples include the European Commission's Ethics Guidelines for Trustworthy AI (European Commission 2019), the OECD's AI Principles (OECD 2019b), and the US National Institute of Standards and Technology's AI Risk Management Framework (NIST 2023).

Example actors to involve: Regulators; national governments; supranational/inter-governmental organisations; academia; civil society organisations.

Priority consideration 3: Identify and establish common ground for practical and actionable international alignment to harmonise governance practices across borders.

Context: International oversight approaches can serve as valuable reference frameworks, providing foundational baselines for the development of national oversight mechanisms. Conversely, some international mechanisms may be too broad for national implementation and include relatively ambiguous guidance on monitoring and enforcement. They may also not sufficiently acknowledge social and cultural variations. For example, the BWC establishes a foundational, normative framework that aims to eliminate biological weapons and is widely supported internationally. However, it does not have an established mechanism for verifying compliance and lacks effective enforcement mechanisms to address non-compliance.

Proposed action: Stakeholders engaged in technology oversight should ensure that international mechanisms extend beyond mere high-level principles or frameworks and include more detailed, practical implementation guidelines that reflect national and social contexts. Although international guidelines cannot address every specific need, a focused effort to identify key universal themes, such as ethics and social values, can be beneficial. When these themes are integrated into practical guidelines, they can facilitate a common foundation for international alignment on the oversight of emerging technologies (including on issues related to cross-border data flows). For example, some of the challenges associated with the BWC (highlighted above) are now being addressed through a suite of proposed amendments to make it more actionable and implementation-focused, with some common approaches to implementation across the signatories. Throughout history there have been several instances of international alignment and collaboration. For example, the establishment of the Global System for Mobile Communications (GSM) standard showcases cooperation among diverse public and private stakeholders across nations who were united by a common objective to realise mutual benefits. The Cartagena Protocol on Biosafety represents a significant international collaborative effort and highlights the ability of a substantial number of nations to collaborate in addressing complex issues related to the impacts of emerging technologies (Gunashekar et al. 2019).

Example actors to involve: National governments; industry; regulators.

Priority consideration 4: Intensify efforts to develop internationally coordinated risk mitigation strategies as part of implementing oversight mechanisms to address global challenges posed by emerging technologies.

Context: In the swiftly evolving landscape of emerging technologies such as AI and biotechnology, the challenges posed are inherently global. These technologies transcend national borders, creating interconnected risks that no single country can effectively manage alone. Issues such as ethical dilemmas, data privacy concerns, cybersecurity threats and the potential for technology misuse often necessitate a coordinated international response. The lack of harmonised standards and regulatory frameworks can potentially lead to fragmented governance, making it difficult to address these risks comprehensively. Disparities in technological capabilities and regulatory maturity among countries further complicate the global governance landscape, potentially exacerbating inequalities and creating loopholes that can be exploited. For instance, in a (hypothetical) scenario where the United States and the United Kingdom establish norms for screening orders of synthetic nucleic acids or nucleic acids with highly toxic or pathogenic properties, it would still be possible to order sequences of concern via a different location, yet the risk of use would be equal in the United States and the United Kingdom.

Proposed action: Linked to priority consideration 3, greater effort should be directed towards developing international collaboration and mechanisms for risk mitigation, with the establishment of common norms and shared principles and standards for global adoption. Collaborative efforts (e.g. global forums, international task forces and treaties) can facilitate the sharing of insights and good practices, enabling countries to learn from each other's experiences and develop more robust and resilient governance frameworks. Harmonisation across borders can also ensure consistent oversight, which could, for example, reduce the risk of regulatory arbitrage where companies can exploit weaker regulations in certain jurisdictions. Joint initiatives can focus on addressing specific challenges and help pool resources and expertise to develop comprehensive solutions, ensuring that the benefits of innovation are widely shared while minimising the associated risks. Recent activities in AI governance have shown a growing focus on international alignment across nations. For example, the Council of Europe Framework Convention on Artificial Intelligence and Human Rights, Democracy and the Rule of Law, signed by multiple nations in September 2024, represents the first legally binding international treaty governing the safe use of AI (Council of Europe 2024b). The Bletchley Declaration, agreed upon in November 2023, is a landmark international agreement on AI safety and governance that was endorsed by several jurisdictions, including the United Kingdom, United States, China and the EU (UK Government 2023f). While not legally binding, it highlights the urgent need to identify and collaboratively manage risks related to highly capable general-purpose AI models.

Example actors to involve: National governments; supranational/inter-governmental organisations; industry; regulators.

Priority consideration 5: Support the implementation and scaling of innovative oversight mechanisms to effectively manage the complexities and dynamics of emerging technologies.

Context: This study has documented significant activities involving the proposal of novel and innovative technology oversight mechanisms. These mechanisms often aim to 'fill in the gaps'

identified in high-level regulations or to efficiently manage the increasing complexity of technology's role in society, and vice versa. However, several of the mechanisms examined for this study lack specific implementation plans or defined pathways for refinement, adoption and uptake. Furthermore, many of the mechanisms remain theoretical constructs, with insufficient evaluation of their potential integration into the existing wider technology oversight ecosystem, or evaluation of their actual performance once implemented. For example, the moral risk frameworks for neural organoids provide conceptualisations intended to future-proof the oversight of neural organoids. However, the full potential of these frameworks can arguably only be achieved through support – including funding – that also targets scaling and adoption.

Proposed action: To move from principles to practice, stakeholders such as regulators and public authorities engaged in oversight – particularly those working with emerging and experimental mechanisms – should critically assess and prioritise promising proposals for technology oversight to facilitate their development and path to implementation. This process could involve seeking broader consensus from various stakeholders, ensuring diverse perspectives are considered, establishing clear ownership and strategically positioning mechanisms within the existing oversight landscape, for example as outlined in priority consideration 1 above. Several countries have implemented regulatory sandboxes to enable the controlled testing of new technologies and business models. The FCA in the United Kingdom pioneered this approach for fintech innovations in 2015, and it has since been adopted by other countries and applied to various technologies (Gunashekar et al. 2019). In March 2024, the UK government launched the Engineering Biology Sandbox Fund, designed as an experimental space for the engineering biology sector and regulators to exchange insights on regulations that potentially support or obstruct innovation (UK Government 2024a). Furthermore, the EU AI Act introduces regulatory sandboxes to encourage AI innovation by offering structured environments where AI systems can be developed, trained and tested in compliance with the EU AI Act (European Parliament 2024).

Example actors to involve: Regulators; national governments; funding organisations; academia.

Priority consideration 6: Facilitate proactive public involvement in the development of oversight frameworks to ensure transparency and accountability.

Context: Public trust and acceptance are crucial for the successful deployment and use of emerging technologies. Engaging the public can ensure that technology governance reflects societal values and needs. However, meaningful and widespread community and public participation are not yet standard practices in the development and implementation of technology oversight mechanisms. While the inclusion of public perspectives is increasingly observed in setting agendas for R&I, it is less frequently applied on a consistent basis to the assessment of technological risks and benefits, and relatively underutilised in determining acceptable trade-offs and appropriate oversight mechanisms. Striking a balance is often difficult, with a tendency for emerging oversight mechanisms to concentrate more on developing consensus among 'experts' and scientists. Although there are instances of emerging good practices, they are relatively infrequent.

Proposed action: Discussions on technology oversight should focus on actively creating communities of interest and developing more accessible public engagement and participation platforms (for example, conducting more regular public consultations, surveys and forums to gather input, discuss and address concerns about emerging technologies; and launching educational campaigns to

inform the public about technologies and their implications). This participatory approach involving a more diverse, general audience could help increase opportunities and streamline processes for gathering public input, which is crucial for shaping policies and building accountability and trust. The evidence indicates that in general, deliberative approaches, including public dialogues, futures workshops and citizen juries, can influence policy, ethical considerations and regulatory measures across multiple sectors related to science and technology (UK Government 2021b). Examples include public deliberation exercises conducted in the development of the SCBEM code of practice, and public deliberation on heritable genome editing to support HFEA updates. A frequently cited example of good practice and innovative public engagement in technology is the use of vTaiwan, a deliberative digital platform, to facilitate a large-scale public debate on Uber regulation in Taiwan (UK Government 2021b).

Example actors to involve: Civil society organisations; academia; regulators; national governments.

Priority consideration 7: Incorporate adaptive practices into oversight processes to foster continuous learning, flexibility and agility in response to technological advancements.

Context: Technological change, especially in fields such as biotechnology and AI, are progressing at a rate that outpaces policymakers' capacity to comprehend the full range of opportunities and risks these technologies present. This rapid pace of technological advancement can present significant challenges for traditional regulatory frameworks, which can struggle to keep up with the evolving landscape. Seemingly static regulations can quickly become outdated, failing to address new safety concerns, ethical issues, security vulnerabilities and societal impacts. This lag can potentially lead to regulatory gaps where harmful practices might go unchecked. Additionally, the unpredictable nature of technological evolution makes it difficult to foresee all potential risks and benefits, necessitating a more flexible approach to governance (see priority consideration 8). Therefore, technology governance frameworks must be flexible enough to keep pace with innovation while still provide adequate oversight and risk management.

Proposed action: Stakeholders engaged in relevant technology oversight debates should consider the proactive development of adaptive governance frameworks. These frameworks could also integrate more agile, experimental oversight approaches – such as regulatory sandboxes – and be regularly updated to remain aligned with rapid technological advancements. For example, by proposing the use of regulatory sandboxes, the EU AI Act contains specific provisions aimed at fostering innovation, with a focus on SMEs and start-ups. Adaptive frameworks are designed to be flexible and responsive, allowing for regular updates and adjustments based on new evidence and technological developments, thereby ensuring that governance remain relevant and effective. These frameworks can also include relevant mechanisms for stakeholders to periodically provide feedback on governance, facilitating continuous improvement and allowing for real-time learning and the iterative improvement of governance mechanisms. As an example, the HFEA has undertaken a consultation on the HFE Act to consider updates that align with recent technological advancements such as emerging genome editing techniques.

Example actors to involve: Regulators; national governments; supranational/international organisations.

Priority consideration 8: Integrate anticipatory strategies into oversight frameworks to prepare for and address future developments in emerging technologies.

Context: As acknowledged, technologies are evolving at a rapid rate, introducing both opportunities and risks. The unpredictable nature of technological advancements makes it difficult to foresee all potential impacts, potentially leading to regulatory gaps and reactive governance. In some cases, this lag could result in the proliferation of inequitable or harmful effects. The challenge lies in creating governance mechanisms that are not only responsive and adaptive (see priority consideration 7), but also anticipatory and capable of understanding the implications of different technological trajectories, addressing future risks and opportunities before they manifest. For example, in the field of neurotechnology research there has been an increasing call for experimental oversight mechanisms that anticipate technological advancements to help create a more flexible and agile oversight system that can evolve in tandem with the progression of neurotechnologies. In terms of frontier AI models, although the current potential for cyber and biosecurity risks remains low, various commentators have highlighted the duty of oversight authorities to foresee and address any future societal risks.

Proposed action: Implementing anticipatory technology governance mechanisms is crucial for effectively managing and future-proofing rapidly evolving emerging technologies. Anticipating future developments and challenges enables proactive and informed decision making, thereby reducing the likelihood of negative impacts and enhancing potential benefits. Establishing dedicated foresight units to help integrate horizon scanning and scenario planning practices into oversight (and wider technology policy) development, and embedding forward-looking risk assessment tools can help ensure that technology governance frameworks remain relevant, effective, and capable of fostering sustainable and equitable technological advancements. For example, the UK Government Office for Science includes a foresight team that engages in a range of futures and foresight activities so that it can provide insights to policymakers and contribute to the creation of policies that are better equipped to withstand future uncertainties (UK Government 2024d). Also in the United Kingdom, the RHC, an independent expert committee, is tasked with identifying the implications of emerging technologies and advising the UK government on necessary regulatory reforms to facilitate the potential deployment of new innovations (RHC 2024). The EU AI Act recognises the potential for new developments in AI, particularly related to general-purpose AI, and has been designed to potentially allow amendments through delegated and implementing acts, ensuring its adaptability and future-proofing over time.

Potential actors to involve: Regulators; national governments; supranational/international organisations; academia.

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Annex A
List of figures

Annex B

List of tables

Annex C
List of abbreviations

AI	Artificial intelligence
APHIS	Animal and Plant Health Inspection Service (USDA agency)
ART	Assisted reproductive technologies
ATMP	Advanced therapy medicinal product
BCI	Brain–computer interface
BDT	Biological design tool
BWC	Biological Weapons Convention
CBD	Convention on Biological Diversity
CBRN	Chemical, biological, radiological and nuclear
CDC	Centers for Disease Control and Prevention
CFREU	Charter of Fundamental Rights (EU)
CRISPR	Clustered regularly interspaced short palindromic repeats
DEFRA	Department for Environment, Food and Rural Affairs (UK)
DSIT	Department for Science, Innovation and Technology (UK)
EBSF	Engineering Biology Sandbox Fund
EDI	Equity, diversity and inclusion
EEG	Electroencephalogram
ELSI	Ethical, Legal and Social Implications
EMA	European Medicines Agency
EO	Executive Order
EPA	Environmental Protection Agency (US)
EPSRC	Engineering and Physical Sciences Research Council (UK)
FAS	Federation of American Scientists
FDA	Food and Drug Administration (US)
FD&C Act	Federal Food, Drug, and Cosmetic Act (US)
FHOB	Foundation Hubrecht Organoid Biobank
FSIS	Food Safety and Inspection Service (USDA agency)
GDPR	General Data Protection Regulation
GINA (US)	The Genetic Information Nondiscrimination Act of 2008
GMOs	Genetically modified organisms
hESC	Human embryonic stem cell
HFE	Human Fertilisation and Embryology
HFEA	Human Fertilisation & Embryology Authority (UK)

HHS	US Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act (US)
HSE	Health and Safety Executive (UK)
HRA	Health Research Authority
HTA	Human Tissue Authority (UK)
IBBIS	International Biosecurity and Biosafety Initiative for Science
ICO	Information Commissioner's Office
ISCBI	International Stem Cell Banking Initiative
ISSCR	International Society for Stem Cell Research
IVF	In vitro fertilisation
LMIC	Low/middle-income countries
LMOs	Living modified organisms
MHRA	Medicine and Healthcare Products Regulatory Authority (UK)
ML	Machine learning
MoST	Ministry of Science and Technology
NASEM	National Academies of Sciences, Engineering and Medicine (US)
NHC	National Health and Family Planning Commission
NHMRC	National Health and Medical Research Council (Australia)
NIDA	Neurological Innovation and Defense Act
NIH	National Institute for Health
NINA	Neuroscience Information Nondiscrimination Act (NINA)
NPL	National Physical Laboratory (UK)
NSCEB	National Security Commission on Emerging Biotechnology (US)
NSF	National Science Foundation (US)
OECD	Organisation for Economic Co-operation and Development
POPIA	Protection of Personal Information Act
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RHC	Regulatory Horizons Council (UK)
R&D	Research and development
R&I	Research and innovation
SaMD	Software as a medical device
SCBEMs	Stem-cell-based embryo models
SME	Small and medium-sized enterprise
SoHO	Substances of human origin regulation
SWOT	Strengths–weaknesses–opportunities–threats
UNESCO	United Nations Educational, Scientific and Cultural Organisation
USDA	United States Department of Agriculture
WHO	World Health Organization

Annex D
Detailed description of methodology

In this annex, we describe the research methods used for this study in six sections: D.1). Jurisdiction selection; D.2) Desk research; D.3) Stakeholder interviews; D.4) SWOT analysis; D.5) Expert elicitation; and D.6) Limitations of the analysis.

D.1. Jurisdiction selection

Based on the analysis in the global technology landscape review report, we extracted key insights related to existing or emerging oversight mechanisms that could be relevant to advancements in research and innovation in each technology area. We also identified some of the uncertainties associated with the oversight of such research and innovation. Multiple parameters[131] analysed in the global technology landscape review report were used as lenses with which to reflect on potential jurisdictions that could provide insightful evidence on oversight mechanisms. With these insights, and in consultation with our expert panel,[132] we developed a longlist of jurisdictions to discuss with Wellcome.

This resulted in a purposive selection of jurisdictions that were analysed in the following ways for each of the four technology areas:

- **High-level overviews**: Development of a range of vignettes providing a high-level overview of technology oversight developments taking place in four key jurisdictions acknowledged for their notable influence on developments in the specific areas of technology: the United Kingdom, the United States the EU and international forums.
- **Specific case studies**: Development of more specific deep-dive vignettes examining diverse examples of oversight mechanisms in a selection of jurisdictions across the globe, spanning different societal and cultural contexts.

D.2. Desk research

Desk research was used for the development of the high-level overviews. The search terms developed were intentionally broad, consisting of key terms for a given technology in combination with the jurisdictions of interest (e.g. regulation of engineering biology/ synthetic biology in the UK; engineering biology as a tool in climate/ tackling environmental hazards/addressing food security/drugs or vaccine development) to identify well-established mechanisms.

131 Parameters included government investment, R&I activity and policy influence.

132 We convened an expert advisory panel at the project inception stage consisting of six subject matter, policy and legal experts across the technology areas.

The focus of the exercise was on striking a balance in terms of the breadth of oversight mechanisms in each technology area, acknowledging that these would potentially be restricted to what are considered by some experts the most important oversight mechanisms rather than an exhaustive list of all relevant mechanisms. In addition to examining several flagship mechanisms, we also focused on identifying a comprehensive range of other oversight developments in the last five years.

The desk research drew on academic literature, reports, government sources in the public domain, and relevant data repositories and observatories associated with each technology area. We used targeted Google Scholar and Google searches to identify relevant articles, as well as snowballing.[133] We also consulted members of our expert advisory panel and Wellcome for insights on these areas of research. In total, we developed a series of 16 high-level overview vignettes (four overviews per technology) outlining the oversight developments in the four key jurisdictions of interest.

Desk research for the development of the 12 case studies (three per technology area) consisted of a more targeted approach where the search terms used were associated with a given technology and the specific oversight mechanism, in combination with the purposively selected jurisdictions (e.g. oversight of neural organoids in Japan). These searches were also limited to the last five years and drew on academic and grey literature. The identified example case study topics were validated with the expert panel and Wellcome.

D.3. Stakeholder interviews

During the desk research phase, we conducted three scoping interviews with experts who have general expertise in emerging technology oversight. These interviews offered insights on important aspects of technology governance that guided and helped in the construction of the high-level overviews. We also conducted a further eight interviews with relevant topic experts such as policymakers and academics (we conducted at least one interview per technology). These were intended to fill in gaps from our desk research while constructing the case studies. We identified interviewees during the desk research, focusing on stakeholders who have published on oversight of a given technology sector in the jurisdiction of interest. Key messages were extracted from the interviews to supplement the write-ups of the high-level overviews and case studies. The interviews were semi-structured and conducted online via MS Teams. Annex E outlines the interview questions used to guide the scoping interviews and the expert interviews.

D.4. SWOT analysis

The insights from the high-level overviews and case studies were analysed through a strengths–weaknesses–opportunities–threats (SWOT) lens. Key developments and trends identified in the high-level overviews were listed under the appropriate SWOT categories to summarise each sector's state-of-play in terms of the oversight mechanisms highlighted. Case studies were used as specific examples of governance to help ensure that the analysis was bespoke to every technology area. The SWOT analysis, with inputs

133 Snowballing, also known as citation chaining, is the process of searching the references and/or citations of a list of articles to identify other relevant material.

from experts (see section D.5), was used to assess the status of technology oversight across the globe and highlight key challenges, gaps and discussions in each sector regarding appropriate governance mechanisms.

D.5. Expert elicitation

The results of the SWOT analysis were captured in an interactive online mural board. We invited 27 experts in the relevant technology areas to engage with the mural board and provide feedback and validation of the aggregated SWOT analysis. The experts were given a three-week window to view, comment and reflect on the content. In total, 16 experts from a range of international organisations and universities took part in the exercise. The inputs from the experts were used to refine the overarching analysis presented in the reports.

D.6. Limitations of the analysis

The analysis in this report is subject to certain caveats concerning the research methodology, the breadth of evidence reviewed and the analytical processes employed. These caveats are summarised below and should be considered when interpreting the findings of this report.

While our goal was to document as many relevant examples of technology oversight for each of the four jurisdictions of interest, the resulting long list of high-level overview vignettes was not meant to be all-encompassing or definitive. The desk research may have missed some important oversight mechanisms given that it was not a systematic review. Moreover, we did not evaluate the effectiveness of each oversight mechanism identified. We mitigated this risk by consulting with our expert advisory panel at regular intervals throughout the study and by conducting an online engagement exercise to seek experts' views on our aggregated analysis of the relevant oversight mechanisms for each technology area. The examples we selected across the high-level overviews and case studies were meant to act as a collection of illustrative vignettes, showcasing the state of the art in technology oversight and offering a broad overview of the current landscape.

Given the short timeframes within which to conduct the study, we interviewed a limited number of stakeholders to complement the desk research. Consequently, the range of expert perspectives included in the research is restricted. However, the interviews were designed to collect insights from a sample of stakeholders to supplement the review of documents. Moreover, we selected vignettes from a diverse range of global jurisdictions and engaged with a wider network of experts in the online elicitation exercise. Finally, conducting the expert elicitation exercise online as opposed to in person had some limitations, namely a lack of an iterative dialogue between stakeholders and the study team, which may have allowed certain nuances of feedback to be underrepresented.

Annex E
Interview protocols

E.1. Scoping interview guide

E.1.1. Questions and prompts

1. Could you briefly introduce yourself – what is your current role and background?
2. Are you involved in any programmes or initiatives in organoids, neurotech, engineering biology and/or human embryology research or oversight?
    a. Can you please elaborate on these?
3. Through your involvement or other experience, are you aware of any existing notable oversight mechanisms in relation to these technologies?
4. How specific are these mechanisms to the technologies of interest?
    a. i.e. are the mechanisms specifically developed for organoids or neurotech, etc. or do they speak to a broader field of research (or to technologies involving any human tissue/ manipulation)? Please elaborate.
    b. Are there other sector-specific regulations that we should consider in relation to the core technology areas? (e.g. biodiversity, industrial policy)
5. Are there emerging mechanisms that are being proposed or are in development that you are aware of? (e.g. G-SCBEMs) If so, could you talk about some examples of these oversight mechanisms.
    a. Why do you think they are being proposed?
    b. What is the value add of these – if any – over and above what is already in place?
6. What are some of the challenges and broader uncertainties that you are aware of in relation to oversight of specific technologies or more broadly?
7. What can you say about broad oversight mechanisms in data and AI such as GDPR, EU AI Act, etc. that may impact oversight of these biotechnologies?
8. Do you think that emerging developments in oversight are likely to be able to support timely and equitable oversight of technologies?
    a. IF yes, why do you think so and what are the mechanisms through which you think this will occur?
    b. IF no, why do you think so and what needs to be done about it?
9. What do you think is the role of organisations like Wellcome in the technology oversight development landscape?

10. Do you have any thoughts about what lessons can be learnt from different technology oversight approaches taken?
    a. What are some of the key factors that should be considered when attempting to govern technologies?
11. Is there anything else that you would like to add that we have not discussed?
12. Is there any organisation or anyone else that you would recommend we speak to? Any further resources you might be able to share or point us to?

E.2. Case study interview guide

E.2.1. Questions and prompts

1. Could you briefly introduce yourself – what is your role and background?
2. We are interested in learning more about X (*insert the case study topic*), how are you connected to this (e.g. involved/interested), if at all?
3. Could you tell us what this oversight mechanism/proposal is about and what it intends to accomplish?
    a. How is it being carried out?
    b. What mechanism or approach of oversight is being used?
    c. How specifically is it being implemented? What was the process involved in its development?
    d. Which are the different actors – e.g. stakeholders, bodies – driving this oversight mechanism? Any other involved stakeholders?
4. Why is/was the oversight required?
    a. What kind of a gap or a need is the oversight fulfilling? Why do you think this is needed?
    b. Are there challenges that it tackles/could tackle?
    c. Are there opportunities that it unlocks/could unlock?
5. What other technology and its oversight mechanisms could potentially impact this work or this technology? And in what ways?
6. What is the trajectory for this oversight mechanism?
    a. If already implemented: has it done what it intended to do?
    b. If in proposal stage: is it being well received by stakeholders? Is there consensus? Is it controversial? Likely to be taken up?
7. How has the oversight impacted/how will it impact research and development in the field of X (*insert technology area*)?
8. Do you have any thoughts about what lessons can be learnt from this oversight approach?
    a. What are some of the key factors that should be considered when attempting to govern technologies?
9. What are some of the challenges and broader uncertainties that you feel may not be addressed through this mechanism? Why?
10. What do you think is the role of organisations like Wellcome in the technology oversight development landscape?
11. Is there anything else that you would like to add that we have not discussed?
12. Is there any organisation or anyone else that you would recommend we speak to? Any further resources you might be able to share or point us to?