iRECS Deliverable 2.2: Recommendations to address ethical challenges from research in new technologies

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D2.2: Recommendations to address ethical challenges from research in new technologies

[WP2 – Ethical challenges of new and emerging technologies and ethics review processes]

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Abstract

This deliverable presents qualitative research on training needs for research ethics committees (RECs), focusing on four technologies selected in the iRECS project: AI in Health and Healthcare, Biobanking, Genome-Editing and Extended Reality. Based on desk research, expert consultations, and a leadership roundtable, iRECS identifies gaps in the current ethics review processes and needs to inform development of training materials. Following this analysis, iRECS formulates recommendations for each technology as well as cross-cutting recommendations. This Deliverable contributes to iRECS pedagogical goals and will inform ongoing and future work in iRECS WP4 and WP5.

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Executive summary

This Deliverable 2.2 is produced as part of Work Package 2 of the Horizon-Europe project iRECS (improving Research Ethics Expertise and Competences to Ensure Reliability and Trust in Science). Based on desk research and expert consultations, this report provides in-depth analysis of ethical issues raised by four technology families selected by the consortium. This report conducts a detailed examination of ethics review processes revealing gaps and challenges, and subsequently provides recommendations tailored to address these issues in four technology families:

(1) AI in health and healthcare,
(2) biobanking,
(3) genome editing (encompassing both human and non-human applications),
(4) extended reality (XR).

iRECS recommendations aim at providing a comprehensive framework for enhancing ethics in research practices, fostering a culture of ethical innovation, and aligning research endeavors with evolving ethical norms:

(1) For AI in health and healthcare, iRECS highlights the necessity of adapting the composition of Research Ethics Committees (RECs) to include AI experts; setting uniform and coherent 'AI in healthcare' guidelines across EU member states; and developing REC methodologies beyond compliance.
(2) For biobanking, iRECS argues for the implementation of a standard consent model across EU member states; addressing regulatory disparities between biobanks and secondary data use across EU member states; and refining and homogenizing the scope of reportable incidental findings.
(3) For genome editing, iRECS underscores the significance of consistently training ethics experts to distinguish between different subcategories and applications of genome editing; adopting a case-by-case approach to gene drive experiments; and highlighting policy differences between countries, including EU member states.
(4) For extended reality (XR), iRECS suggests establishing "digital subcommittees" in RECs; ensuring that AI-generated content in XR can be identified by users; finally, addressing surveillance capabilities of XR, in particular in virtual work environments.

This deliverable also delves into institutional approaches to research ethics and integrity, drawing insights from a leadership roundtable and a focus group organized by EUA. Based on this work, the iRECS consortium formulates three cross-cutting recommendations emphasizing, in particular, the need to develop appropriate scientific expertise in REC practice. It is urgent to address the lack of AI ethics experts across Europe. iRECS also calls for a shift of REC operation model from one-time compliance checks toward ongoing evaluation and ethics-by-design, meaning that the model of RECs may evolve into establishing permanent university teams or laboratories devoted to research ethics.

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List of acronyms/abbreviations

Abbreviation	Explanation
AI	Artificial Intelligence
ANN	Artificial neural networks
AR	Augmented Reality
BBMRI-ERIC	Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium
CAD	Computer-Aided Diagnosis
CAR-T (cells)	Chimeric Antigen Receptor T cells
CAT	Committee for Advanced Therapies
CCNE	Comité Consultatif National d'Éthique (France)
CHAI	Coalition for Health AI
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CNRS	Centre National de la Recherche Scientifique (France)
CT (scan)	Computer Tomography
CTEG	Clinical Trials Expert Group (European Commission)
CVE	Collaborative Virtual Environments
DEC	Digital Ethics Committee
DNA	Deoxyribonucleic Acid
DPA	Data Protection Authority
DPO	Data Protection Officer
EC	European Commission
ELSI	Ethical, Legal and Societal Issues
EMA	European Medicines Agency
ENERI	European Network for Research Ethics and Integrity
ETC (group)	action group on Erosion, Technology and Concentration
EU	European Union
EUA	European University Association
FDA	Food And Drug Administration
FPIC	Free, Prior, and Informed consent
GA4GH	Global Alliance for Genomics and Health
GDPR	General Data Protection Regulation
GMO	Genetically Modified Organism

HUGO	Human Genome Organization
IANUS	Inspiring and Anchoring Trust in Science
INRIA	Institut National de Recherche en Sciences et Technologies du Numérique (France)
ISBER	International Society for Biological and Environmental Repositories
IVF	In Vitro Fertilization
MR	Mixed Reality
MRI (scan)	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
NIH	National Institutes of Health
NLP	Natural language processing
OECD	Organisation for Economic Co-operation and Development
PANELFIT	Participatory Approaches to a New Ethical and Legal Framework for ICT
REC	Research Ethics Committee
SIENNA	Stakeholder-Informed Ethics for New Technologies with High Socio-Economic and Human Rights Impact
STS	Science and Technology Studies
UMC Utrecht	Universitair Medisch Centrum Utrecht
UN	United Nations
UNDRIP	United Nations Declaration on the Rights of Indigenous Peoples
UNESCO	United Nations Educational, Scientific and Cultural Organization
VR	Virtual Reality
WHO	World Health Organization
WMA	World Medical Association
XR	Extended Reality

Table 1: List of acronyms/ abbreviations

Glossary of terms

Term	Explanation
Artificial intelligence in healthcare	Artificial Intelligence (AI) in healthcare refers primarily to the application of machine learning to improve various aspects of healthcare and medical practices, e.g. diagnostics or remote consultation.
Biobanking	Biobanking refers to collecting and storing biological materials and their associated data.
Embedded ethics	Embedded ethics implies collaborative work between ethicists and the development team to consider and address these sorts of issues via an iterative and ongoing process, borrowing from established approaches such as clinical ethics advisory in hospital settings, or ethical, legal and social aspects (ELSA) research in biomedical research (McLennan et al. 2022)
Ethics by design	Ethics-by-design emphasizes the early integration of ethical principles in the development of technologies or systems. It encompasses essential principles such as proactive ethical

	reflection with a focus on design and ongoing ethical evaluation, adapting to evolving ethical standards.
Extended reality	Extended Reality (XR) and the 'metaverse' refers to a spectrum of technologies merging physical and virtual environments.
Genome editing	Genome editing (GE) modifies an organism's DNA by adding, removing, or replacing specific sequences using programmed proteins or protein/RNA complexes.
Metaverse	A shared, persistent, real-time 3D, digital model environment. Metaverse is the contraction of the Greek prefix meta ("beyond" or "transcending") and the word universe.
Presence	First-person impression of attending to events or agents in a virtual world (Suzuki et al. 2023). Lived experience hard to represent by a third person narrative.

Table 2: Glossary of terms

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Introduction

Background

This deliverable is the outcome of qualitative research into the training needs for research ethics committee (REC) members and EU ethics appraisal scheme experts. The iRECS consortium has selected four technologies: AI in health and healthcare, Biobanking, Genome-Editing and Extended Reality. These technologies pose numerous challenges in terms of ethical assessment for REC members and EU ethics appraisal scheme experts. In Task 2.2, we have selected challenges that present the greatest difficulties, therefore raising most urgent training needs. This research will inform further research into the needs to adapt RECs ethical assessment processes (WP 2.4) and pedagogical research in WP4.

Methods

The methods employed to carry out the research presented in this report consisted of (1) desk research, (2) expert consultations (3) a leadership roundtable and (4) focus group discussions.

(1) The screening work in WP 2.1 enabled the consortium to use a survey to determine not only the technologies of interest, but also the ethical issues related to these technologies. On this basis, the consortium was able to begin in early March 2023 to examine within WP 2.2 the literature on the training of experts in these areas. The wide range of expertise in science and technology ethics among the members of iRECS enabled to carry out a literature search, which helped to define issues of concern for REC members.

(2) Based on the preliminary desk research, iRECS formulated an analytical framework and devised a blueprint for expert consultations in April 2023. To identify training needs, task 2.2 of iRECS imagined two formats of training modules: a short awareness action (one-hour lecture) and a longer training course (one full day). Specialized teams assigned to each technology undertook the process of consultation according to a common methodology by engaging with top-level experts, most of whom are also REC members. This approach substantially extended and amplified the consortium's findings from the initial desk research, incorporating firsthand narratives pertaining to the main challenges faced by REC members.

(3) To comprehensively complement these aspects at the institutional leadership level, iRECS organized a leadership roundtable on May 31st, 2023, in line with the guidelines of Task 2.2 (see Annex 1). This platform not only facilitated gathering additional information to assess the ethics training needs in academia, but also provided valuable insights into cross-cutting issues. Distinguished figures, including rectors and vice-rectors from universities across Europe, contributed their perspectives to enrich our understanding.

(4) To complement the EUA Leadership Roundtable organized in May, and better evaluate the recommendations and fine-tune their formulation, a focus group was gathered on November 13th, 2023 (see Annex 2). EUA brought together this group, composed of a selection of 41 individuals representatives of ethics in academia (university leaders, directors of research and innovation offices, researchers, members and chairs of research ethics committees, directors of doctoral schools, research ethics

and integrity officers, research managers and open science delegates), from 19 EU and non-EU countries, to hear their views on the relevance, clarity, applicability, completeness, and priority, of the recommendations. This Focus group provided exceptionally valuable feedback on the cross-cutting recommendations (see Section 5).

Expert consultations

Expert consultations were based on the following questions, which add to a comprehensive framework for analyzing gaps in ethics review procedures and training needs for REC members. These questions have been subdivided into two distinct sets, one pertaining to the needs for informing the development of training materials and awareness initiatives, and the other addressing gaps in the current ethics review processes at the EU, Member State, and non-EU state levels:

Gaps in the current ethics review process at EU, Member State and non-EU state levels

- *Describe an existing ethics review procedure. What part of the evaluation process raised most competence problems? Was there something unclear that required external expertise?*
- *Which use cases or applications fall in an ethical or regulatory grey zone? How do evaluators deal with these grey areas at this time?*
- *Can you describe a real-world successful evaluation procedure that proved to be very efficient? Or an ideal procedure that would be satisfactory for all parties involved?*
- *Which evaluation model is best fit: one-time ethics evaluation at the start of the project? Compliance checks? Ethics-by-design ongoing evaluation? Other?*
- *Based on your analysis of risks for humans, society, animals, or environment, what practical steps would you take to ensure that research is reflective and anticipatory?*

Needs to inform development of training materials and awareness actions

- *Provide a brief list of most relevant ethical issues and concerns. Are scientists aware of these issues in their work? Do scientists address these issues adequately in their research proposals? Is this changing over time?*
- *List several core scientific concepts that must appear in a short lecture. Is this list quickly changing due to ongoing research or is it stable?*
- *Besides these concepts, a full-day training course can cover other scientific concepts. List several additional topics that are highly relevant for ethical analysis.*
- *What are key uncertainties at this time? Is this list quickly changing due to ongoing research or is it stable?*
- *What fundamental ethical dilemmas appear in relation to this technology? Can you give an example of a previously known dilemma that also applies to this new technology?*
- *List several up-to-date, open-source and reliable resources for use in building training modules*
- *Does the concept of compliance apply to this technology? If yes, what are the main advantages and weaknesses?*

- *Does the concept of ethics-by-design apply to this technology? If yes, what are the main advantages and weaknesses?*
- *Which EU or international guidelines or standards are the most relevant ones? Most clear, operational and applicable?*

Consulted experts

- Dr. Laurynas Adomaitis (CEA, France)
- Prof. Costas Charitidis (National Technical University, Greece)
- Dr. Hervé Chneiweiss (CNRS, France)
- Prof. Rosemarie de la Cruz Bernabe (University of South-Eastern Norway, Norway)
- Philip Engström (Linköping University, Sweden)
- Prof. Pascal Guitton (INRIA, France)
- Renata Kleviene (Vilnius Regional Biomedical Research Ethics Committee, Lithuania)
- Dr. Harald König (Institute for Technology Assessment and Systems Analysis, Karlsruhe Institute of Technology, Germany)
- Prof. Laura Palazzani (Università di Roma LUMSA, Italy)
- Cristiana-Anca Voinov (University of South-Eastern Norway, Norway)

EUA Leadership roundtable

EUA's online roundtable on research ethics and integrity, titled 'Institutional approaches to research ethics and integrity: let's talk about new technologies,' gathered 26 participants, including rectors and vice-rectors from European universities. The meeting comprised a panel discussion with experts and open discussions among participants, adhering to the Chatham House Rule for confidentiality (see Annex 1).

EUA Focus Group meeting

This focus group convened by EUA on November 13, 2023, comprising diverse representatives in academia, aimed to assess and refine the recommendations (see Annex 2). In preparation for the focus group, participants were provided with a brief questionnaire ahead of the session. Their responses to the following questions contributed to the preparation and targeting of presentations and discussions during the meeting:

1. *Are the proposed recommendations relevant?*
2. *Are the proposed recommendations clearly formulated?*
3. *Are the proposed recommendations applicable in the short term?*
4. *Are the proposed recommendations applicable in the medium term?*
5. *Are the proposed recommendations comprehensive?*
6. *Do you want to add any other comment on a specific recommendation? Please select the recommendation and use the text box to provide feedback.*
7. *In your view, what are the most urgent or pressing recommendations?*
8. *Anything else you would like to add?*

Structure of the report

This report comprises five sections: four thematic sections, each dedicated to one of the technologies pre-selected in Task 2.1, and a fifth one containing the cross-cutting recommendations. Each thematic section is subdivided into two further sections, dealing respectively with gaps in the assessment processes as currently practiced by

ethics committees and the training needs of ethics committee members. Each of these sections culminates with recommendations for REC members and EU ethics appraisal scheme experts. Section 5 contains cross-cutting recommendations that arise from the entire set of technologies selected in iRECS. They should inform the general design of any training of ethics experts in ethical questions of new technologies.

Annex 1 presents the results of the consultation with rectors and vice-rectors (the Leadership Roundtable), to obtain their more general views on the difficulties encountered by ethics committees in their institutions.

Annex 2 presents the results of the focus group on the recommendations formulated in the deliverable. It focused primarily on the cross-cutting recommendations and included a perspective from Eastern and Southern Europe, as well as from a REC member from Nigeria. The question of implementation of the recommendations has been discussed extensively. This annex also provides detailed feedback from focus group members on AI and generative AI.

1. AI in health and healthcare applications

1.1 Gaps in the current ethics review process of AI in Health research at EU, Member State and non-EU state levels

1.1.1 Problems encountered by REC members in ethics assessment procedures

In Europe research on AI in healthcare, like other health-related research, is typically reviewed by RECs that operate in the field of biomedicine. Medical RECs have traditionally focused on protecting the well-being of research participants (Ferretti et al. 2021), so their composition and ethical review processes are designed with that goal in mind. However, many RECs still face various organizational challenges, such as struggles with independence and difficulties in finding and training experts to serve on the committees (Ferretti et al. 2021; ENERI classroom 2019). While these problems have – at least to an extent – persisted ever since RECs were created, they have become more prominent and urgent in recent years, especially with the emergence of new ethical challenges in research involving AI and other new technologies in healthcare that raise different ethical issues than most other strands of medical research.

One of the major challenges faced by medical RECs is that they often lack the expertise to properly evaluate research involving AI. Ensuing problems tend to be twofold:

- On the one hand, they may become overly cautious when reviewing AI research projects, arbitrarily raising the ethical standards for researchers in this field.
- On the other hand, they might overlook significant ethical dimensions of a research project because they fail to grasp the issues it raises in their entirety, which could erode trust between the research community, patients, public, and RECs. Furthermore, this could potentially harm the reputation of responsible institutions like universities, if any issues arise (Kerasidou et al. 2023; Ferretti et al. 2021).

Similar problems arise when evaluating AI projects not only within different countries but also at the European level. Unlike most European countries, the European Commission has developed some guidelines for ethics experts on how to assess such studies and for researchers on how to conduct studies ethically, such as the Ethics guidelines for trustworthy AI (High-Level Expert Group on Artificial Intelligence 2019), Guidance on ethics by design and ethics of use approaches for AI (European Commission 2021) or EU ethics appraisal scheme (European Commission 2021). While the ethics appraisal scheme establishes a review procedure in which the Ethics guidelines for trustworthy AI serve as guiding document, use of Guidance on ethics by design and ethics of use approaches is only recommended but not binding. Also, finding experts capable of competently evaluating these studies following the guidelines is challenging. As these guidelines cover issues not (or at least not to that extent) previously assessed in ethics reviews, even experienced ethics reviewers face difficulties in applying them. Especially issues related to novel problems that are not easily translatable into established key concepts of research ethics, such as algorithmic bias and potentially detrimental societal effects of technologies, can create challenges. Moreover, as a high amount of funding is currently directed toward research on AI, often many ethics reviewers are involved in project proposals and thus

not available to conduct reviews due to conflicts of interest (Personal communication with EC representatives).

European Commission guidelines for AI research

Chapter 8 of the ethics issues table in the EU ethics appraisal scheme (European Commission 2021) is of particular importance in Horizon Europe as it specifically addresses research ethical aspects of AI. Other relevant chapters include chapter 1 on human participants, chapter 4 on personal data and chapter 10 on the potential misuse of results.

The inclusion of a chapter on AI in Horizon Europe is a recent addition. The EC introduced this chapter because it identified pressing ethical concerns related to discrimination and bias, safety and liability, transparency and opaque algorithms, as well as privacy and data protection. These concerns were deemed highly urgent and thus warranted a dedicated section within the ethics appraisal scheme.

Projects must adhere to essential requirements, which encompass (but are not restricted to):

1) making people interacting with an AI system aware of the fact that they are doing so, as well as its abilities, limitations, risks, and benefits;
2) devising and implementing mechanisms for human oversight, transparency, and audibility in AI systems;
3) designing AI systems in ways that avoid bias in both input data and algorithmic design;
4) and complying with data protection and privacy principles, such as data minimization.

The key values to be respected are (1) human agency and oversight, (2) privacy and data protection, (3) fairness, diversity and non-discrimination, (4) accountability, (5) transparency, and (6) societal and environmental well-being.

EC Ethics Appraisal Process for AI research

Applicants are required to conduct an ethics self-assessment focused on the development, deployment and post-deployment phases, in which they have to explain how potential bias, discrimination and stigmatization will be avoided and how they intend to follow an ethics by design methodology. Project applications are (sometimes) pre-screened by at least two ethics evaluators, who can be external experts or qualified staff members of the EC. If no ethics issues are identified based on a review of a simplified version of the ethics issue table, projects obtain ethics clearance, otherwise they are flagged for an ethics screening.

Projects developing AI in healthcare

Projects developing AI in healthcare will virtually always be flagged for ethics screening as they typically include human participants and process personal data, often including special categories of data. An ethics screening is conducted by at least two external expert evaluators and aimed at identifying proposals that raise complex ethics issues because such proposals are, in a next step, scrutinized more closely in a full ethics assessment, during which usually ethics requirements are defined. Proposals that do not raise complex issues are either cleared without additional ethics requirements and only are obliged to follow relevant national and EU legislation or conditionally cleared but required to appoint an external ethics advisor or board. Ethics advisors or boards support projects in addressing ethics issues and reporting to the funding body, yet they

do not assume any formal responsibility for compliance and remain independent. Due to their high degree of ethical sensitivity, it is plausible to assume that AI in healthcare projects usually must undergo a full ethics assessment. These assessments are conducted by a panel of at least five external experts and aim to identity and define measures projects must implement either during the grant preparation or during the project implementation (e.g., ethics deliverables or ethics work packages).
Requirements should be proportional to the severity of ethics issues from a risk-centered perspective. If proposed projects neither receive ethics clearance nor conditional ethics clearance, they cannot be funded.

1.1.2 Current ethical or regulatory gray zones

- **First, it is important to note that not all research involving AI in healthcare is subject to the traditional ethical review conducted by medical RECs.** This discrepancy arises because different countries have different definitions for what constitutes medical research or who qualifies as a research participant (Friesen et al. 2021). In non-biomedical fields of research, ethical review infrastructures in European countries are still evolving, highly diverse and not yet aligned. Consequently, AI studies falling outside the traditional biomedical framework may be left without any evaluation or be evaluated according to different standards and procedures.
  In some countries even more complications arise when conducting commercial research involving AI in healthcare. **Commercial companies, in their rush to launch their AI products as quickly as possible, may seek to avoid ethical review** because it often takes time and effort. However, there are instances where also the narrow mandate of institutionally based RECs poses a challenge. Commercial companies, even if they seek ethical review, may not have a REC available to assess their applications. In an attempt to address this issue, commercial companies have begun establishing their own RECs. However, these internal committees often do not apply the same level of ethical scrutiny to their projects as academic RECs typically do and tend to lack transparency (Ada Lovelace Institute 2022).

- **When medical RECs evaluate research involving AI in healthcare, they primarily focus on consent and privacy issues**. This emphasis emanates from the longstanding tradition of medical RECs delving into these areas and the emergence of new challenges related to them brought by research involving AI. For instance, REC members may find it easier to grasp the limitations of consent in AI projects than identifying other ethical issues by drawing parallels with similar issues encountered in fields they are more familiar with, such as biobanking. When discussing consent, one of the challenges is the impossibility of anticipating and disclosing all future uses of data, mainly due to the unknown nature of these uses at the time of data collection.
  As a result, broad consent or consent waivers are considered as alternatives (Ferretti et al. 2021). However, once a research project is completed, the task of a REC in relation to that project ends as well, even though the scope of applications resulting from that project can increase significantly, so that important ethical aspects are de facto left unreviewed. Also, broader societal implications are usually outside the scope of RECs because RECs primarily focus on safeguarding the rights and interests of research participants (Ferretti

et al. 2021). This is because **medical research, specifically focused on developing drugs or medical devices, operates on the assumption that research is beneficial to society and generally a good thing**. While this might be plausible for medical research, the assumption does not necessarily hold true for other areas of research. If societal desirability of research is contentious, ethical issues may arise not only with regard to safeguarding the rights and interests of research participants, but also with regard to the potential wider effects of research (Stahl 2021). What is more, competently assessing some ethical issues, such as risks related to profiling, also requires knowledge of data protection law and other pertinent regulation, which not all RECs possess as the role of RECs in ensuring compliance of research projects with data protection law is unclear and not harmonized across Europe (PANELFIT project 2021).

- **While consent and privacy are important aspects of any good and thorough ethical review, they are not the only important ethical dimensions of AI in healthcare research.** There are other important ethical issues that may fall outside the purview of traditional ethics reviews, and thus risk being inadvertently eschewed from scrutiny. For instance, ethical issues pertaining to bias, accuracy, security, transparency, and explainability fall into that category, to name a few.

1.1.3 How to ensure the most satisfactory or effective approach to ethics review in AI in health research

When attempting to envision the ideal framework for governance of AI research and innovation in the health sector, several approaches seem viable in principle. **Key to high quality ethics review in AI in healthcare are especially the availability of sufficient expertise in RECs** (such as knowledge about the concepts outlined in the needs analysis above) **and a review procedure that allows for a systematic assessment of the risks a project gives rise to** – something the established ex ante model of ethics review is not always well-equipped to do. In the following, some options are introduced:

- Blassime and Vayena **advocate for a systemic oversight model which does not confine itself to a specific phase of the data-processing lifecycle, nor is it restricted to a specific body charged with oversight responsibilities in health research** (Blasimme & Vayena 2020; Vayena & Blasimme 2018). This model encompasses six key characteristics: adaptivity, flexibility, inclusiveness, responsiveness, reflexivity, and monitoring. While further deliberation is required to fully explore and operationalize this model, it is possible to implement certain measures in the field of research, such as adapting the composition of RECs to review health research involving AI, already in the short term (Blasimme & Vayena 2020; Vayena & Blasimme 2018).

- Another interesting approach suggested is by **Bernstein and colleagues** (Bernstein et al. 2021). They **suggest the adoption of so-called ethics and society review boards alongside institutional review boards** (by and large the equivalent of a REC in the US) for AI research irrespective of the field of research a given project falls into. While institutional review boards primarily

focus on the ethical obligations of researchers towards research participants, ethics and society review boards would have a broader scope, encompassing the responsibilities that researchers bear towards society as a whole. The evaluation of this approach in the context of a large interdisciplinary AI program at a university suggests that "researchers found it valuable in broadening their ethical lenses and are willing to continue to submit to it despite the added commitment" (Bernstein et al. 2021).

- It is also important to note the observations made by **McLennan and colleagues**, who state that when applications are evaluated by RECs, it typically occurs after significant parts of the development process have been completed. Thus, they **suggest implementing what they call an "embedded ethics approach"** (McLennan et al. 2022). Ideally, the practice of embedded ethics would mean having ethicists involved throughout the entire development process. This would include their participation in early decision-making during planning, design, and programming stages, as well as providing support for navigating the regulatory pathway as the project progresses. For instance, they would facilitate adherence to REC requirements and guidelines in a meaningful way (McLennan et al. 2022). Such an approach has many similarities with ethics by design and ethics of use approaches already recommend by, for example, the EC.

- Additionally, given the limited information available on whether and how health research involving AI projects undergo ethical review in various European countries and beyond Europe, it would be valuable to systematically gather such information to identify already existing potential best practices in ethics reviews across different countries/institutions. In that regard, **specifying the potential role of RECs in implementing ethics by design and ethics of use approaches could be a promising venue for future research**, not least because these are already recommended by important research funding organizations, such as the EC. **A crucial aspect meriting closer investigation would be to develop approaches that systematically integrate ethical considerations into excellence assessments to avoid delegating almost all practical aspects of ethics governance to RECs**, which might not be ideally positioned to assess all ethical issues a project gives rise to (Stahl 2021).

1.1.4 Choosing an ethics evaluation model for AI in healthcare

As already sketched in the previous section, **the ex-ante model of ethics review has weaknesses that might become apparent when RECs evaluate AI in healthcare projects**. Whether and to what extent these weaknesses are significant, depends crucially on the types of risks a project raises. Whenever important ethical risks only become clear during the research and thus are not precisely specifiable ex ante, one-time ethics evaluations of a project often are not adequate. As the previous section has shown, this seems broadly recognized, yet no clear alternative model has so far emerged as widely recognized best (or at least good) practice. Problems with existing models are perhaps most pronounced if the research does not involve research participants narrowly conceived, but rather data subjects whose data is processed in, for example, machine learning applications. Consequently, ethics by design, ethics of use or other ongoing evaluation models are often more appropriate to assess and

address the ethical risks of AI in healthcare projects. However, it is not yet clear what the role of RECs and other ethics review bodies should ideally be in these models as they refer to a broader research ethics governance approach that extends beyond pure review.

Like one time ex ante ethics review, **pure compliance checks also have inherent problems, as many ethical issues are not about compliance per se but involve reflection, justification and decisions on ethical appropriateness.** Considerations related to privacy and profiling, for example, extend beyond the GDPR so that a legal compliance check would often remain incomplete and fail to grasp all relevant ethical dimensions of a given research project. Thus, an ongoing ethics by design or ethics of use evaluation or one of the possible review schemes mentioned in the previous section seems preferable, yet it would require a clear specification of the role of RECs in such a scheme as well as the provision of a sufficient amount of resources to RECs to fulfill their obligation. The resources most RECs currently have, for example, would not be sufficient to carry out comprehensive in-project reviews, so the resource criterion is by no means trivial. Unless sufficient resources are provided, moving towards a more extensive review model with a large role for RECs would risk overburdening them and threaten the already often precarious quality of ethics review of AI research (which is key for its legitimacy). In a nutshell, tasks and resources need to be aligned when (and if) the role of RECs and other ethics review bodies is adapted.

When creating the most suitable evaluation model, it is important to note that not all AI in healthcare research necessarily needs to be evaluated using the same model. On the contrary, it is important to consider the risks involved and ensure that ethics review stringency is proportionate to risk. Recent legal developments also anticipate different governance models based on these risks. For example, in the proposal for the AI Act, requirements become more stringent as the level of risk increases. These requirements encompass a range of approaches, "from non-binding self-regulatory soft law impact assessments accompanied by codes of conduct to heavy, externally audited compliance requirements throughout the life cycle of the application." (Kop et al. 2023)

1.1.5 Reflective and anticipatory research in AI in healthcare

In general, **ethics review ideally should extend beyond ex ante review whenever projects are likely to entail risks that will only unfold during the research.** Ideally, such reviews should provide ethical guidance and support in addition to monitoring. In that way, ethics review could **facilitate reflection and help integrate ethics into research**. This presupposes ethics reviewers are adequately trained to provide practical guidance and a sufficient degree of ethical awareness and competences among researchers. Key principles of research ethics should be extended to include principles applicable to AI research. Consequently, research ethics needs to extend to digital ethics, algorithmic ethics. Also, operational and easy-to-understand guidance for both ethics reviewers and researchers is crucially important to ensure that they have the awareness of ethical issues and the skills to address them competently.
Additionally, **it would perhaps be desirable to create research and innovation ecosystems that support integration of ethics into conceptions and practices of excellence rather than delegating almost all practical research ethics governance to RECs** because RECs are not necessarily ideally positioned and

equipped to address all ethical risks research outside the biomedical field poses. Especially if the social value and societal desirability of research is a matter of contention, RECs are not necessarily well-positioned to serve as primary loci to mitigate risks. How such an ecosystem could look like is tentatively sketched by, for example Stahl (Stahl 2021).

1.2 Needs to inform development of training materials and awareness actions on AI in Health and healthcare applications

1.2.1 Most relevant current ethical issues and concerns: training and awareness needs

Solving the complex challenges of AI requires a deep understanding of its diverse ethical issues. To achieve this, we categorize these issues, examining them individually and how they interconnect. This approach simplifies communication and raises awareness about AI's ethical implications in healthcare.
The categories include technical considerations, privacy and confidentiality, legal issues, Social Justice and Equality, human rights, and overarching issues.

Ethical principles for AI systems – some important values and principles include:

- **Human Oversight** – The EU High-Level Expert Group guidelines on trustworthy AI define this principle as follows: “Human oversight helps ensuring that an AI system does not undermine human autonomy or causes other adverse effects. Oversight may be achieved through governance mechanisms such as a human-in-the-loop (HITL), human-on-the-loop (HOTL), or human-in-command (HIC) approach. HITL refers to the capability for human intervention in every decision cycle of the system, which in many cases is neither possible nor desirable. HOTL refers to the capability for human intervention during the design cycle of the system and monitoring the system’s operation. HIC refers to the capability to oversee the overall activity of the AI system (including its broader economic, societal, legal and ethical impact) and the ability to decide when and how to use the system in any particular situation. This can include the decision not to use an AI system in a particular situation, to establish levels of human discretion during the use of the system, or to ensure the ability to override a decision made by a system.” (European Commission HLEG 2019) Human oversight is particularly needed if and when foundation models with generative capacity are used in healthcare context.

- **Transparency** – Many AI systems, such as deep learning algorithms, operate as "black boxes," making it challenging to understand how they arrive at their decisions. Transparent AI systems can help avoid the perception of "black box" decision-making and foster accountability. Ensuring transparency of AI systems is crucial to building trust, enabling healthcare professionals to understand and validate the reasoning behind AI-generated recommendations. To ensure transparency, it is essential to provide clear and accessible information about the purpose and goals of the AI system. This includes communicating its intended use, whether it is assisting in diagnosis, treatment recommendations, or other healthcare tasks. By being transparent about the purpose of the AI system, stakeholders can better understand its intended benefits and limitations

(Andersen, 2018). Transparency is particularly difficult to achieve when foundation models with generative capacity are used in biomedical context.

- **Explainability** – AI technologies should be designed in a way that ensures they are intelligible or understandable to various stakeholders, including developers, medical professionals, patients, and regulators (WHO, 2021). Intelligibility refers to the ability to comprehend and interpret the functioning, reasoning, and outcomes of AI systems. Such understanding is crucial for fostering trust, enabling effective collaboration, and ensuring the responsible and ethical deployment of AI technologies in healthcare. It may involve using interpretable machine learning models, providing visualizations or summaries of AI decisions, or employing techniques that can generate understandable explanations for the outputs generated by AI systems. Additionally, clear documentation and guidelines are in the understanding and effective utilization of AI technologies by different stakeholders.

- **Cybersecurity (including data security**) – Cybersecurity and data security are critical considerations when implementing AI systems in healthcare, as these technologies often require access to sensitive patient data. The need for robust cybersecurity measures arises from the potential risks associated with unauthorized access, data breaches, or misuse of patient information. Healthcare organizations are prime targets for cyberattacks due to the wealth of valuable data they possess (Murdoch, 2021). Data breaches can lead to the compromise of patient information, resulting in identity theft, fraud, or other malicious activities. Implementing stringent cybersecurity measures, including intrusion detection systems, firewalls, and regular security audits, helps minimize the risk of data breaches and unauthorized data access.

- **Accountability (of algorithms and AI systems)** – Accountability is a crucial category that holds AI developers, deployers, and users responsible for the actions and consequences of AI systems. Ensuring clear lines of responsibility and liability can mitigate potential harm and provide recourse in case of unintended negative outcomes. Appropriate mechanisms should be adopted to ensure that individuals and groups affected by algorithmically informed decisions can question and seek redress. This should include access to prompt, effective remedies and redress from governments and companies that deploy AI technologies in healthcare (WHO, 2021).

Privacy and confidentiality

- **Privacy** – The collection, use, analysis, and sharing of health data have consistently sparked significant concerns regarding individual privacy (Jones, 2023). The lack of privacy in this context can potentially cause harm to an individual in various ways, including future discrimination based on their health status. Additionally, the lack of privacy can result in wrongful acts that infringe upon a person's dignity, particularly when sensitive health data is shared or exposed to others without their consent or appropriate safeguards in place.

- **Consent** – AI systems have the potential to significantly impact medical decision-making processes, potentially bringing about changes in the traditional doctor-patient relationship. With the integration of AI in healthcare, it is important to educate patients about how AI systems are utilized in their care (Morley et al., 2020). This includes providing information about the purpose, benefits, and limitations of AI technologies in medical decision-making. Obtaining informed consent becomes particularly relevant in scenarios where AI systems play a significant role in diagnosing conditions, suggesting treatments, or guiding clinical decisions. Patients should have a clear understanding of how AI-generated recommendations are integrated into their care, including any potential risks or uncertainties associated with the technology. This empowers patients to make informed choices and actively engage in shared decision-making processes with their healthcare providers.

Social Justice and Equality

- **Bias** – this is a critical ethical issue for AI in healthcare that has gained significant attention and concern. AI systems, including machine learning algorithms, are increasingly being used in various healthcare applications, such as diagnostic support, treatment planning, patient monitoring, and drug discovery. However, these systems are only as good as the data they are trained on, and if the data contains biases, the AI will inherit and potentially amplify these biases. For example, Gionkar, Kim and Macyszyn (2020) point out that models trained using electronic health records are more likely to have incomplete data on people from lower socio-economic status and therefore not representative and cannot be ethically used for people from such populations.

- **Fairness** – Fairness is another important ethical issue for AI in healthcare, closely related to the problem of bias. Ensuring fairness in AI systems is crucial to avoid discrimination and promote equitable healthcare outcomes for all individuals. As the WHO (2021) points out, although automated AI programming might be more accurate, its use might be unfair and unsafe. Thus, AI algorithms should be designed and deployed in a way that treats all patients fairly, regardless of their demographic attributes, such as race, gender, age, or socioeconomic status.

Legal Issues

- **Liability** – the use of AI systems can introduce complexities in determining responsibility when things go wrong. When AI technologies are involved in healthcare decisions, questions arise about who should be held accountable for adverse outcomes or errors (Khullar et al. 2021). Also, determining the extent of each party's liability can be challenging as the complex web of liability issues may involve healthcare providers, AI developers and when AI technologies are used across borders, multiple legal jurisdictions and regulatory frameworks could also be involved (European Commission AI Liability Directive 2022).

As the preceding text indicates, **many core ethical issues are raised by the use of AI in health**. It should be noted that **many of these also constitute or involve legal issues**, which are also highly important in terms of regulating and reviewing AI:

- For example, privacy and data protection violations are not only an ethical issue but are also punishable by law; if users of AI are discriminated against by algorithms this could also lead to legal action.

- Similarly, if decisions are made that are not explainable, or if AI systems lack sufficient accountability, those decisions could be challenged, and compensation potentially sought.

- Finally, if AI systems are used without users understanding their implications or being asked about their use, legal action could also result from this lack of informed consent.

1.2.2 Core scientific concepts that must appear in a short lecture

- **Predictive Modelling**: Predictive modelling is an emerging discipline of predictive medicine used to identify people at risk of diseases and health issues. Predictive modelling can use medical records and other biometric and genomic data to identify patterns that may be predictive of a person's future health (Chapman et al., 2019)

- **Neural Networks**: also referred to as Artificial Neural Networks (ANN) are computing systems inspired by the human brain and the structure of neurons in the brain, composed of large clusters of linked artificial neurons (Sordo, 2002). ANN can also be described as a kind of artificial intelligence that consists of an interconnected group of neurons that use weighted connections to amplify or adjust input signals. It can be used to process inputs and make predictions, similar to the way the human brain does. Neural Networks can be used for supervised and unsupervised learning, as well as for recognizing patterns, performing predictions or classifications, and even generating new data. In healthcare, ANN has been applied for the prediction and diagnosis of diseases (Shaikhina and Khovanova, 2017).

- **Machine Learning**: Machine learning refers to statistical techniques for fitting models to data and to learn by training models with data (Davenport and Kalakota, 2019). In health care advanced analytics involving machine learning is applied to enable patterns to be recognized from data, allowing for the development of insights that can support decisions related to patient care. In this - process machines are given access to data and allowed to use it to learn and build predictive algorithms.

- **Reinforcement Learning**: Reinforcement learning is a learning method in which an agent interacts with an environment and learns to maximize some form of reward and/or minimize some form of penalty through trial-and-error (Sutton and Barto, 2015). It is inspired by behavioural psychology and is concerned with how software agents ought to take actions in an environment so as to maximize some notion of cumulative reward. Reinforcement learning is one of three basic

machine learning paradigms, alongside supervised learning, and unsupervised learning. In reinforcement learning, the agent chooses an action from a set of possible actions and receives an immediate reward or penalty for this action, depending on the state of the environment. Based on this experience, the agent adapts its behaviour for future interactions with the environment. Reinforcement learning is most commonly used in decision-making, such as playing a game or controlling a robot.

- **Deep Learning**: it focuses on using large neural networks and algorithms to build powerful learning models. Deep learning enables machines to learn and make decisions using complex data redundantly. It has become a very popular research field due to its ability to solve problems such as image recognition, speech recognition, language understanding, automated driving, and medical diagnosis. Deep learning borrows from traditional machine learning and utilizes algorithms that are inspired by the structure and function of biological neural networks in the brain (Alzubaidi et al., 2021). These algorithms often involve the use of various layers (hence the name: deep learning) to process data and produce results, making it one of the most popular techniques for AI applications.

- **Natural Language Processing (NLP)**: "Natural language processing (NLP) encompasses a wide range of techniques designed to transform written text into meaningful and analyzable datasets, which can then be utilized by statistical and machine learning (ML) models" (Harrison and Sidey-Gibbons, 2021). It also refers to the ability to process and understand natural language written or spoken by humans. It enables AI technologies to understand and respond to spoken or written language, which can be useful for the processing of medical data from EHRs and medical notes. NLP offers valuable applications for healthcare such as enabling better understanding of public health concerns expressed on social media, improved handling of vast amounts of medical records, and evaluating patient outcomes and experiences by extracting relevant information from their own narratives.

- **Foundation models** are AI models "trained on broad data (generally using self-supervision at scale) that can be adapted to a wide range of downstream tasks" (Bommasani et al. 2022). The latest draft of the European AI Act defines foundation models as "AI model]s] that [are] capable to competently perform a wide range of distinctive tasks" (Bertuzzi 2023). In healthcare and biomedicine, foundation models may accelerate drug discovery, draft medical reports and documents, or generate synthetic data for training other AI systems. Challenges include handling diverse medical data types, ensuring explainability and truthfulness, and adhering to forthcoming regulation.

- **AI in medical diagnostics or Computer-Aided Diagnosis (CAD)**: Computer-aided diagnosis (CAD) refers to the use of computer systems to analyze medical images, such as Radiography, MRI scans, CT scans, or ultrasounds, to help in the diagnosis of diseases, abnormalities, and other medical conditions (Castellino, 2005). CAD often employs AI techniques such as deep learning and most of the focus revolves around identifying and characterizing different

diseases through image analysis. However, there is a growing interest and dedicated efforts towards utilizing CAD techniques for quantitative analysis of tumor heterogeneity, establishing connections between image phenotypes and underlying genetic/biological processes, distinguishing between cancer subtypes, determining cancer stages, planning treatments, and evaluating treatment responses (Chan, Hadjiiski, and Samala, 2020).

This list of core scientific concepts in AI is subject to ongoing research and development. The field of AI is rapidly evolving, and new techniques, algorithms, and applications are continuously emerging. As researchers and scientists make advancements in AI technology and explore novel use cases, the understanding and implementation of these concepts may evolve.

1.2.3 Additional highly relevant topics for ethical analysis in a full-day training course

The following additional topics have been suggested by Morley et al. (2020):

- **Protection of equality of care:** This concept refers to modalities for guaranteeing that every individual is granted to receive fair and equitable healthcare services irrespective of their demographic characteristics, socio-economic standing, or other personal attributes. Despite the potentially transformative impact AI is poised to have on healthcare (e.g. through enhanced diagnostic accuracy, treatment planning, and better outcomes for patients) there are concerns that AI could inadvertently perpetuate existing healthcare disparities or introduce new biases into the system, ultimately resulting in unequal availability of high-quality care. Therefore, strategies for mitigating biases and enabling the inclusive representation of diverse patient populations in the data used to develop AI systems and algorithms are necessary. By adopting such measures, the adoption of AI in healthcare will not only enhance the effectiveness of medical care but also uphold the core principle of equal access to healthcare for all individuals.

- **Fair distribution of benefits**: A prevailing concern centers around the potential imbalances in the distribution of the manifold advantages stemming from the integration of AI in healthcare. Although these advantages include improved diagnostic accuracy, personalized treatment plans, and enhanced patient monitoring, there is a risk that such benefits might not be fairly accessible to all individuals and communities. There is also concern that such benefits could inadvertently disproportionately benefit certain groups or exacerbate existing healthcare disparities. As such, mitigation strategies should include mechanisms that facilitate diversity and inclusiveness in the developmental processes of AI in healthcare. The involvement of a diverse spectrum of perspectives and individuals regardless of their socioeconomic status or demographic location, latent biases and oversights can be better understood and mitigated. The fair distribution of benefits might also necessitate that challenges related to infrastructure cost and healthcare disparity in underserved communities be addressed.

- **The protection and promotion of societal values**: Regarding the development and use of AI in healthcare, the protection and promotion of societal values have received only little consideration thus far. This is a critical ethical concern that arises due to the potential impact of AI technologies on individuals, communities, and the entire society. There are specific concerns on how to ensure that AI systems in healthcare not only align with societal values but contribute positively to patient well-being and those of the broader public. It is important to carefully evaluate the broader ethical and social impacts to minimise any unintended consequences.

1.2.4 Key uncertainties concerning AI in Health at this time

Some key uncertainties in relation to AI in healthcare include:

- **Efficacy and Accuracy**: One uncertainty is how effectively AI algorithms can diagnose and treat medical conditions compared to human experts (Davenport and Kalakota 2019). While AI has shown promising results in certain areas, there is still a need to evaluate and validate the accuracy, reliability, and overall efficacy of AI systems in healthcare settings.

- **Safety and Risk**: The safety of AI systems in healthcare is a major concern. There are uncertainties regarding the potential risks and unintended consequences of relying on AI for critical healthcare decisions (Challen et al. 2019). AI systems need to be thoroughly tested and monitored to ensure patient safety.

- **Excessive trust (overtrust) in AI systems:** Excessive trust (overtrust) in AI systems is a phenomenon where humans rely too much on the capabilities and reliability of artificial intelligence, even when they have seen it fail or make mistakes. This can lead to potential risks, such as deception, manipulation, or loss of control by autonomous systems. Overtrust can be influenced by factors such as the task difficulty, the human's confidence, the system's performance, and the feedback mechanisms (Ullrich et al. 2021, Aroyo et al. 2021).

- **Regulatory Frameworks**: The rapid advancement of AI in healthcare has outpaced the development of comprehensive regulatory frameworks (Reddy et al. 2019; Morley et al. 2022). There is uncertainty around how AI systems should be evaluated, approved, and monitored to ensure they meet the necessary standards for safety, efficacy, and ethical use.

- **Legal and Liability Issues**: The question of legal and liability issues arises when AI systems are involved in medical decision-making. If an AI system makes an error or causes harm, it may be challenging to determine who is responsible—whether it's the AI developer, healthcare provider, or both. Clarifying legal and liability frameworks is necessary to address this uncertainty and is necessary for the responsible use and development of AI in healthcare settings (Schönberger 2019).

1.2.5 Fundamental dilemmas in AI in healthcare

Several ethical dilemmas are raised by the use of AI in health. Among the selected below, two are essentially traditional dilemmas that take on new dimensions due to the involvement of novel technology, while the third presents a new challenge:

- The first dilemma centers around **autonomy, trust and responsibility**. If AI is integrated into medicine, this raises issues regarding *explainability*. It is possible that doctors and patients will not fully understand why AI is making particular decisions or giving the advice that it does. This calls into question the evidence base for shared decision making and informed consent, and raises issues of liability and responsibility for any harm that arises as a result. To address this, it could be ensured that all AI decisions are entirely explainable, but this would probably come at the price of compromised efficiency. This is perhaps the key dilemma in the use of AI and is closely related to the following two issues.

- Second, there is the issue of **algorithmic bias**. Ethnic minorities, disabled people and other vulnerable populations are already subjected to discrimination by medical systems and institution. AI solutions are engineered to be bias-free, but this aim is often not achieved due to biases present in the data used to train such systems. If algorithms and their outputs are biased against minorities, further compounding existing disparities and discrimination, this poses major ethical challenges to their implementation in practice. Should AI systems be introduced if there is uncertainty regarding whether they are potentially discriminatory? This issue is also connected to explainability; if AI systems cannot explain their decisions, that will increase the risk of bias going undetected.

- Finally, there is a novel ethical issue that is more relevant to AI in general but also relevant to AI in health. **Capability overhang** is the phrase used to refer to the possibility that AI solutions are sometimes deployed without their creators being entirely sure how they work or what they are capable of (this again relates to the issue of explainability). Here, the dilemma is really whether to deploy such systems given the potential risks of unforeseen capabilities. In the field of clearly targeted AI health solutions this may not be such an important issue, but it must be borne in mind that AI systems will sometimes give unanticipated responses and may make unintended discoveries.

1.2.6 Useful resources to build training modules

The international guidance listed in section 1.2.9 provides a useful resource for building training modules.

- French CCNE and CNPEN Joint **Opinion on Medical Diagnosis and Artificial Intelligence**: Ethical issues https://www.ccne-ethique.fr/en/publications/joint-opinion-opinion-no141-ccne-opinion-no4-cnpen-medical-diagnosis-and-artificial (2023)

- Deutsche Ethikrat Opinion "**Humans And Machines – Challenges Of Artificial Intelligence**" (2023) https://www.ethikrat.org/en/publications/publication-details/?tx_wwt3shop_detail%5Bproduct%5D=168&tx_wwt3shop_detail%5Ba

ction%5D=index&tx_wwt3shop_detail%5Bcontroller%5D=Products&cookieLevel=accept-all&cHash=4d430bf45ea980ea5f83daad9550ef88

- Blueprint For Trustworthy AI Implementation Guidance And Assurance For Healthcare: Coalition For Health AI (CHAI) https://www.coalitionforhealthai.org/papers/blueprint-for-trustworthy-ai_V1.0.pdf

- **AI ethics**, by Mark Coeckelbergh (MIT Press, 2020) is a good textbook on AI ethics listing all main topics of interest.

- The **Oxford Handbook of Ethics of AI**: Edited by Markus D. Dubber, Frank Pasquale, and Sunit Das, this handbook offers a comprehensive exploration of ethical issues surrounding AI. It covers healthcare-specific topics, such as clinical decision support systems, AI diagnostics, and ethical implications in patient care. (Link: https://academic.oup.com/edited-volume/34287)

- **Ethics Guidelines for Trustworthy AI** by the European Commission: The European Commission has released a set of guidelines for the ethical development and deployment of AI. It covers various sectors, including healthcare, and provides detailed principles and requirements for responsible AI. (Link: https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai)

1.2.7 Applicability of the concept of compliance to AI in health and healthcare

The concept of compliance does apply to AI, but in a more limited sense due to the relatively unpredictable capabilities of AI. Those designing AI systems can attempt to ensure compliance with regulation and legislation but given that they cannot always anticipate what a given AI system will do in the future, ensuring compliance is maintained can be very challenging. Furthermore, even if compliance with regulation is perfect, the regulations and legislation itself may be outpaced by innovation in AI and AI's own innovation, meaning that the concept of compliance may not be fit for purpose as its uses may not have been anticipated in regulation either.
In terms of AI in healthcare, these general concerns are less pressing, as the systems involved are less open. Nonetheless, the way in which AI changes and challenges the concept of compliance must be borne in mind when designing and reviewing AI projects.

1.2.8 Applicability of the concept of ethics-by-design to AI in health and healthcare

Ethics-by-design approaches can be applied to AI systems, as described in the European Commission guidance "Ethics By Design and Ethics of Use Approaches for Artificial Intelligence". This states that the following principles should govern the design of AI systems:

- respect for human agency;
- privacy, personal data protection and data governance;
- fairness;
- individual, social, and environmental well-being;

- transparency;
- accountability and oversight.

However, ethics-by-design does suffer from some limitations in the context of AI, for reasons similar to those concerning issues with compliance mentioned above; **it is difficult to anticipate all the uses of AI systems, and thus also to anticipate all the ethical issues that might arise**. As the EC guidance itself states, "For many AI projects, the relevant ethical issues may only be identified after the system's deployment." Despite this accurate statement, the EC guidance nonetheless states that "Ethics by Design is intended to prevent ethical issues from arising in the first place by addressing them during the development stage, rather than trying to fix them later in the process" without addressing the tension between this aim and the fact that issues may only be identified later on.
Given these issues, some sort of ongoing ethics by design evaluation procedure would be necessary, as stated in section 1.1.4.

1.2.9 Most relevant EU or international guidelines or standards related to AI in Health and Healthcare

- French CCNE and CNPEN Joint Opinion on Medical diagnosis and artificial intelligence: Ethical issues https://www.ccne-ethique.fr/en/publications/joint-opinion-opinion-no141-ccne-opinion-no4-cnpen-medical-diagnosis-and-artificial (2023)
- Deutsche Ethikrat Opinion "Humans And Machines – Challenges Of Artificial Intelligence" (2023)
  - https://www.ethikrat.org/en/publications/publication-details/?tx_wwt3shop_detail%5Bproduct%5D=168&tx_wwt3shop_detail%5Baction%5D=index&tx_wwt3shop_detail%5Bcontroller%5D=Products&cookieLevel=accept-all&cHash=4d430bf45ea980ea5f83daad9550ef88
- WHO Ethics and governance of artificial intelligence for health (2021)
  - https://www.who.int/publications/i/item/9789240029200
- UNESCO Recommendation on the Ethics of Artificial Intelligence (2022) https://www.unesco.org/en/artificial-intelligence/recommendation-ethics
- European Commission: Ethics By Design and Ethics of Use Approaches for Artificial Intelligence (2021)
  - https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/ethics-by-design-and-ethics-of-use-approaches-for-artificial-intelligence_he_en.pdf
- European Commission: Ethics guidelines for trustworthy AI (2019)
  - https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai
- OECD Recommendation of the Council on Artificial Intelligence (2019)
  - https://legalinstruments.oecd.org/en/instruments/oecd-legal-0449
- Council of Europe Guidelines on artificial intelligence and data protection (2019)
  - https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/ethics-by-design-and-ethics-of-use-approaches-for-artificial-intelligence_he_en.pdf
- As long as the EU Regulation on Medical Devices (EU 2017/745) and the EU Regulation on In Vitro Diagnostic Devices (EU 2017/746) apply, **AI systems**

falling under these Regulations are considered to be high-risk AI systems in the sense of the Proposal for a regulation of the European Parliament and of the Council on harmonized rules on Artificial Intelligence (Artificial Intelligence Act). This position is consensual between EU Commission, Council, and Parliament. The classification of AI systems in healthcare as “high-risk” will entail mandatory certification measures.

1.3 Recommendations

1.3.1 Adapt the composition of RECs to include AI experts

Like in other fields using new AI solutions, envisioning potential ethical issues of AI applications in healthcare requires appropriate scientific and technical expertise. To tackle this challenge, research institutions should consider integrating "AI subcommittees" (REC assemblies specialized in AI projects) into existing RECs mandated primarily for health-related research, or alternatively establishing dedicated "digital ethics committees" (DECs). Without replacing existing RECs, these bodies would bring together AI experts, research professionals, and specialists in social and human sciences. They would conduct ethics reviews for AI-related research projects and may occasionally serve as advisory bodies for policymakers. By allowing sufficient mutual learning time and providing appropriate training and resources, the ethics appraisal process can be significantly widened and improved to cover all AI-related research projects in healthcare.

1.3.2 Set uniform and coherent ‘AI in healthcare’ guidelines across EU member states

To address discrepancies in the ethical review of AI-related research in healthcare and to avoid ethics dumping, collaborative efforts among EU member states are essential. Homogenized guidance on ethical appraisal of AI-related research in healthcare should be provided at the EU level to ensure consistency in RECs' evaluations and to facilitate cross-border research projects, empowering researchers to navigate regulatory challenges effectively. Addressing regulatory disparities between countries (e.g. the French CCNE recently adopted an opinion on the use of AI in medical diagnostics, while most other EU members do not provide any guidance at all), as well as between the public and private sectors, is crucial. To achieve this, comprehensive and mandatory training for ethics reviewers on the application of EU HLEG guidelines for Trustworthy AI and the HLEG ALTAI checklist is recommended.

1.3.3 Develop REC methodologies beyond compliance

The use of AI systems in healthcare requires ongoing evaluation beyond a one-time compliance check. RECs should be involved in the ethical appraisal of AI systems at regular intervals during the design process, following the ‘ethics-by-design' methodology via regular consultations involving all stakeholders (designers, medical professionals, and patient organizations or patients). The frequency of this monitoring should be determined based on foreseeable risk to ensure that the ethics recommendations issued by RECs are proportionate and relevant. RECs should move away from assessing compliance toward helping researchers to perform ongoing ethical reflection, anticipation, and evaluation.

2. Biobanking

2.1 Gaps in the current ethics review process of biobanking research at EU, Member State and non-EU state levels

2.1.1 Problems encountered by REC members in ethics assessment procedures

Ethics review processes for biobanking vary across Europe. In many countries, independent ethics review bodies, typically research ethics committees (RECs), evaluate the ethical acceptability of research projects that intend to use biobank resources. In some countries, RECs also review the establishment of a biobank itself, as seen with Biobank Graz (Medical University of Graz 2015). In other countries, REC approval for biobank research is only necessary in exceptional cases. For example, in the UK, biobanks may obtain general ethics approval to conduct a broad range of biobank research, thereby relieving researchers of the need to seek separate ethics approval (UK biobank 2021). In Finland, REC permission is required to set up a biobank, and the evaluation of biobank research is typically performed by the director(s) of the biobank, with REC approval necessary only under specific circumstances (NordForsk 2017).

It is also worth noting that **in some countries, RECs are responsible for additional obligations,** such as allowing biobank controllers to identify and contact gene donors to get their written consent for renewing, supplementing or verifying a description of their state of health (Estonia, Human Genes Research Act (2019), Article 24.2.3), or authorizing the transfer of biobanked samples and health-related data to other biobanks established in the same country or abroad or to research studies carried out abroad (Lithuania, Law on Ethics of Biomedical Research (2020), Article 17.2).

Different ethics governance practices across different biobanks in Europe also reflect different models of oversight recommended at the international level. For instance, the OECD guidelines recommend for RECs to assess biobank research with a specific focus on determining whether the purpose of the planned biobank research study falls within the scope of previously given consent or whether it requires (re)consent (OECD, Guidelines on Human Biobanks and Genetic Research Databases (2009), clause 3.1). Meanwhile, the WMA Taipei Declaration expands the scope of ethical oversight by recommending that RECs should evaluate not only biobank research, but also approve the establishment of a biobank and monitor ongoing biobank activities (WMA 2016, paragraph 19).
As for the monitoring activities, it may be interesting to note the example of the UK biobank. Since the establishment of the UK biobank, it was connected to the UK Biobank Ethics and Governance Council which monitored and reported publicly on the conformity of the UK biobank project with the UK Ethics and Governance Framework and advised more generally on the interests of research participants and the general public in relation to UK Biobank. However, it was recently replaced by the Ethics Advisory Committee, which has been assigned a smaller role of ethics oversight, namely, to identify ethical issues and advise. **It is worth noting that many biobanks establish bodies such as ethics committees or advisory committees to provide ethics advice or recommendations related to biobank strategies and organizational management, beyond the REC approval system** (Gille et al. 2020).

2.1.2 Current ethical or regulatory gray zones

Primo, RECs face various difficulties in assessing different aspects of biobank research, with **choosing the consent model** being one of the challenges**. Broad consent** is still prevalent in biobank practice (Gille et al. 2020), and it is often formulated in a way that seemingly allows any biobank research to be carried out (Serepkaite et al. 2014), making it difficult for RECs to evaluate the scope of consent in a meaningful way. If previously the broadest future research scope was biomedical research, today the resource of biobanks can also be useful for research that does goes beyond this scope (e.g., innovation purposes, non-biomedical research purposes).Given that RECs must assess whether the research application falls within the scope of the previously given broad consent, this can result in a formalistic evaluation that fails to consider the complexities of biobank activities. Another layer of complexity arises due to the changing capacities of what biobank research can be conducted, what scope of information can be collected about a biobank participant, what research methods can be applied, and what risks may arise to the privacy of biobank participants and their families. It can be difficult for a REC to assess whether individuals who gave consent e.g., a decade ago would have given consent to a particular biobank research study, especially if the research is ethically more sensitive (e.g., stem cell research, research using whole genome sequencing, research involving commercial partners).

> To mitigate this problem, **more attention should be paid to ethical evaluation when establishing a biobank.** When it comes to consent**, it is especially important to assess from the start whether it is possible to apply dynamic consent**, whether biobank participants could object to certain types of biobank research, whether the scope of future research could be explained more concretely, e.g., by providing the sub-area of medicine for which samples and data can be used in the future, e.g. cardiovascular disease, cancer, degenerative muscle disease (UMC Utrecht 2020, Manchester Cancer Research Centre 2022) or by giving at least an example list of diseases which may be investigated (UK biobank 2010) or would not be investigated unless additional ethics approval is obtained.

Secundo, **another issue that RECs may face is related to the return of individual findings** that may be relevant to the biobank participant or their relatives. Due to the increasing availability of next-generation sequencing technologies, the list of important findings identified in the context of research and biobanking has expanded. Also, the moral and legal duty of researchers to report findings has been increasingly recognized (Global Alliance for Genomics and Health 2021, Berkman 2017). However, **many biobanks in Europe still do not have policies on the return of individual health-related findings**. Even if they do, those policies differ in "when results must, should, may, or must not be returned" (Thorogood 2019). Further complicating matters are varying criteria for determining the utility of findings, including their relevance to medical treatment, familial implications, reproductive decisions, and personal preferences (Thorogood 2019). Due to the policy and legal uncertainty in international and sometimes even national guidelines, RECs may face challenges in assessing the issue of return of individual findings, especially due to disagreements on what to consider an actionable finding and under what circumstances it should be returned. There may be inconsistent interpretations regarding this issue among RECs not only

across different countries but also within the same country. **It is also important to mention that not only the unclear policy and legal regulation can influence the complicated assessment of the issue of returning individual findings, but also the potential lack of certain competences among REC members**. For instance, considering the currently researched AI-driven polygenic risk scores (Fritzsche 2023), RECs may lack the understanding of ethical challenges of using such tools to return health-related findings to the biobank participants.

> **To address these issues, in the long run it is crucial to establish a more coherent approach for defining the utility of findings.** Given the significant diversity in criteria used to define reportable (useful) findings, it is recommended to develop guidance on how to weigh various utility approaches, particularly when dealing with complex (e.g., multifactorial) diseases (Lekstutiene et al. 2021). In the short run, refining the scope of reportable findings by employing the gene list provided in the guidelines of the American College of Medical Genetics and Genomics (Green et al. 2013, Miller et al. 2022), or by following the criteria provided by Berg and colleagues (Berg et al. 2016) might be a solution.

Tertio, **in studies that are mostly dealing with personal data, including biobank research, there is also an issue related to the role of RECs in data protection** and how this should be organized in practice (PANELFIT project 2021). The lack of clarity regarding the role of RECs in data protection may lead to variations in how different RECs or even members within the same REC assess data processing issues in research proposals. Unclear boundaries on what aspects to assess in terms of data protection may lead to duplication of work carried out by other entities such as RECs and Data Protection Officers (DPOs). Poorly defined roles and responsibilities may cause hesitation among RECs, or other relevant actors in adequately reviewing data protection issues.

> There are several suggested solutions to address this issue. **One possible solution is to assign RECs a role as ethics reviewers within the data protection framework**. However, to avoid redundancy and ensure efficient collaboration, the specific relationship between DPOs/Data Protection Authorities (DPAs) and RECs would need to be clearly defined. **Another approach could be to delegate the responsibility of addressing legal and ethical issues arising from the GDPR to researchers and research institutions**, such as legal departments, research support units, and DPOs. In this scenario, REC assessment will focus primarily on determining if a proposed protocol aligns with recognized research ethical standards and includes considerations for risk/benefit ratios, confidentiality etc. In such a model, RECs could also play a facilitative role by requesting statements from researchers affirming that their proposals have undergone evaluation regarding personal data protection and are compliant with the GDPR (PANELFIT project 2021).

Quarto, **ethics reviews can also be challenging due to narrow definitions of biobanks in national regulations and the lack of guidance for RECs on how to ethically assess collections of human biological material and data that are similar (or even the same) to biobanks.** In some countries, legal regulations (e.g.,

requirements for consent) are focused on large population and disease-oriented biobanks. Thus, difficulties in assessing may arise when a (smaller) collection of samples and data for future research is being created during a specific research study, particularly if the collection is to be stored in a different country than the one where the samples and data were collected. Similar problems e.g., related to consent withdrawal also arise when samples are collected in one country and then sent to an existing biobank in another country. Another challenge for RECs may arise when old collections that were originally collected for non-research purposes are integrated into a biobank and used for future research. In such cases, RECs may lack guidance on what requirements to apply. The requirements that apply to, e.g., population biobanks may be too strict, such as drafting the same consent document, and some requirements, like obtaining consent for the integration of old collections into the biobank, may be impossible to implement.

RECs in institutions that establish broad definitions of biobanking are generally obliged to review creating a collection of samples and data in combination with a specific research study (UMC Utrecht 2013). The same applies on the EU level when a collection of samples and data for future research is created within the clinical drug trial (CTEG 2022). However, not all RECs, where biobanking is defined more narrowly, apply the same requirements in ethics reviews outside clinical drug trials.

- **The Finnish model provides an interesting example when it comes to incorporating existing (old) collections into a biobank**. In line with this model, obtaining REC approval is necessary before transferring old collections to the biobank for biobank research purposes. Additionally, the sample donors are informed about the planned transfer through either personal letters or, in specific cases, by publicizing the information through media channels. After the notification period, the samples can be transferred to the biobank, provided that the donor does not explicitly prohibit the transfer (Finland, Biobank Act 2022, Auria Biobank 2023).
- **UMC Utrecht REC serves as another interesting example in this context**. When utilizing an old collection, UMC Utrecht REC assesses various factors, including but not limited to the following: they evaluate whether a broad consent was initially obtained. If not, they examine whether alternative conditions are met, such as: 1) determining if the collection is no longer required for quality assurance purposes or any additional individual diagnostic procedures; 2) verifying whether it can be reasonably assumed that the donor was adequately informed about the usage and did not raise any objections; 3) ensuring that the data is either fully anonymized or appropriately encoded; 4) confirming that there are no commercial interests involved, and 5) ensuring that human samples are not being amplified with the intention of creating immortal (stem) cells or cell lines (UMC Utrecht 2013).

Quinto, **It is important to note the regulatory disparities between biobanks and other European and national initiatives that involve the secondary use of data.** Biobank regulations tend to be more stringent, with ethics reviews still being common across various European countries. In contrast, secondary data use initiatives seem to have more relaxed ethical review policies. For instance, on the EU level the proposal for the European Health Data Space initiative leaves ethical review as an optional

governance element, allowing each country to decide for itself whether it is necessary (European Commission 2022). On the one hand, biobanks differ from the national initiatives involving secondary research use of data in that they not only store data but also collect and store biological samples, which are a valuable and limited resource. Additionally, biobanks as data repositories may duplicate some of the data that is already stored in healthcare facilities, which is not typically the case for national initiatives involving secondary use of data. On the other hand, in both cases, we may deal with equally sensitive health-related data.

As a result, **the question arises as to whether the ethical oversight for biobanks and national initiatives involving secondary use of data should be similar.** If so, questions arise how ethical review should evolve: whether it should be applied to both biobanks and secondary data use initiatives, or whether biobank research should in most cases be exempted from ethical review.

2.1.3 How to ensure the most satisfactory or effective approach to ethics review in biobanking research

It is difficult to name one, but it is likely that most would agree that, as a starting point, **it would be useful to share information about ethics review requirements across different countries** to establish a more harmonized and collaborative research environment (Casati et al. 2021).

2.1.4 Choosing an ethics evaluation model for biobanking

When it comes to biobanks, **we can identify at least two stages of ethics review**:

1) In the first stage, the REC reviews the biobank's framework related to consent, return of individual health-related findings, access procedures, and so on.
2) In the second stage, the REC reviews specific research projects that utilize the biobank's resources.

D. Strech argues that “only a few research-related risks remain for the second stage of ethical review, and that a self-regulated body, such as a biobank internal access committee, would suffice (in principle) to address these risks” (Strech 2015).

However, it is important to note that **this model may not be suitable for all biobanks due to cultural sensitivities, varying levels of awareness and trust in health care and research across different countries, the strength of social security structures that ensure non-discrimination and the protection of vulnerable individuals, and other factors.** Ongoing monitoring of biobank activities may also be necessary given their dynamic and evolving nature. In cases where there is a high risk of re-identification (such as when combining biobank data with other data) or other ethical challenges arise related to discrimination or research that is treated controversial in a society, it may be necessary to involve REC to evaluate the research more thoroughly.

2.2 Needs to inform development of training materials and awareness actions on biobanking

2.2.1 Most relevant current ethical issues and concerns

Ethical and/or legal issues	Questions
Consent for participation in research	How to achieve and obtain consent?

	How to make sure all participants are well-informed and understand the purpose of research with its expected benefits and risks?
	In the case of withdrawal of consent, what exactly can be withdrawn, and at which point of study?
	Should there be a universal, standardized consent form, or rather the forms should be specific, with geographical, social, and religious differences taken in account, together with different research purposes?
	What should be done in the case of participant's death?
	Is it acceptable to use the samples that did not have consent in cases when it was not realistically possible to obtain it?
Privacy and identifiability of the samples	How to protect the identity of research participants?
	Should simple coding, double-coding, or even triple-coding (one to three codes are needed to provide a link between sample and data) be acceptable in standard research practice, and at the same time are safe enough to ensure a satisfactory level of privacy?
Returning the results to the examinees	Should biobanks consider returning the findings of high clinical relevance to participants?
	Which results of research should be returned?
	When should they be returned, and under what circumstances?
	How should they be returned and communicated and by whom (with what level of training)?
Ensuring and sustaining public trust	How can biobanks continue to maintain and improve levels of public trust?
Children and incompetent adults as study participants	Should biobanks involve children?
	If children are not involved, would medical research on children lag behind the research on adults?

	How to actively minimize the risk for children and incompetent adults?
	Should data sharing on children be banned until children reach adulthood and give specific consent to share their samples from population databanks?
	Would that delay research on children – possibly leaving the whole generation behind? Should parents obtain the results of research findings on their children?
	Do parents have a right to decide whether they want to involve their children in a biobank and they also have a right to give informed consent instead of the children? However, the children must decide if they want to know about their own results when they reach adulthood.
	What should be done with incidental findings that could potentially save a child's life?
	Should children always be asked for consent or in some instances, could research be conducted without parental or child's consent?
	How to protect and obtain consent from incompetent participants, for example, those suffering from psychiatric diseases?
Commercialization	Should private companies be able to use biobank data for their own interest?
	In that case, how to prevent exploitation, ensuring fairness to study participants, and balancing costs and benefits?
	Is it ethical to create financial benefits from free donations and who has the right to a share in these profits?
	How should costs and benefits be balanced and how should intellectual property be shared between companies, researchers, and participants?
Role of Ethics Review Boards	How to improve the quality of their contribution in the process of reviewing biobanking activities?

Data exchange	How to encourage international collaboration and data exchange between research groups who work on different biobanks?
	How to establish national and international cooperation rules and norms?
	How to handle digital data in biobanks, especially sharing and storing the data in public repositories?
	How to handle some journal policies that require all the materials to be made publicly available before publication of the research results?
Ownership of the biological samples and data	What happens when a participant donates a part of body to a biobank?
	Could biobanks become owners of the samples or do they remain in the ownership of the participants?
	Would complete anonymization make biological materials ownerless?
	Should samples be the shared property of donors, researchers, and institutions?
Legislative framework for biobanks and other emerging issues	Is it better to invest in the existing large collections of biologic materials from longitudinal epidemiological cohorts and enrich it with additional measurements to harmonize several existing data sets or to build them brand new and from the start?

Table 3: List of ethical and/or legal issues related to biobanking

2.2.2 Core scientific concepts that must appear in a short lecture

The following core scientific concepts could be presented:

- **Biological samples**: Understanding what biological samples are, how they are collected, and why they are significant. This can include samples of blood, tissue, cells, DNA, and more.

- **Data management**: Managing of data with the biological samples, including clinical data and 'omics' technologies (including genomics, proteomics, and metabolomics). How to organize, store, and retrieve this data efficiently is important to biobank operations.

- **Genomics and genetic analysis**: Many biobanks are used for genomics research, so understanding the basics of genomics and how genetic analysis works is crucial. Biobanks help identify disease-related genetic markers through techniques like Next Generation Sequencing (NGS). This vast data highlights the importance of effective data management.

- **Quality control**: Ensuring the integrity and quality of samples and data in a biobank, including practices for quality assurance and control.

The ethical issues in these concepts are changing with the shifts of technological advancements. For instance, ethical issues in stem cell research changed as new methods have enabled extraction from fat cells, rather than solely embryos. Similarly, the rise in data digitization has transformed data management, mandating ethical considerations in the digitized era. The rapid advancement of artificial intelligence presents fresh ethical dilemmas.

2.2.3 Training and awareness needs: short and long courses

In this section on biobanking, we have decided to present both the main ethical issues on the matter and ways of incorporating them into training courses or awareness actions.

The two training formats include four key modules, detailed, depending on whether the training is short (1h course) or long (full day course):
(1) understanding the different types of biobanks,
(2) different consent models,
(3) discussing data sharing and protection, and
(4) incidental findings.
The one-hour program provides a broad but insightful overview of these critical areas. However, a more granular approach in an expanded, full-day training course should dissect the four overarching themes into smaller, detailed sub-topics, allowing for a deeper dive into the nuances of each area (see table below).
To better illustrate this curriculum breakdown, we have provided a table that lays out the structure of our proposed plan for needs to inform development of training materials and awareness actions on biobanking.

1 hour training	
Types of biobanks	
Models of consent	
Incidental findings	
Data: sharing and protection	
Full day course	
Types of biobanks	• Population-based • Disease-based More on biobank classification can be found here: https://link.springer.com/chapter/10.1007/978-3-030-87637-1_3

Model of consent	Choosing consent model: • Broad consent • Dynamic consent • Study specific consent • Tiered consent • Meta-consent (A short description for each type of consent can be found here: https://cloudlims.com/informed-consent-dynamic-broad-tiered-and-meta-consent-for-biobanking/) Consent related issues: • Handling of consent for deceased participants • Involvement of children and minors • Withdrawal of consent • Using tissue without consent
Data sharing and protection	Protection: • Types of sensitive data • Methods for protecting sensitive data Sharing: • Ownership of data • Benefit of sharing • International data exchange • Commercialization
Incidental findings	• Should biobanks inform participants about findings of high clinical relevance? • Other types of findings to be communicated to participants • Procedures and conditions for informing participants about incidental findings

Table 4: Structure of the training formats on biobanking

To summarize, **the short lecture covers**:

- Different types of biobanks and their unique ethical challenges.
- An in-depth look at informed consent models and their ethical implications.
- Discussion on the balance between promoting research via data sharing and ensuring the protection of sensitive personal information, encompassing data security, international data exchange, and ethical considerations of sample ownership and benefit sharing.
- The ethical dilemmas surrounding incidental findings, including disclosure to participants.

The purpose of **the full-day training is**:

- to highlight the most important ethical issues for researchers and REC members;
- cover in more detail and depth the identified challenges;

- discuss key issues and their relevance to the training of researchers.

Types of biobanks

The ethical issues related to biobanks largely overlap but also have their unique characteristics due to their different focuses and sample sources. Understanding these subtleties is crucial for handling ethical issues in biobanking:

- **Population-based biobanks:** population-based biobanks collect samples and data from a broad cross-section of the population, often with the aim of investigating the complex interplay of genetic, environmental, and lifestyle factors in the development of common diseases. Such biobanks are valuable resources for epidemiological research and have been pivotal in many significant discoveries about the genetic risk factors for diseases like cancer, diabetes, and heart disease (Sudlow et al. 2015). The ethical challenges associated with population-based biobanks revolve around issues of consent, data privacy, and the return of research findings to participants.

- **Disease-based biobanks**, on the other hand, focus on collecting samples and data from individuals with specific diseases or conditions. These biobanks provide crucial insights into the pathogenesis of diseases and are essential for the development and testing of new therapeutic interventions. The ethical issues associated with disease-based biobanks include those related to consent (especially in cases of severe or life-threatening conditions) and the return of research findings with potential implications for the participants' health (Hansson et al. 2006).

While various typologies of biobanks exist (Gramatiuk & Huppertz 2022), the primary focus here lies in disease-based and population-based biobanks. Discussing these two categories allows for a comprehensive approach to addressing challenges across biobank types, as issues often overlap.

Model of consent

Biobanking research often necessitates different models of consent due to its long-term, evolving nature. Similar to the typology of biobanks themselves, consent models exhibit variation (see table above). The primary focus will be on the two main models discussed: dynamic consent and broad consent.

- **Broad consent** empowers participants to provide a one-time consent for an unspecified range of future research providing a practical mechanism for biobanks to accommodate diverse research needs over time. The primary ethical challenge with broad consent lies in the balance between respecting participant autonomy and promoting research utility (Ploug & Holm 2016). For instance, it is unclear whether participants fully comprehend the implications of broad consent given its open-ended nature, leading to questions about its validity in truly respecting participant autonomy. While it's important to acknowledge the presence of uncertainties in the application of different consent models (Steinsbekk et al. 2013, Gefenas et al. 2022) - broad consent stands out as an effective solution due to its simplicity and practicability, particularly in the context of longitudinal and multifaceted research, as it

alleviates the necessity for repeated consent processes, which can be resource-intensive and may potentially lead to participant fatigue and drop-out. Advantages broad consent offers underline its utility in biobanking.

- **Dynamic consent** leverages digital technology to enable ongoing communication with participants. It allows participants to tailor their consent preferences over time, providing a mechanism for enhanced participant engagement. While it fosters a more participatory approach to consent, its implementation can be resource-intensive and may pose technical and practical challenges (Williams et al. 2015). Practically, the need for continuous engagement puts a greater administrative burden on biobanks. This includes the labour associated with managing participant inquiries, concerns, and requests for consent withdrawal or modification, which can escalate costs and require more personnel. Furthermore, it can create a potential "digital divide" if some participants lack access to or familiarity with the necessary technology to engage with the consent process, potentially raising issues of equity and inclusivity. Despite challenges, there are examples of working biobanks with dynamic consent model. The Malta Biobank has developed Dwarna (Mamo et al. 2020), a web portal for dynamic consent that connects biobank managers, researchers, research partners, and the general public. Dwarna uses blockchain technology to store research partners' consent in a secure and transparent way.

Example of consent form recommended by the German Medical Ethics Committees: https://www.akek.de/wp-content/uploads/ICF-Biobanks-FINALapproval-_2020-10-20-Clean.pdf

Other consent-related topics

Consent, a cornerstone of biobanking ethics, extends beyond choosing an appropriate model—broad or dynamic—to other nuanced issues that need addressing in the training of researchers. These include managing consent upon a participant's death, involving children in biobanking, allowing for the withdrawal of consent, and handling samples used without consent (see the above table).

- The **death** of a participant can create ambiguity in terms of ongoing consent for the use of their samples. Guidelines differ globally: some suggest that consent should be presumed to continue after death, others advocate for re-consenting next of kin. Some authors suggest that ethics committee members should propose solutions in cases where there is no consensus. Proposals like that demonstrate the necessity of training in consent related issues (Ursin & Stuifbergen 2018).

- The **involvement of children** in biobanking raises questions about the age of consent, assent for younger children, and whether re-consent should be sought when children reach the age of majority (Casati et al. 2022, Berkman et al. 2018).

- The **right to withdraw consent** is a fundamental aspect of ethical research, and in biobanking. While the motives behind withdrawal can differ greatly

operationalizing remains complex despite the reasons, particularly if data or samples have already been used in research, (Steinsbekk 2022). Research must learn navigating between benefits for science and respect for autonomy.

- The **use of samples without consent**, often in the case of historical or residual samples, is another complex issue. This topic is common for teaching students about ethical challenges related to maintaining respect for persons while also recognizing the potential scientific value of such samples. It demonstrates how different ethical issues of biobanking are intertwined – as this case represent both – consent and issues of data sharing and privacy.

Data protection and sharing

Data protection:

Ensuring the protection of sensitive personal information is paramount in the field of biobanking. Personal information linked to biospecimens include genetic data, health records, and lifestyle information, which, if improperly handled, could potentially lead to discrimination or stigmatization (Kaye 2012). Thus, measures to de-identify personal data and employ secure data storage and transmission protocols are critical to minimize potential risks (Shabani et al. 2014). Safeguarding data against unauthorized access, misuse, and data requires robust security infrastructures and stringent protocols as well as emergency response plans in case of breaches (Dove et al. 2012). Methods for data protection involve use of secure data storage and transmission protocols, including the use of encrypted databases, secure servers, and secure transmission methods when data needs to be shared among researchers or institutions. Moreover, it requires preventing unauthorized access and data misuse, thus strict access control mechanisms, firewall protections, regular security audits, and training for staff members on data security procedures are required.
Lastly, data protection needs contingency or emergency response plans. These plans outline the steps that must be taken in case of a data breach, for example: notification of affected individuals and isolation of the breach.

Data Sharing:

The true potential of biobanking is unlocked by harnessing the power of big data. With the capacity to process vast and diverse datasets, big data techniques can reveal nuanced patterns and connections that would otherwise remain hidden, driving breakthroughs in understanding disease processes and developing novel therapies. Big data serves as the engine propelling biobanking to fulfil its purpose in advancing biomedical research and personalized medicine.
However, the question of data ownership in biobanking remains a complex issue, involving legal, ethical, and practical aspects. Generally, donors retain some rights over their samples and associated data, but biobanks also have responsibilities to steward these resources for the public good.
The rise of private biobanks has shifted the discourse to the commercialization of data, particularly human data. Although commercialization can catalyse innovation and propel the translation of research into healthcare benefits, it also raises ethical questions. The primary concern is not necessarily the operation of private biobanks, but the use of human data by private entities. Issues center on profit-driven motives, conflicts of interest, and the potential for data exploitation, all of which have stirred mixed public sentiments on the matter (Nicol et al. 2016).

The complex issues of data ownership and benefit sharing demand a comprehensive understanding of the associated legal, ethical, and practical aspects. The rise in private biobanks and subsequent data commercialization brings added dimensions of ethical considerations around profit motives, conflicts of interest, and potential data exploitation.

Incidental findings

The management of incidental findings, or unexpected discoveries that are beyond the objectives of the original research, poses significant ethical and practical challenges in biobanking (Lin et al. 2019).
The question regarding the **return of incidental findings** from biobanks pertains not only to the act of returning them, but also to discerning what findings should be returned to participants. High clinical relevance usually denotes that the findings carry significant implications for a participant's health and that actions can be taken based on them.
The results should be scientifically valid, confirmed, and bear clear health implications for the participant, however, the scope of what findings should be returned extends beyond these basics. Some ethicists lean more on moral duty to disclose such findings (Bredenoord et al. 2011), others rely more on case-by-case decision-making (Blasimme et al. 2020). It may depend on the nature of the findings, the preferences of the participants, and the capabilities of the biobank. Decisions depend on the urgency of the finding, the participant's current health status, and their ability to understand and act on the information.

The **BBMRI guide on incidental findings**:
https://www.bbmri.nl/sites/bbmri/files/Erasmus_MC_Handreiking_Interactieve_pdf_Engels_29_04_2020_V3.pdf

2.2.6 Useful resources to build training modules

- **Biospecimen research methods** is an online course designed to enhance the quality and reliability of scientific investigations https://www.edx.org/course/biospecimen-research-methods-6?index=product&queryID=d6e24a288dddf12308a514276dc47a8f&position=1

- **BBMRI-ERIC** (Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium) - is an international organization that provides resources and support for biobanking, including guidelines, ethical considerations, and educational materials https://www.bbmri-eric.eu/

- **Global Alliance for Genomics and Health** (GA4GH) aims to accelerate progress in genomics research by promoting data sharing, collaboration, and the development of ethical guidelines. URL: https://www.ga4gh.org/

- **HUGO Ethics Committee** (Human Genome Organisation) - provides resources and recommendations related to the ethical, legal, and social implications of genomics research, including biobanking.
  URL: https://www.hugo-international.org/committees/ethics-committee/

2.2.7 Applicability of the concept of compliance to biobanking

The concept of compliance is integral to the operation of biobanks. It involves adhering to a broad range of regulations and guidelines that encompass ethical standards, privacy and data protection laws, and protocols related to the acquisition, storage, and use of human biological materials and related data (Bledsoe 2017). One of the main advantages of compliance in biobanking is that it establishes trust and ensures the ethical integrity of the operations, providing reassurances to donors, researchers, and the broader community (Hofman et al. 2014). Further, compliance with legal and regulatory frameworks may shield biobanks from legal liabilities, thereby promoting their long-term sustainability (Chalmers et al. 2016).

However, there are also challenges associated with compliance in biobanking:

- **One primary issue is the complexity and diversity of regulations across jurisdictions**, which can make international collaboration and data sharing more challenging. Additionally, the dynamic nature of the field means that ethical guidelines and legal regulations frequently change, requiring continual monitoring and adaptation.

- **Compliance in biobanking also demands substantial resources**, which can pose difficulties for some institutions (Kaye 2011). Despite these challenges, adherence to compliance principles remains a responsibility for ethical biobank management.

2.2.8 Applicability of the concept of ethics-by-design to biobanking

The concept of ethics-by-design can be easily found in AI technology; however this is not the case in biobanking. After making a literature review in google scholar and PubMed databases– no relevant results were found. However, applying the principles to biobanking, in parallel to its use in AI, means embedding ethical considerations into the technology's development at an early stage. This proactive approach fosters trust with donors, researchers, and the public while preventing future ethical issues. It encourages collaborative research under common ethical norms and ensures regulatory compliance, mitigating potential legal and reputational hazards. Despite its significant advantages, practical implementation of 'ethics-by-design' in biobanking faces certain challenges that must be navigated carefully.

2.2.9 Most relevant EU or international guidelines or standards related to biobanking

- Recommendation of the European Council on biological material
- OECD guidelines on biobanks and databases
- CIOMS guidelines
- WMA Declaration of Taipei
- GDPR
- ISBER (International Society for Biological and Environmental Repositories) https://www.isber.org/page/BPR
- BBMRI-ERIC Common Service ELSI https://www.bbmri-eric.eu/services/common-service-elsi/
- Genomic Data Sharing (GDS) Policy (NIH)

2.3 Recommendations

2.3.1 Implement a standard consent model across EU member states

It is crucial to elaborate an appropriate consent model at the creation stage of a biobank. Ethical considerations should include the implementation of dynamic consent options, allowing biobank participants to object to specific types of research and providing a clear explanation of the scope of biobank research. To facilitate cross-border sharing of biobank resources and improve transparency in cross-border use of biobanks, there should be efforts to standardize consent model across EU member states and internationally (to avoid ethics dumping).

2.3.2 Address regulatory disparities between biobanks and secondary data use across EU member states

RECs need homogenized guidance at the EU level to elaborate reasonable but flexible requirements that do not hinder cross-border research projects and allow researchers to address regulatory challenges effectively at all levels. Biobank regulations are typically highly demanding, with ethics reviews common across European countries. In contrast, secondary data use initiatives have more permissive ethical review policies and optional governance. Policy makers should determine the circumstances under which biobank research could be exempted from ethical review to align with secondary data use initiatives. Specific criteria should be established to guide the regulatory distinctions, if any, between biobank regulation and other secondary data use initiatives. A coordinated and consistent approach to ethical review for various data initiatives should be implemented at the national and international levels.

2.3.3 Refine and homogenize the scope of reportable incidental findings

RECs should establish unified criteria for reporting incidental findings to subjects. To achieve this goal, the EU should devise and implement a coherent approach to determining the level of importance of incidental findings. In the short term, refining the scope of reportable incidental findings can be achieved by adopting one of the existing gene lists or by following a set of general criteria. This will help to determine the findings to be reported with a clear benefit for medical institutions and for subjects.

3. Genome editing (including both human and non-human applications)

3.1 Gaps in the current ethics review process of Genome Editing research at EU, Member State and non-EU state levels

The following subsections, **(A) address overarching aspects** (including some that are not specific to genome editing but can be fruitfully discussed with reference to this field of research and development and to discourse on its ethical, legal and societal issues, implications or aspects (ELSI/ELSA), then **(B) human genome editing** (including human enhancement), and finally **(C) non-human genome editing** (with a focus on gene drives).

3.1.1 Current ethical or regulatory gray zones

With regard to (A): Beginning with the ELSI activities in the **context of the Human Genome Project in the 1990s**, and subsequently with the emergence of nanotechnology as an important area of research funding, there are **increasing tendencies to embed applied ethics in broader philosophical analyses and to consider research findings and reflections from the cultural and social sciences more systematically**. One of the expectations associated with these efforts is that they will better enable the participation of actual and potential users in the research and development processes and in the discourse on their ELSI/ELSA and, in a broader sense, contribute to embedding the field in society. These tendencies should therefore also be reflected and taken up in the RECs, also with regard to their composition. Otherwise, important ethical and potentially also legal aspects of genome editing could be given too little consideration or even ignored in the work of RECs.

However, there are structural problems for RECs that already affect them in fulfilling their existing tasks:

- Leigh Turner has argued, for example, that: “national variations in laws, regulatory vacuums, gray areas in legislation, and under-resourced regulatory bodies create environments in which genome editing hype could fuel premature commercialization of purported therapies” and that, in order to prevent this outcome, **“ethical principles need to inform and be connected to regulatory frameworks”**. He pointed out that regulatory bodies also need “to have the capacity, in both financing and personnel, to uphold legal standards” (*Third International Summit on Human Genome Editing: Expanding Capabilities, Participation, and Access: Proceedings of a Workshop in Brief, 2023*).

- At the same event, Piers Millett summarized the results of a survey of national and regional laws and regulations, research ethics guidelines, governance frameworks, key institutions, informal policies, non-governmental initiatives, and approaches and practices related to genome editing (cf. Millet et al. 2023).

- One **crosscutting finding was that in some countries there is a lack of distinction in guidelines between somatic and heritable editing and between research and treatment (Millet et al. 2023)**. New rules and regulations are being developed, Millet reported, though most respondents felt

that somatic human genome editing was regulated in their countries. Challenges and potential shortcomings that were mentioned "included a need for key definitions, insufficient public consultation, and a lack of monitoring to detect illegal activities".

Another structural problem – this one with regard to the EU – is that, **while ethics already is an essential requirement in several areas, the requirements are often vague, and their effectiveness depends on diverse national implementation and oversight.** It has thus been argued that comprehensive EU action is needed to overcome this problem, by introducing a particular standard and allocating adequate means (SIENNA Project Consortium 2021).
In summary, governance reforms are needed in terms of structures, processes, and objectives.

With regard to (B): **As far as human applications of genome editing are concerned; we find ourselves in a somewhat paradoxical situation worldwide.** On the one hand, **largely conceptual or speculative ethical and legal deliberations on powerful genome editing technologies have been taking place for decades**, including the elaboration of governance-oriented guidelines. On the other hand, **the practical relevance of this work is still low**, for two main reasons: the still existing technical limitations and the structural problems of research ethics governance.

- As regards **germline editing regulation**, there is broad consensus that altering embryo DNA for reproductive purposes should remain forbidden (The Lancet 2023): a 2020 study showed that 75 of 96 surveyed countries have banned it. In the USA, use of funds by the FDA for the purpose of reviewing any application to begin a clinical trial for heritable germline editing is prohibited. While this, in effect, makes some reproductive editing illegal, it falls short of a ban on the practice itself. Moreover, ambiguities and exceptions exist in many countries, and many do not have effective oversight and governance mechanisms. There is a lack of policy alignment between countries, which allows scientists exporting their research to evade constraints established in their home jurisdictions. The UN may be able to deal with this issue and provide guidelines to prevent or mitigate these issues but did not act so far. In Europe, the Oviedo Convention, a legally binding instrument established by the Council of Europe, permits somatic genome modifications for preventive, diagnostic, or therapeutic purposes, and prohibits germline editing, but only 29 countries have enacted it into law.

- As regards **embryo research regulation** (Adashi/Cohen 2022), an extension of the 14-day rule for embryo research (which is legally binding in some countries) is under discussion since many years. The International Society for Stem Cell Research (ISSCR) relaxed its guideline on this limit in 2021. Therein, it is suggested that studies proposing to grow human embryos beyond the two-week mark be considered on a case-by-case basis, involving institutional or national bodies as well as extensive public engagement (*Guidelines for Stem Cell Research and Clinical Translation* https://www.isscr.org/guidelines; cf. Lovell-Badge 2021). Allowing embryos to grow past 14 days may improve understanding of human development and, e.g., provide knowledge why many

pregnancies fail. This also raises the question of whether or how RECs may have to decide on the importance of potential findings using genome editing in embryos and how public engagement or consultation activities are taken into consideration (depending of course on the national legislation, which can also be stricter than the 14-day rule). As one expert pointed out, the legal framework is very different from country to country, making international cooperation especially difficult:

- "In research with embryos or their modification through genome editing, the legal requirements are already different within Europe or the EU (e.g., UK, France, Germany) (and where permitted/possible, to my knowledge, the procedure and the requirements for ethical assessments are also different). Or in the USA, experiments with embryos or with the production of embryos are not publicly funded, but privately funded experiments are possible (and partly also further regulated at state level)."

- Since the main issue for European RECs will most probably be **risk assessment regarding somatic genome editing**, specific and more detailed guidance is needed for this application. Bittlinger et al. (2022) conducted an expert interview study to investigate the demands for a structured risk assessment approach to gene therapy/genome editing. They found that a risk assessment approach using case-sensitive (for every disease and patient population) mechanistic categories (e.g. germline transmission, insertional mutagenesis, epigenetic instability), complemented by further information (e.g. about validity of relevant animal models and long-term risks), is a suitable approach. Experts interviewed for this study pointed out that a risk framework should not be legally binding and may also have downsides like increasing the bureaucratic workload. Furthermore, a standardized approach may not be so helpful in a state of insufficient knowledge about risks, when uncertainty plays a big role, as in the case of new genome editing technologies, where other forms of toxicity not yet known could hypothetically emerge. The idea of risk assessment based on different types of mechanistic risk categories is already partly reflected in the "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products" of the European Medicines Agency (EMA). The Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP) adopted this guideline in 2018.

Although all risk assessments may use similar approaches in principle, **an important distinction to be made, in regulatory terms, is between clinical studies** (to obtain data on the effectiveness and safety) **of therapeutic approaches** (as are necessary for the approval of drugs, including gene therapies) **and experimental treatments or "compassionate use", i.e., if no approved, effective drugs are available**. While the former are clearly and extensively regulated (harmonized between e.g. EU, USA or Japan), national legal designs play a role in the case of experimental treatments or compassionate use, for example national exceptions under EU law.

- **The SIENNA project consortium** (2020) argued that setting up governance frameworks for experimental treatment using novel genomics and genetics technologies on a local level at each hospital is not feasible since there will not

be many cases. Even on a national basis a specially assigned monitoring and governance system would not have much to do. The SIENNA team therefore suggested that international organizations such as EMA, WHO, and OECD could play an important role and argued for setting up a Patient Ombudsman system.

- **A recent study (Millet et al. 2023)** aimed at surveying, documenting, cataloguing, and analyzing empirical information regarding regulatory capacity and governance approaches for somatic genome editing research interventions in China, India, Mexico, Nigeria, Singapore, South Africa, South Korea, Uganda, and Ukraine. The survey and analysis encompassed national and regional laws and regulations, research ethics guidelines, governance frameworks, key institutions, informal policies, and where applicable, approaches and practices relevant to the regulation of scientific innovation, clinical research, and technology adoption. It identified challenges and potential shortcomings: the need for greater clarity regarding differentiation between somatic human genome editing and heritable human genome editing, as well as between research and treatment, shortcomings in public consultation procedures, and a lack of information on enforcement of regulation. As was stated in interviews led for the IANUS project:
    - "The questions of the regulatory mechanisms and the regulatory assessment are very complex and even for ways that are already submitted to agencies. The different agencies work differently and are currently elaborating their processes of evaluation, but still the question is how long they will take to evaluate and if evaluation will be a one-time process or will go on continually. This can also be considered a grey zone because it is clear that we don't know exactly today what should need to be done as a regulatory framework tomorrow. The precise regulations still need to be elaborated. […]"

There are some reports on what the general framework of government should be, for example the 2021 WHO report:
https://www.who.int/publications/i/item/9789240030060

In these reports are general frameworks of government but no specific recommendation on what kind of bureau should get the file, what kind of evaluator should make the evaluation.

On the topic of human enhancement, the SIENNA project recently found that there are no guidelines for REC members, but that many of them would welcome such guidelines as well as additional education on the ELSI of human enhancement technologies. One problem, however, is that the distinction between therapy and enhancement is often difficult to make. Moreover, there are often 'dual use' (therapeutic and enhancement) options, although non-therapeutic enhancement of performance is mostly not yet possible at present.

With regard to (C): **Many potential human enhancement technologies are first tested on animals and the "enhancement" of animals for human purposes is an**

essential feature of our human relationships with them (Ferrari et al. 2010). **By approving of certain technological interventions in 'other animals'** – as the critical animal studies community and others call animals, in order to remind us of our biological kinship with them –, **RECs may thus also pave the way for human enhancement applications.** Moreover, in many parts of the world there are not only growing tendencies to rethink – for example in terms of the 'dignity of living beings' – the moral and legal status of animals (e.g. of great apes), but also attempts to ethically and legally redefine our relationship with plants (ECHN 2008) and with non-human nature as a whole. As far as the latter is concerned, several states around the world (e.g. Bolivia, Canada, Ecuador, India, and the US) have already granted 'environmental personhood' and thus the status of a legal entity to rivers in particular – but also e.g. to forests, a mountain, and 'Mother Earth' –, including one EU Member State (Spain with regard to the lagoon Mar Menor).

Such tendencies to weaken anthropocentrism in ethics and law and to create or strengthen 'rights of nature' may increasingly affect the work of RECs.

In addition to the agricultural use of genome editing in plants and in livestock, its use for the development of gene drive technologies is increasingly discussed. These technologies promote the rapid spread of a particular genetic element in a population of non-human organisms and can therefore potentially be used to control or eradicate animal-borne diseases, invasive species, and agricultural pests. The most frequently discussed and probably most researched aim is a modification of the mosquito population that leads to a sustainable global interruption of the transmission of malaria parasites. Key issues concerning gene drive technologies are the uncertain risks of these technologies, their advantages and disadvantages compared to alternatives, and what role humans should play in nature. Focusing on possible eradication strategies and on issues of global justice, fundamental critics (e.g., ETC Group 2019) use the Playing God argument to denounce these technologies as another instance of human hubris within nature and argue that they will further increase the power imbalance between populations in the global South and transnational corporations. These critics have also warned about potential uses of gene drive technologies for warfare, e.g., for attacks on the food production. **While the use of gene drive technologies for non-eradicative control of animal-borne diseases, invasive species and agricultural pests may merit less fundamental criticism, the emerging ethical debates about such uses of gene editing technologies are also controversial**, with disagreements, for example, over the following questions:

(1) whether uncertainty is a reason to refrain from field trials or to proceed with incremental testing to gain more knowledge given the disadvantages of the status quo,

(2) whether alternatives to control vector-borne diseases, invasive species and agricultural pests should be considered (un)feasible and (un)adequately researched, and

(3) whether the use of these technologies is compatible with the role of humanity in nature (de Graeff et al. 2021).

There is broad consensus, however that any use of gene editing technologies must not be conducted without the informed consent of the affected local communities and inclusive participatory approaches. It has, for example been argued that it "is essential to include field-site practitioners, stakeholders and community leaders in the academic conversations and debates surrounding these subjects" and that "new value needs to be placed on reaching these voices and creating a space for sharing their knowledge and prioritizing their perspectives" (Kormos et al. 2022). Without this, it was argued, the guidelines and recommendations for gene drive technologies presented by the academic community and funders and institutions from the global North will fail to meet the ethical goals and commitments they want to achieve.

As regards legal gray zones, in the EU, Directive 2001/18/EC regulates under which conditions genetically modified organisms (GMOs) may be released into the environment. The generation of any organisms with a synthetic gene drive by current techniques (mainly genome editing) results in a GMO. According to the Directive, any release of a GMO requires authorisation – which may only be granted if prior risk assessment indicates that the release will not have harmful effects on human health or the environment. However, some EU Member States see weaknesses in their current national regulation on the contained use of organisms modified with gene drive technologies (i.e., for experiments in closed research facilities) in that the specific characteristics of these organisms should be considered on a case-by-case basis. Currently, the risk classification and containment measures in use are tailored to GMMs (genetically modified microorganisms) (EC 2023).

The UN Convention for Biological Diversity (which is, in principle, legally binding for the countries which signed it) negotiated gene drives in 2018. There is currently no global moratorium on gene drives, but 196 countries agreed on strict rules on the use of gene drives. A final agreement emphasized uncertainties inherent in the use of gene drives and called for caution with regard to experimental research. Case-by-case risk assessments should be carried out and risk management measures put in place to minimize potential adverse effects. **Organizations seeking to release gene drive organisms should also obtain the "free, prior, and informed consent" (FPIC)** of potentially affected communities. FPIC is a specific right that applies to indigenous peoples and local communities and is recognized in the United Nations Declaration on the Rights of Indigenous Peoples (UNDRIP). According to critics such as the ETC Group, FPIC is often ignored, or members of communities are manipulated. A recent review found ten key guideline documents on gene drive risk assessment, but many do not prescribe engagement of local communities and thus lack an important element (Hartley et al. 2022)

3.1.2 How to ensure the most satisfactory or effective approach to ethics review in genome-editing research

With regard to (C): For the evaluation of gene drives, **an ideal process that is satisfactory to all stakeholders requires input from end-users and stakeholders. This requirement has not yet been met**, as global frameworks, standards and guidelines have been written with too little input from end-users and stakeholders (Kormos et al. 2022, Hartley et al. 2022). **There is no successful stakeholder**

consultation process in practice, nor are there good practices for case-by-case integrative assessment.
The participatory aspect needs to be strengthened to prevent premature use of the technology, to raise awareness of the vulnerability of research participants and to adequately consider the needs and concerns of potential users. The latter should have opportunities to engage with regulators and RECs to discuss knowledge gaps, and researchers may even be required to consult potential users prior to commencing research. Scientists should also be encouraged by RECs to engage more with the public, especially with underrepresented voices (such as disabled people and patient organizations).

3.1.3 Choosing an ethics evaluation model for genome-editing

With regard to (B): **As regards human genome editing, compliance checks have their weaknesses and limitations in a still evolving legal framework**. Whether a one-off assessment or a continuous assessment is more appropriate might depend on the specific application and is still under discussion in RECs, according to one consulted expert. Another expert advocated for continuous assessment, anticipating that certain technical issues with ethical implications will likely be resolved in the near future. This expert also emphasized the importance of prioritizing ethics by design. The latter, however, would also need to be continuously updated; there is also a risk that the current ethics by design discussion will focus on the costs of new therapies, which could have negative consequences for patients. As regards non-therapeutic human enhancement through genome editing, it is far too early to discuss these issues, as activities with this explicit aim would not be accepted by any REC. For a possible 'dual use' where a therapeutic technology is used for mere enhancement or other wish-fulfilling purposes, compliance checks may be appropriate in addition to the evaluation at the start.

With regard to (C): **Since gene drives can lead to unexpected, unintended, and harmful impacts, an ongoing assessment would be most appropriate**. However, such effects may eventually be irreversible, so this approach can be inadequate depending on the exact technology. Gene drive neutralising systems are currently being developed, but their effectiveness in nature is uncertain (Bier 2021). It has also been criticized that contemporary gene drive technology development is guided by a specific, intervention-oriented, form of coproduction (Boersma et al. 2023) and that the perspective should be broadened by addressing empirical, moral, and ontological concerns explicitly, in parallel and in their interplay rather than in disciplinary isolation from each other.

3.1.4 Reflective and anticipatory research on genome-editing

With regard to (A): **To make ethical analysis and work more reflexive and anticipatory, the above-mentioned embedding in a broad range of disciplines should be encouraged.** Ideally, RECs themselves would have the necessary expertise. However, as the structural problems may not be overcome in the near future, at least not in all countries, mitigating measures should be considered. These could include, for example, regular training activities on conceptual and empirical research in areas such as disability studies, citizen science, cultural studies, science and technology studies (STS) and technology assessment. The design of such activities should take into account the often very limited time resources of REC members and

thus provide incentives for REC members to participate in them, for example by combining them with work on interdisciplinary publications of interest to REC members. In general, they could be designed as high-level academic and thus not purely training activities. Reflection and anticipation should be enabled through such activities, ideally in parallel with stronger incentives for responsible research and innovation for scientists and technology developers. Another, less resource-intensive option would be for each REC to have an advisory group (or network of advisors) with the broader expertise required, which would not be involved in the usual work processes of the RECs but could be consulted as needed.

With regard to (B): **The participatory aspect in genome editing research needs to be strengthened to prevent premature use of the technology, to raise awareness of the vulnerability of research participants and to ensure that there is a medical need from the patient's perspective** (and that there are no less risky and costly alternatives that could be explored first). The saviour attitude towards disabled or sick people should be systematically curtailed, which requires, above all, constant involvement of future potential users at all levels that interest them. Participant-centred consultation (Kleiderman and Ogbogu 2019) would allow patients and participants to engage directly with regulators and RECs to discuss knowledge gaps that would enable better engagement in such research. Researchers working in innovative or pioneering areas of clinical research could even be required to secure and demonstrate such consultation prior to commencing research and as a condition of ethical approval. Furthermore, the general public needs to understand these technological developments and the work of RECs should take this into account. Scientists should also be encouraged by RECs to engage more with the public (Birney 2023), especially with often neglected voices (such as disability and patient organisations, parents with genetic predispositions and genetic counsellors). REC members should be aware, and ideally themselves have intimate knowledge, of the mechanisms and drivers of the use of genome editing and related technologies by the global fertility industry. This is necessary to ensure that RECs can support the research community in applying the precautionary principle to specific research directions with dual benefit potential (e.g., therapy of life-threatening diseases vs. selection of desirable traits). With regard to the issue of human enhancement, the above steps would be even more important, as research and development aimed at non-therapeutic enhancement and overcoming disabilities could increasingly stigmatise people with disabilities and have a negative impact on public investment in other inclusion measures. Moreover, in the longer term, such research and development activities may exacerbate socio-economic inequalities in general. Consideration of such social aspects should be systematically included in any work undertaken by the RECs in relation to developments relevant to this topic.

With regard to (C): Genome editing in animals that is not explicitly planned as animal modelling for later applications in humans but focuses on capabilities and traits of the animals themselves – so-called **'animal enhancement'** (e.g., Ferrari et al. 2010) **should never only be evaluated with a view to animal suffering during the research and developments activities and the later use of the technologies in animals but also always with regard to what the technologies may mean in terms of possible future applications in humans**. Furthermore, certain non-human application ideas can be questioned with regard to the dignity of non-human living

beings. In the case of non-human applications of genome editing in agriculture or gene drive technologies, anthropocentric approaches can also be critically reflected upon. Here, RECs could increasingly incorporate or at least use expertise from environmental sciences, critical animal studies, philosophy (beyond applied ethics), legal studies on animal rights and environmental personhood, and science and technology studies (STS). In relation to gene drive technologies, co-development of research designs with local stakeholders is needed to harness local expertise and gain community acceptance. The risks and benefits should be communicated transparently and honestly to local stakeholders. If local communities prefer other measures for the same purpose, this should be respected. Risk assessment procedures need to be developed on a case-by-case basis.

3.2 Needs to inform development of training materials and awareness actions on genome editing

3.2.1 Most relevant current ethical issues and concerns: training and awareness needs

Safety issues:

- **Off target effects**: DNA is edited at a position that was not intended to be edited which can cause unwanted gene expression in the subject. In case of germline editing, it can lead to the development of inheritable illnesses (Guo, Ma, Gao et al 2023).

- **On target effects**: the DNA is altered in the wrong way at the target region. Usually, these effects consist of unwanted deletions or insertions (Lee, Kim 2018).

- **Mosaicism**: “Genetic mosaicism is the presence of more than one genotype in one individual. […] it can result from manipulative mechanisms such as genome editing.” (Mehravar, Shirazi, Nazari et al 2019). Some cells in the target region are edited while others still carry the original DNA. That can lead to problems in communication between cells.

- **Germline gene editing:** modifications in the germline can change the human genome in a heritable way. If these modifications turn out to be harmful, they will have not only consequences for a single individual, but for future generations as well (Palazzani 2023).

Issues concerning informed consent:

- **Gene editing in an embryo** could ensure that the subject won’t have to suffer from a heritable disease. On the one hand, an embryo cannot give consent to this procedure. On the other, parents can take over the decision as they already do with many other aspects of a child’s life (Collins 2015).

- **Germline gene editing** can affect future generations without their consent. The risks being unknown, it might anyway be difficult to give an informed consent to it.

Justice and equality issues:

- **Therapies involving genome editing** are costly and may thus be restricted to mostly wealthy patients or citizens in countries with corresponding health insurances or social security systems. The treatments in question, which are already undergoing clinical trials for marketing approval in the EU and the US for certain diseases, are likely to cost no more than the (already very costly) conventional gene-based therapies used for rare genetic diseases, or in the case of CAR-T cells, for certain leukemias/lymphomas (Chan 2018, Palazzani 2023). If provided to a larger number of citizens, they may push healthcare systems, even in wealthier nations, to their limits, resulting in decreased resource availability for other patient groups.

- **Benefit sharing** becomes a concern when gene editing relies on particular resources. This dynamic could lead to a divide between affluent and less prosperous nations. For instance, if gene editing is employed to develop climate-resistant crops, the presence of a patent could bar poor countries from utilizing them. This potential scenario might result in famine for those nations, while wealthier ones could employ the modified crops for survival (Smyth, Macall, Phillips et al. 2020).

Human enhancement:

- **The application of genome editing for enhancing the human body and brain** raises numerous ethical concerns, encompassing issues of accessibility, safety, the concept of 'designer babies,' potential discrimination against non-enhanced individuals, and long-term effects (Bostrom, Roache 2008). Some ethicists worry that gene editing, initially aimed at therapy, might lead to **non-therapeutic enhancements**, sparking controversy. On the other hand, some argue for the moral duty to use gene editing to eliminate hereditary diseases (Savulescu, Pugh, Douglas et al. 2015).

- In the realm of enhancement, there's a notable concern about **children being subjected to parental experimentation** without their informed consent. This procedure carries significant risks and the weighty implication of biological predetermination, profoundly impacting their entire lives. This imposition risks limiting their potential for an open and self-determined future (Palazzani 2023).

- The rise of genetic enhancement poses a significant ethical dilemma: the potential for societal **pressure to enhance** (Palazzani 2023). If we view genetic enhancement as ethically acceptable, there may be a moral urge to optimize a child's genetic potential right from the start. This might lead to an expectation for all parents to engage in enhancement measures, ensuring their children can effectively navigate a world filled with enhanced individuals. However, for this expectation to be fair, access to enhancement must be universally available to prevent favoring the privileged. Moreover, the necessity of in vitro fertilization for enhancement adds complexity, potentially steering parents in this direction. This situation may inadvertently lead to difficult decisions about pregnancy

termination or embryo selection if enhancements are unsuccessful. Finally, widespread availability of enhancements might unintentionally foster a societal intolerance for imperfection, intensifying the pressure already faced by parents (Palazzani 2023).

- If gene editing becomes widely available, there's a risk of selectively enhancing desirable traits and suppressing undesirable ones. This could reinforce social divisions and possibly lead to **eugenic drifts** (Palazzani 2023).

Other issues related to Human applications:

- To develop and improve methods of germline/heritable gene editing, **research on human embryos** is necessary (unless editing can in future be performed and verified through generating germ cells in vitro). This leads to moral objections from people because the embryos will be destroyed when being taken for research. **Producing embryos to use them for research** is also commonly frowned upon. If the moral status of an embryo is not agreed on, some people will categorically be against research on human embryos (Simon 2002).

- **Genome editing** has the potential to be used not only for civil purposes, but **also for military purposes, dual use or misuse**. It might be used to design a biological weapon or to destroy the crops of an enemy (see section 3.2.5). An effective regulation of this potential use of the method is difficult, so there is the risk that some countries might develop powerful weapons with the help of gene editing methods (Mir, Wani, Akhtar et al, 2022).

Ethical problems in non-human applications:

- Genome editing can be used to propagate a particular suite of genes throughout a population of plants or animals. This technique of **gene drive** can cause massive changes for populations and ecosystems. Unforeseen changes, potentially risky for various species, including humans, may result from gene drive. This risk is difficult to accurately gauge (Kormos, Lanzaro, Bier et al. 2022)."

- Gene editing could help bring back extinct species as well as it could help to fight off invasive species. This however could imbalance the ecosystems which can have **devastating consequences on diversity or the protection of species** (Then 2020).

3.2.2 Core scientific concepts that must appear in a short lecture

- **CRISPR/Cas9-based tools**: CRISPR/Cas9-based editing tools are often used for genome editing because they can be easily programmed to specifically recognize a DNA target sequence The Cas9 nuclease and genetically engineered versions of it (such as base editors) make double and single strand breaks, respectively, at the target sequence, that are instrumental in initiating various DNA changes, such as small deletions, inserions of gene sequences or changing DNA bases (Asmanaw, Zawdie 2021).

- **Off-target effects**: see safety issues in 3.2.1
- **On-target effects**: see safety issues in 3.2.1
- **Mosaicism**: see safety issues in 3.2.1
- **Gene drive**: see ethical problems in non-human applications in 3.2.1

3.2.3 Additional highly relevant topics for ethical analysis in a full-day training course

- Stem cells and genome editing: the risks and benefits of working with embryonic stem cells, induced pluripotent stem cells, adult stem cells and their potential for different types of research would be a relevant topic for ethical analysis in a full-day training course.
  Stem cell research can be used to generate models to study gene function and/or mechanisms of human diseases. The generation of germ cells (sperm, egg cells) from stem cells, including iPCS ("In vitro gametogenis"), would offer the possibility to proceed to germline interventions and their verification in such germ cell lines.
  There are **three main types of stem cells**, embryonic stem cells, induced pluripotent stem cells and adult stem cells:
  - **Embryonic stem cells** derive from human embryos at very early human embryonic stages which get effectively killed when their cells are being taken away for research purposes. This is considered unacceptable by some people. Embryonic stem cells can either be omnipotent or pluripotent depending on the developmental stage the embryo was in when the cells were harvested.
  - As an alternative to embryonic stem cells, **induced pluripotent stem cells** derive from somatic cells which get to be reprogrammed. Because one can use any type of somatic cell for the reprogramming, induced pluripotent stem cells are considered less ethically questionable than embryonic stem cells. However, there is currently no way to make these types of stem cells omnipotent, so some research might not be achievable with induced pluripotent stem cells which would be achievable with omnipotent embryonic stem cells.
  - **Adult stem cells** can be found in some adult organs such as the liver and they are mostly multipotent which means that they can only differentiate into certain types of cells. This makes them less valuable for certain types of research. They are not considered controversial if they are harvested from adult tissues with the informed consent of the patient (Lo, Parham, 2009).

- Genome editing research can involve the **use of fetal tissues for research**: instead of stem cells, fetal tissues are sometimes used for research purposes. This is controversial because fetal tissue is most obtained after an abortion or when an embryo had been grown in the lab and then killed. As the latter form is illegal in most countries, usually fetal tissue comes from aborted embryos (Wadman 2015).

- **Genome editing in organoids** (see also Hybrida project on this issue): organoids are models of a human organ which can be grown in a lab. They are used to study the effects of different drugs on the organ and give a better insight into how the organ works. They are usually grown from stem cells.

- **Genome editing and embryoids**: embryoid bodies or “synthetic embryos” are used for researching early human development. They are stem cell-based models for human embryonic stages and embryonic development. Embryoids are so far not able to grow beyond early embryo stages. Some people fear that they might one day be able to grow into a human upon transfer into a woman’s uterus which would make them babies that are not derived from sperm and egg cells (Nicolas et al., 2021).

- **Xenotransplantation** is the use animals for growing human organs which can then be used as transplants: Xenotransplantation is used to address the shortage of organ donors. The organs of certain animals (often pigs) are altered with the help of genome editing and when the animals are fully grown, they are slaughtered, and their modified organs are used as transplants (Rollin 2020).

- **Genome editing and reproductive technologies:** there are numerous reproductive techniques and prenatal diagnostics that can help parents to have a healthy child. However, all these technologies can potentially harm the baby or the embryo, although in-vitro gametogenesis could avoid this issue (though for humans still a 'future scenario'). Apart from that, some people frown upon reproductive technologies and prenatal diagnostics because they fear that it can lead to babies by design and to more abortions if a risk for a certain disease is found (Kaye 2023).

3.2.4 Key uncertainties concerning genome editing at this time

- **Technical uncertainties:**
  - Will we be able to eradicate off target effects eventually?
  - Will we eventually be able to edit all cells of a living organism in its adult phase of life?

- **Uncertainties concerning the genome itself:**
  - Scientists are still trying to understand which gene plays which role in the human body.
  - The human genome carries approx. 20 000 to 25 000 different genes with two different copies of each gene.
  - Genes sometimes have multiple roles in processes of the body and most processes involve multiple different genes. That is why scientists are only beginning to understand how the human genome works.

- **Uncertainties concerning epigenetics and gene regulation:**
  - Various molecular mechanisms determine how, and which genes are expressed or silenced during development, in disease or in response to environmental cues.

- From the 20 000 to 25 000 different genes that every human has two different copies of, not all of them are active at the same time.
- How epigenetic and other gene regulatory mechanisms control genes and gene networks under these conditions is not sufficiently understood to make predictions on all possible effects of a given intervention or "edit" in the genome.

3.2.5 Fundamental dilemmas related to genome editing

Dilemmas related to genome editing can be broadly divided into two categories: concerning human applications and concerning non-human applications.

Dilemmas regarding human applications of genome editing:

- **Germline gene editing** aims to allow certain couples to have a child free from severe genetic diseases. It becomes crucial in cases where couples, due to genetic mutations, face challenges in conceiving healthy embryos through conventional means or preimplantation diagnostics. Nevertheless, the long-term risks of germline manipulation remain uncertain. Errors in this process could have far-reaching consequences for future generations, which may only be rectified if none of these individuals ever have children of their own.

- There is **a risk of misuse in gene editing that may be enabled by research on well intended applications**. Its applications range from studying pathogens to potentially creating more hazardous biological weapons, manipulating the human microbiome, weaponizing gene drives, developing super soldiers (Paris 2023), or being exploited for sports doping. This is a significant concern that may persist as long as knowledge about gene editing is readily accessible.

- The **dilemma of resource allocation** poses questions about the development of extremely expensive therapies. Should they be pursued if healthcare systems are unlikely to reasonably afford them, potentially leading to reduced healthcare for other patient groups? Such decisions may require cost-benefit analyses, factoring in potential savings in lifetime treatment costs for genetic illnesses.

- Another dilemma centers on **the ethical and societal implications of using advanced medical interventions to eradicate or prevent milder, non-life-threatening disabilities.** While individuals may benefit personally, concerns arise about the broader societal impact and how it may affect those already living with disabilities. This raises questions about inclusivity, diversity, resource allocation, and the rights of individuals with disabilities. Balancing individual autonomy with societal well-being is at the core of this dilemma.

Dilemmas regarding non-human applications of gene editing:

- Gene editing can be used to save **some species from extinction, and it can also help to de-extinct species** which are long gone. This however could lead to a mass **extinction of species that are still alive today** if a species that is saved from extinction is the cause for the extinction of the other species.

- **Gene drives,** intended to eliminate disease-carrying organisms, can **inadvertently alter the environment and/or biodiversity**. For instance, if a specific mosquito, known for carrying malaria, is targeted for elimination through gene editing, it could disrupt an entire ecosystem. This mosquito may be a food source for a bird that plays a role in pollinating certain flowers, which in turn are food sources for various insects. Eradicating the mosquito could unintentionally lead to the collapse of this ecosystem.

- **Gene drives may be used as weapons.** For training purposes, one may refer to the example of **DARPA's *Insect Allies* project**: the DARPA *Insect Allies* project aims to protect mature plants from rapidly emerging threats to secure the US crops. The insects and the plant viruses they transmit are used to bring modified genes to plants. The program involves three technical areas: viral manipulation, insect vector optimization and selective gene therapy in plants (https://www.darpa.mil/program/insect-allies). However, it can also be used to specifically target an enemy's crop.

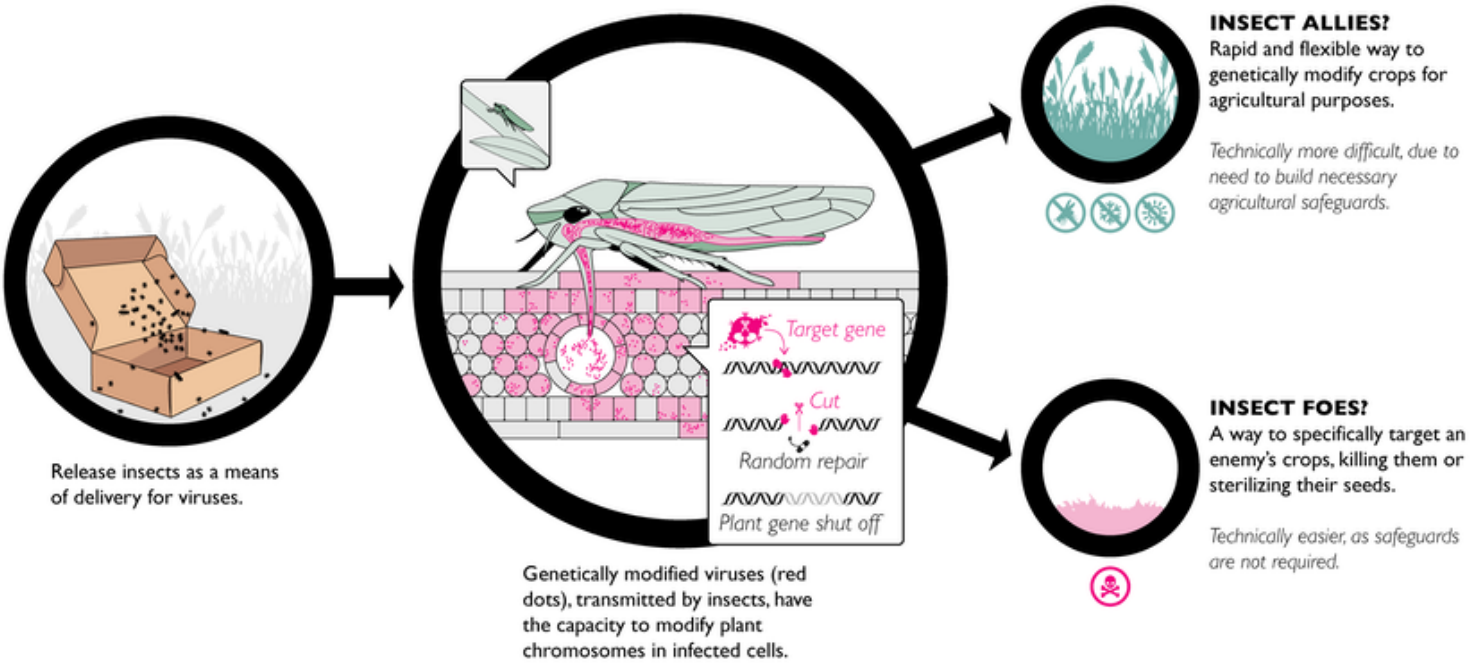


Figure 1. Insect Allies overview (Derek Caetano-Anolles, 2023)

3.2.6 Useful resources to build training modules

- UK Genetic Technology (Precision Breeding) Act 2023 : https://www.legislation.gov.uk/ukpga/2023/6/contents/enacted
- Association for Responsible Research and Innovation in Genome Editing (ARRIGE): https://www.arrige.org/
- European Parliament, Directorate-General for Parliamentary Research Services, A Nordberg, et L Antunes. *Genome editing in humans – A survey of law, regulation and governance principles*. European Parliament, 2022. https://doi.org/10.2861/07058.
- The Nuffield Council on Bioethics ethical review on genome editing: this document gives a good overview of the technique of gene editing as well as the

ethical and legal questions surrounding it. From the examples given, there could be case studies being developed https://www.nuffieldbioethics.org/assets/pdfs/Genome-editing-an-ethical-review.pdf

- The Nuffield Council on Bioethics social and ethical review on genome editing and human reproduction: very helpful background information on the topic of gene editing which can be used for designing case studies or other kinds of training modules https://www.nuffieldbioethics.org/assets/pdfs/Genome-editing-and-human-reproduction-report.pdf
- A case study from The Royal Society about gene editing in human embryos: https://royalsociety.org/-/media/policy/projects/gene-tech/case-studies-keywords/case-study-genome-edited-human-embryos.pdf
- A case study from The Royal Society about non-heritable human genome editing: https://royalsociety.org/-/media/policy/projects/gene-tech/case-studies-keywords/case-study-non-heritable-genome-editing.pdf
- An overview of success stories related to gene editing and can be used for real life examples for what gene editing can and can't do: https://media.nature.com/original/magazine-assets/d41586-021-02737-7/d41586-021-02737-7.pdf
- This article reflects on the fundamental ethical dilemma of using gene drives in mosquitoes and its possible effects on people in Africa: https://www.sciencenews.org/article/gene-drives-mosquito-malaria-crispr-africa-public-outreach
- This article discusses the events involving the birth of the first human babies who were genetically edited by a Chinese researcher to be resistant to HIV. Despite the researcher's intention to protect the babies from HIV, his actions were against the law according to the Chinese government and the scientific community. As a result, he was imprisoned. Nevertheless, the babies are currently alive: https://www.science.org/content/article/did-crispr-help-or-harm-first-ever-gene-edited-babies

3.2.7 Applicability of the concept of compliance to genome editing

In the realm of gene editing, the principle of compliance prevails, with the notable exception of He Jiankui's gene-edited babies (as discussed in "Did CRISPR help or harm the first-ever gene-edited babies?" https://www.science.org/content/article/did-crispr-help-or-harm-first-ever-gene-edited-babies).
Scientists are obliged to adhere to the guidelines established by their nations or international regulatory bodies. Compliance serves as a pivotal advantage, seeking to bolster security for both individuals and the environment. Through compliance, all participants engaged in gene editing can trust that their counterparts will uphold the legal protocols governing this practice. Yet, a significant challenge within compliance lies in consistently training all involved parties, as there exists a perpetual necessity to reinforce their responsibilities and commitments. Thus, everyone contributing to gene editing must undergo regular updates regarding the laws and regulations that govern the field. This ensures a clear understanding of permissible actions and those that remain prohibited. However, in some countries, a drawback of this approach arises from vague or rapidly changing regulations.

3.2.8 Applicability of the concept of ethics-by-design to genome editing

Applying ethics-by-design to genome editing involves interdisciplinary discussions. This method adds ethical awareness to scientists working on genetic modifications, prompting careful thought about potential moral implications. Deliberating consequences encourages cautious action and may discourage risky ventures. However, overthinking outcomes and technical details might hinder practical progress, causing delays and unnecessary suffering for those needing swift genome interventions.

3.2.9 Most relevant EU or international guidelines or standards related to genome editing

- WHO guidelines:
  - Human genome editing: recommendations : https://www.who.int/publications/i/item/9789240030381
  - Human genome editing: a framework for governance : https://www.who.int/publications/i/item/9789240030060
- The EU has a survey of law, governing and regulation principles:
  - https://www.europarl.europa.eu/RegData/etudes/STUD/2022/729506/EPRS_STU(2022)729506_EN.pdf
  - https://www.europarl.europa.eu/RegData/etudes/IDAN/2022/690194/EPRS_IDA(2022)690194_EN.pdf (in agriculture)
- The National Academies published a consensus study report: https://nap.nationalacademies.org/catalog/25665/heritable-human-genome-editing
- A good overview of regulations in countries and regions can be found here: https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org
- Overarching principles of EU primary law: Precautionary Principle, art. 191 para 2 TFEU
- Identification and clarification of legal problems concerning the contained use of genetically modified micro-organisms, Dir 2009/41/EC
- Identification and clarification of legal problems concerning the deliberate release into the environment of genetically modified organisms, Dir 2001/18/EC
- Overarching principles of EU primary law (e.g. Charter of Fundamental Rights of the EU ECHR)
- European pharmaceutical law (e.g. Reg Nr. 1394/2007 EC)
- Enhancement: Reg 2016/679/EU (GDPR)
- 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

3.3 Recommendations

3.3.1 Consistently train ethics experts to distinguish between different subcategories and applications of genome editing

To improve competence and to formulate relevant and operational recommendations for researchers, ethics experts should be trained on complex use cases to evaluate the relevance and limits of projecting human qualities, including moral values, on non-human biological systems. This particularly applies to projects involving plants and animals. Anthropomorphic projections may remain relevant for projects involving

genome editing in animals if there exist of foreseeable future applications in humans ("animal models").
Ethics evaluators should be trained to consistently distinguish the applications of genome editing to different types of biological systems (plants, animals, or humans), between the types of genome editing (heritable or not), and the types of cells involved (somatic cells, stem cells, embryonic stem cells). Further, ethics evaluators should be trained to reflect on the complexity of moral 'gray zones' in research projects operating at the therapy/enhancement frontier.

3.3.2 Case-by-case approach to gene drive experiments

For the test of gene drive technologies, risk assessments should be carried out and risk management measures put in place to minimize potential adverse environmental effects. These procedures should be devised on a case-by-case basis depending on the purpose of research and the type of genome editing involved. In particular, organizations seeking to release gene drive organisms should obtain "free, prior, and informed consent" (FPIC) from potentially affected communities, including for tests in the Global South. REC members should also consistently evaluate the accessibility of genome editing technologies striving for fair benefit sharing.

3.3.3 Highlight policy differences between countries, including EU member states

Both human genome editing and genome editing in plants or animals are regulated at the national level as well as at the international level, resulting in a lack of policy alignment between countries. While it is unrealistic to achieve a common international homogenous policy framework, ethics experts should be aware of the differences and of the risk of ethics dumping. When evaluating research projects, they should - whenever possible - apply a unified standard science-based approach based on standard use cases. If important differences arise because of regulatory discrepancies, ethics experts should explicitly inform researchers and policy makers about such differences.

4. Extended reality (XR)

4.1 Gaps in the current ethics review process of extended reality research at EU, Member State and non-EU state levels

4.1.1 Problems encountered by REC members in ethics assessment procedures

This paragraph will illustrate the challenges encountered by members of RECs in ethics assessment procedures through the example of a research **with humans using a 3D smartphone/internet application to view possible changes in areas of their city and eventually incorporate new ideas in city planning**. The aim was to oversee the use of the application and receive feedback from users to inform planners and promote the application to involve citizens in city planning.

Although there was **no use of VR hardware**, questions were still raised as to the extent of personal data collection and subsequent issues of privacy and confidentiality. Although not the case in the specific application, it was still unclear whether future applications of such software would be able to gather sensitive personal data (e.g., biometrics) or bystander data (e.g., images). External expertise was not necessary in this case, but members lacked the technical knowledge to appreciate the potential of such applications.

Generally, **experts feel that they lack full understanding of the inner workings and the potential of XR technologies. Particularly when XR is combined with AI**, experts feel that more technical information is needed to appreciate the ethics issues that could be involved in such applications. For instance, it is unclear how algorithmic sequences can be evaluated in terms of creating bias or, whether sensitive data can be extracted, or even, whether collection of masses of anonymized data can lead to eventual identification of individuals.

Another expert mentioned the **gaps regarding immersive technologies that can be applied in medical areas.** For instance, VR headsets that can potentially be used for trainings or medical applications. Here, as described by the expert, immersive technologies are not regulated, and the risks are often downplayed. This stems from a disregard of these technologies as being more than just for gaming as well as the unknown outcomes on humans. Within ethics committees in the medical area, the specific medical perspective is traditionally the focus, and this makes the ethical reflection of such new technologies difficult, for instance regarding ethics complaints. Therefore, **challenges in this area revolve around the basic understanding (and even trying out) of immersive technologies by the ethics committee members**, the potential long-term risks as well as taking these technological applications seriously within the medical field.

4.1.2 Current ethical or regulatory gray zones

There are **many potential cases and applications of XR technologies** that fall in an ethical grey zone in the current understanding. The following are possibilities that have been discussed with experts and in the project **XR4Human** (https://xr4human.eu/):

- The main issue related to XR data relate to concerns regarding **breach of privacy and confidentiality**, the **volume of data extracted**, and **lack of clarity in language or jargon** when information is shared.

- Moreover, **users of immersive technology may experience physical world re-entry problems** due to issues related to virtual embodiment (Behr et al., 2005; Lee & Hu-Au, 2021; Luro et al., 2017; Madary & Metzinger, 2016; Slater et al., 2020). Certain virtual environments and especially embodiments in VR can induce changes of one's attitudes during or after the experiment (Madary & Metzinger, 2016). Changes of perception after re-entry into the physical world also affect decision making by the participant due to a false sense of or loss of agency (Madary & Metzinger, 2016).

- At the **societal level**, there are concerns regarding discrimination against vulnerable and marginalised populations such as those with mental illness and children. Of additional note is the lack of access and representativeness for persons with varying levels and types and degrees of disabilities. In addition, users of immersive technologies may experience a sense of not belonging, especially true for users of the Metaverse.

- From a **psychological perspective**, the **welfare of children using immersive technologies** is widely discussed, with children identified as the most vulnerable group. Immersive technologies may incorporate nudges and control the social interactions of individuals in the virtual space, whereby children are particularly amenable to such controls.

- Furthermore, AR applications raise concerns about reasonable expectations of **privacy in public space**, as they cannot only record audio-visual information, but also process and aggregate data about a user's surroundings in real time (with the so-called passthrough capabilities of recent headsets). This information gathering may present special considerations for bystander privacy, especially when government and law enforcement use the technology.

- The **use of immersive technologies within the workplace** is also a grey area (Fox & Thornton, 2022). There has been increased use of immersive technologies in workspaces, and attention needs to be placed on the impact (positive or negative) on these spaces. If the technology is not inclusive of all workers, then this raises ethical concerns. Current commercially available XR tech may only be comfortable to wear for about 50–60% of the population.

- Finally, there is concern about an **increase in crime** (real or virtual). Crime is discussed in the context of whether a crime in the real world would be considered a crime in the virtual world. For example, rape or other forms of virtual assault/violence on an avatar. On the other hand, there are concerns about actual cybercrimes such as fraud, identity theft, stalking and hacking.

4.1.3 How to ensure the most satisfactory or effective approach to ethics review in extended reality research

There are **few XR applications that have gone through ethics reviews at present**. The focus has been on hardware development, and it appears that interoperability issues limit the extent to which data can be commonly exchanged. But the grey ethics issues described above will certainly come into play with the continuous developments in the field.

The current standard constitution of RECs, whether in the biomedical or social sciences fields, **lacks expertise in XR**. For many cases, this would be no significant problem as e.g., data protection, privacy, and confidentiality in XR, appear to be common issues with other technologies.
More difficult **issues that require additional expertise are the involvement of children**, **perception of reality**, **work training** and even **cybercrime**. The ideal ethics approval process would require expertise in relevant fields that are not standard in current RECs.

4.1.4 Choosing an ethics evaluation model for extended reality

Experts believe that ethics-by-design is the preferred mode of ethics evaluation in XR research. The current state of a one-time evaluation followed, perhaps, by compliance checks, is satisfactory as it allows for a one-fit-all approach. This would also include a continuous reexamination and reidentification of risks. For instance, adhoc members within ethics committees could bring in expertise from developers (industry) and users. This would be an ethics-by-design perspective on ethics reviews themselves.

Further, this is also important regarding evaluations of projects in big research programmes, like the Horizon Europe. Such programmes involve thousands of projects that require ethics evaluation and would be impractical to have a case-by-case evaluation process. Smaller programmes, such as local university research, could be more flexible in their approach.

Saying this, **emerging technologies such as XR or AI, are developing rapidly and it is entirely possible that specific technological developments would supersede the state-of-art upon which the original ethics evaluation was based.** In such cases, the **ethics-by-design approach presents the only possibility for a comprehensive ethics overseeing and avoidance of ethics barriers along the implementation of the research project.** This on the other hand would require a new perspective on ethics evaluation processes that goes against the current thinking.

4.1.5 Reflective and anticipatory research on extended reality

At present **XR does not require a different approach on reflection or anticipation than other emerging technologies**. Established methods that allow for internal (with researchers) and external (with stakeholders) discussions on the subject matter of the research, are sufficient for XR as well:

- For instance, regular feedback sessions with researchers about their experiences in the implementation of research and their thoughts about the ethics issues surrounding their work, would be desirable. At the same time, stakeholder discussions (even including interested public, if possible) on the

aims and impact of the specific research, are also vital in achieving reflection and anticipation.

When it comes to **XR and AI applications**, research subjects would require particular information about the functions and properties of the system they are using:

- For instance, upon entering any virtual realm, **participants should be provided information about the nature of algorithmic tracking and mediation in the environment they are using.** This would allow them to provide more accurate and useful feedback on anticipatory aspects of the research.

A further aspect, as mentioned by an expert, would be **a truly international perspective** which would regard and require local **culturally specific ethics reviews**. Often ethics reviews are based on high-income countries, creating a homogeneity. Even though a level of institutionalization is needed, risks and their degree may be different among countries and regions of the world as well as differences in approaches to deal with them.

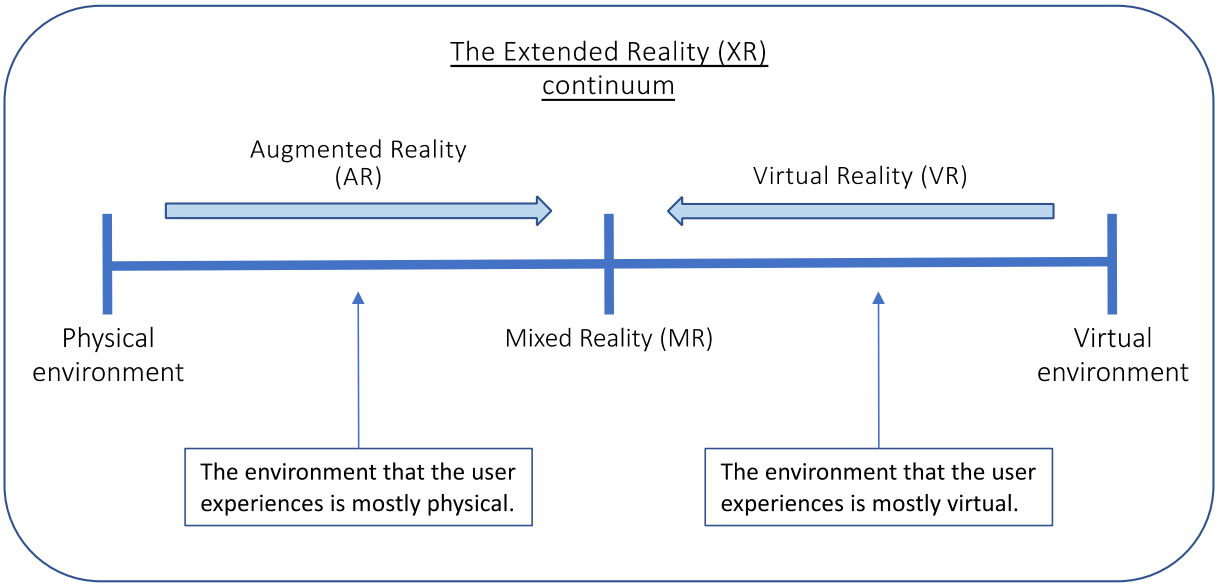
4.2 Needs to inform development of training materials and awareness actions on Extended Reality

4.2.1 Most relevant current ethical issues and concerns: training and awareness needs

A distinction ought to be made between ***virtual reality*** (VR) and ***augmented reality*** (AR): VR immerses the user completely in a digitally simulated environment, while AR creates a combination of material and digital objects or effects. These environments are sometimes described in the current literature as “metaverses” or “the metaverse”. The notion of ***metaverse*** is based on the earlier notion of collaborative virtual environment (CVE). Historically, CVEs were defined as computer-enabled, distributed virtual spaces or places in which people can meet and interact with others, with agents and with virtual objects” (Redfern & Naughton 2002). In line with this earlier concept, a **metaverse** is a shared, persistent, real-time 3D, digital model environment: “the concept of an immersive and persistent virtual world where users can communicate and interact with other users and the surrounding environment and engage in social activities, similar to interactions in the physical world” (Zhu 2022). Thus, in a metaverse, users can share immersive experiences, communicate between themselves, or conduct economic activities.

Mixed reality (Milgram et al. 1994) was considered earlier as a continuum between AR and VR. iRECS endorses a meaning of ***Extended reality (XR)*** as an umbrella concept, encompassing various forms of AR and VR, in which Mixed Reality (MR) describes a rather theoretical state of indistinguishability between physical reality and the virtual environment (see figure 2). This understanding of XR presents the advantage to define an ideal blend between the physical environment and the virtual environment, from which can be described **levels of AR or VR**.

Figure 2. The XR continuum



While some ethical questions apply to all XR, others are specific to some of its forms. The continuum of immersive experience perceived by human users highlights the impossibility to draw rigorous or fixed boundaries between the material and the virtual environments at which ethical questions of XR would no longer apply.
Interesting **ethical issues and concerns** regarding XR arise since the status of the agent involved in an interaction, whether a human being or an AI system, cannot always be known. Common and specific ethical issues include:

- **Autonomy and Manipulation** (Adomaitis et al. 2022)
  - Nudging via XR devices presents a concerning aspect of influence and persuasion through immersive technologies.
  - The emergence of virtual beings, including avatars representing deceased individuals, introduces complex ethical questions regarding identity and agency

- **Privacy concerns,** including new types of biometric data, and the issue of informed consent.
  - The advent of eye-tracking technology reveals personal habits, preferences (including sensitive areas like sexual preferences), and health conditions, raising significant privacy concerns (Kröger et al. 2020).
  - Privacy in specific applications such as telemedicine (Evans et al. 2022) is a crucial area of concern, particularly regarding the confidentiality of medical information.
  - Issues surrounding governmental surveillance and control in the metaverse (Miller et al. 2020) highlight the broader implications of XR technology for personal freedom and privacy.

- Data collection for industry purposes (Happa et al. 2021) and the potential use of brain data (Behnke et al. 2022; Tricomi et al. 2023; Susser & Cabrera 2023) further complicate privacy considerations.

- **Dignity issues**
  - Instances of harassment, hate speech, violent content, and XR pornography underscore the challenges surrounding user dignity and respect within virtual environments.

- **Violence in XR,** by projection (Grinbaum and Adomaitis 2022)
  - Concerns about sexual assault and rape of avatars (Hartmann et al. 2010) raise questions about virtual crimes and their impact on users' emotional well-being.
  - Issues like killing, murder, or unwanted disappearance of avatars, as well as child crime in XR, demand ethical scrutiny regarding the depiction and consequences of violence in these digital spaces.
  - The involvement of non-human agents, including AI, in violent or criminal acts complicates the attribution of responsibility in virtual environments.

- Issues related to **health or mental health**
  - Cybersickness (Hughes et al. 2020) poses immediate health concerns for XR users, potentially leading to discomfort and disorientation.
  - The potential for virtually created stimulations, such as flashing lights triggering seizures (Fisher et al. 2022), has critical safety implications.
  - Psychological impacts, including addiction and the need for a resting period after extended XR use, underscore the mental health dimensions associated with immersive technologies (Basu 2021).
  - In psychotherapeutic settings, XR can worsen dissociative disorders.

- **Educational or developmental effects**
  - The possibility of negative transfer in education, where virtual learning interferes with or replaces real-world knowledge, raises concerns about the effectiveness of XR in educational settings.
  - Impacts on psychological and visual development in children necessitate careful examination to ensure the healthy growth of young XR users.

- **Energy and resource consumption** (including Rare Earth Elements (REE))
  - The environmental impact of XR technologies is significant, particularly in the extraction of Rare Earth Elements (REE) required for headsets, highlighting the need for sustainable practices.
  - XR's energy consumption in public spaces (Feldman 2018) and the power consumption associated with cloud gaming server farms further contribute to environmental concerns.

4.2.2 Core scientific concepts that must appear in a short lecture

The main concepts concerning XR are technical or practical rather than scientific, and describe user experiences or objects and environments with which the user interacts in XR:

- **Metaverse:** a recent concept (it has existed since 1992 in science fiction) describing a shared, persistent, real-time 3D, digital model environment. Metaverse is the contraction of the Greek prefix meta ("beyond" or "transcending") and the word universe.

- **Immersion**: first-person phenomenal experience of being in a virtual environment (Adomaitis et al. 2022). For a more thorough and philosophical account of the notion of **immersive experience**, see: Chasid 2021; Langland-Hassan 2020; Liao 2018; Schellenberg 2013.

- **Immersive technology:** XR is always mediated by immersive technology.

- **Presence**: first-person impression of attending to events or agents in a virtual world (Suzuki et al. 2023). Lived experience hard to represent by a third person narrative.

- **Interaction:** “interaction refers to the natural interaction between the user and the virtual scene. It provides the users with the same feeling as the real world through feedback” (Yang et al. 2019). AR and VR are modalities of extended reality interaction.

- **Interoperability:** interoperability is a decisive technical concept for thinking towards a universal, or at least global, metaverse: it can define as “the ability to deliver an immersive and persistent virtual experience seamlessly across multiple networked platforms or interconnected virtual spaces” (Zhu 2022). It is a technical prerequisite for the metaverse and the other immersive experiences we could be making in it.

This list is not likely to change much, but it may well depend on:

- The popularity of the metaverse.

- Technical **progress** (headsets or other) to make the interaction more realistic: for instance, passthrough and remote passthrough technologies.

- The **affordability** and the market of XR devices (headsets, haptic systems, etc.): economic inequalities are likely to jeopardize the achievement of a unified, global metaverse.

4.2.3 Additional highly relevant topics for ethical analysis in a full-day training course

- **Experiential training/First person experience**: experiential knowledge is considered of primary importance because the whole purpose of this technology is to simulate a human experience of another environment than the physical reality. The main concepts above describe such subjective feelings or experiences (immersion and presence, in particular) provoked by XR.
    - A full-day training course could include experiential training: trainees could try for themselves a headset and experience a virtual or augmented environment.

- As XR devices can be very costly, especially if there are many trainees, the virtual reality or metaverse experience need not be fully immersive. VR can be experienced by other means, or with DIY headsets (usually made of cardboard, into which a smartphone is inserted). The following means can give an idea to trainees of what it is like to experience virtual reality:
  - National Geographic Youtube 360° channel: https://youtube.com/playlist?list=PLivjPDlt6ApRq22sn082ZCC9893XtV8xc
  - 360 Cities : https://www.360cities.net/
    - For instance: https://www.360cities.net/video/tranquil-river-journey/vr
  - Games (free or opensource):
    - https://konterball.com/
    - Create a virtual environment: https://gurivr.com/
  - Phone apps:
    - Cardboard (google)
    - Fulldive VR
  - Cardboard VR headsets can be purchased for around 3 to 5 euros a piece (or can be homemade)

- **Generative AI in XR**:
  - How do ethical issues around generative AI translate when considered with XR?
  - Applications of the AI-XR combination: autonomous cars, robotics, military, medical training, cancer diagnosis, entertainment, gaming applications, advanced visualization methods, smart homes, affective computing, driver education and training, etc.
  - See Adomaitis et al. 2022; Reiners et al. 2021

- **Cross-cutting topics** (see also Techethos (Adomaitis et al. 2022))
  - With biotechnology:
    - Nanotechnology
    - Organoids
    - Add-ons/suits/implants interfaces
  - Modes of interaction:
    - Parasocial interaction: in this type of interaction, the viewer develops a sense of familiarity, attachment, or even a one-sided friendship with the media figure, even though there is no actual personal relationship or direct communication between them.
    - Real human interaction in a virtual setting.
  - Labour and economics in the metaverse:
    - Telecommuting/remote work
    - NFTs
    - Tokenization
    - Property in the metaverse

- **Philosophical (metaphysical and epistemological) distinctions between virtual, and actual, or physical, reality**:

- Virtual fictionalism (McDonnel &Wildman): the idea that virtual objects are not real but fictional (Walton).
- Virtual realism (Chalmers 2022): the thesis that virtual reality is genuine reality.
- Other **reflections on the ontological and ethical status of objects and beings** in the metaverse:
  - To address common concerns and/or **avoid trivial matters in evaluating a project as a REC member**, such as: is it worth considering, issues like the dignity or responsibility of artificial beings (humanoid AIs, for instance) themselves in the metaverse?

4.2.4 Key uncertainties concerning extended reality at this time

- **Distributive justice**: the main uncertainty is about the number of users. As some XR devices/hardware become relatively inexpensive or accessible to the public (currently between around 500€ for Meta's headset to 3500€ for Apple's headset), this might encourage many mainstream users to become metaverse players: the fee to access the metaverse will be decisive (and a distributive justice issue).

- **The full impact of generative AI on the metaverse** remains uncertain, encompassing aspects such as avatars and environments.

- **Inclusivity issues:**
  - **Disabilities**: Addressing the needs of individuals with disabilities is crucial for creating an accessible and welcoming metaverse.
  - **A less attractive market (for industry)**: Industries might perceive the market of people with disabilities as less lucrative, potentially leading to a lack of tailored offerings.
  - **VR headsets are unadapted to certain disabilities**: The design of VR headsets can inadvertently exclude individuals with specific disabilities, limiting their participation in the metaverse.
  - **Inclusive development**: Prioritizing inclusive development ensures that the metaverse accommodates diverse needs, fostering equal access and participation for everyone.

4.2.5 Fundamental dilemmas related to extended reality

- Is there a **preference for material reality**? (Adomaitis et al. 2022 [TechEthos])
  - Are experiences mediated via XR equivalent to experiences gained in the real world?
  - "This debate raises important questions regarding the status of experiences in XR. Are they the same as they would be in material reality, given a high immersion and resolution? Is there a preference for material reality despite pleasures offered in virtual environments? Is the preference constant or evolving with time? Is it based on desire or rationality? How do the ethics of real environments relate to the ethics of virtual environments?" (TechEthos)

- What **ontological status** should be given to **virtual objects**? (Adomaitis et al. 2022 [TechEthos])

- Are objects and environments in extended reality of the same nature as material objects and environments?
- "If simulated objects are real objects, and if our beliefs about these objects are true, then from an ethical point of view real and virtual environments are equivalent."
- What ontological status should be given to virtual beings (for example animals, but also AI generated humans, for instance)?
  - If we cannot distinguish between an actual and a virtual being in extended reality, should we grant a (moral and ontological) quality of being sentient to everything that looks like it in the environment generated by XR?
  - Do we have an indirect duty to humanity to treat sentient-like beings as sentient beings? (Kant, *Groundwork for the Metaphysic of Morals*, 1785)

- **Equivalence between virtual and material actions or beliefs** (Adomaitis et al. 2022 [TechEthos])
  - If we keep the distinction between virtual objects and material objects, consequences of actions in material reality certainly do not equal the consequences of actions in virtual reality. But if we don't, moral principles and reflections in actual reality should apply in extended reality.
  - Cognitive equivalence (Adomaitis et al. 2022 [TechEthos]): "For the transfer of behavior from virtual to material realities to work, an equivalence needs to hold between virtual and material actions and beliefs. To establish the equivalence, some scholars claim that VR produces stimuli equivalent to the material ones, while others argue that it induces the same sense of immersive presence."
  - Emotional projection (Adomaitis et al. 2022 [TechEthos]): "Despite the fact that cognitive equivalence is not expected to hold, there are emotional effects in XR that do not require cognitive equivalence. They are already functioning in the current state of the art. These effects depend on people anthropomorphizing virtual subjects as having psychological, emotional and moral traits."

- **Cross-cutting topics** (previously known dilemma that also apply): **justice, equity, and accessibility**
  - Accessing the metaverse requires resources not available to most humans:
    - a steady electrical supply
    - high speed internet connection
    - headset and/or haptic devices for an immersive experience
    - a powerful computer
  - Inclusion of people with disabilities:
    - How to adapt the metaverse and the technical means of navigating it to visually or hearing impaired (or other disabilities) persons?

4.2.6 Useful resources to build training modules

Reports/Grey litterature

- IEEE SA - The IEEE Global Initiative on Ethics of Extended Reality: https://standards.ieee.org/industry-connections/ethics-extended-reality/
- Techethos website (page on Digital extended reality): https://www.techethos.eu/digital-extended-reality/
- Zhu, Ling. « The Metaverse: Concepts and Issues for Congress ». Congressional Research Service, 26 August 2022. https://sgp.fas.org/crs/misc/R47224.pdf
- INRIA's Website: https://www.inria.fr/en/how-does-virtual-reality-works
- Basdevant, Adrien, Camille François, et Ronfard. « Mission exploratoire sur les métavers ». Rapport interministériel. France, octobre 2022. https://www.economie.gouv.fr/files/files/2022/Rapport-interministeriel-metavers.pdf
- The Metaverse Standards Forum: https://metaverse-standards.org/

Video

- Kent Bye's XR Ethics Manifesto:
  - https://www.youtube.com/watch?v=CXgY3YXxqJ8
- Masterclass on XR in the classroom (Central Queensland University, Australia):
  - https://www.studyaustralia.gov.au/english/masterclasses/extended-reality-xr-in-the-classroom

EU Research projects involving XR:

- Empower Refugee Women through XR supported Language learning (XRWomen): https://www.motion-digital.eu/post/project-xr-women
- Volumetric 3D Teachers in Educational reality: https://vol3dedu.eu/
- REalisation of Virtual rEality LearnING Environments (VRLEs) for Higher Education (REVEALING): https://revealing-project.eu/
- Extended Reality For DisasteR management And Media plAnning (xR4DRAMA): https://xr4drama.eu/_project_/
- Augmented Reality Instructional Design for Language Learning – ARIDLL project: https://aridll.eu/
- XR4HUMAN — Responsible development and uptake of XR technologies: https://xr4human.eu/

4.2.7 Applicability of the concept of compliance to extended reality

Compliance currently only covers the issue of privacy and potential health applications. No overarching framework exists.

4.2.8 Applicability of the concept of ethics-by-design to extended reality

The concept of ethics by design applies to XR, but it is rarely applied for lack of operational translation of the values and principles.

4.2.9 Most relevant EU or international guidelines or standards related to extended reality

- General Data Protection Regulation (GDPR)
- There are **no straightforward EU or international guidelines governing XR** per se.
- The main contemporary issue is to regulate the metaverse.

- A not-for-profit organization, The **Metaverse Standards Forum** brings together most of the industrial players involved in the metaverse, with the aim of creating the conditions for its worldwide interoperability: https://metaverse-standards.org/
- **AI Act: the EU AI Act of April 2021** included in its annex the following statement:
  - Annex III, article 1: "Biometric identification and categorization of natural persons: (a) AI systems intended to be used for the 'real-time' and 'post' remote biometric identification of natural persons;"
  - This statement applies in part to XR, to the collection of biometric data during the user's real-time 3D experience.
- **Council of the European Union**, Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain Union legislative acts, paragraph 16, 2022 :
  - "AI systems deploy subliminal components such as audio, image, video stimuli that persons cannot perceive as those stimuli are beyond human perception or other subliminal techniques that subvert or impair person's autonomy, decision-making or free choices in ways that people are not consciously aware of, or even if aware not able to control or resist, for example in cases of machine-brain interfaces or **virtual reality**. »

Other Guidelines/Codes of conduct

- The Open AR Cloud Code of Conduct (CoC) : https://www.openarcloud.org/documents/code-of-conduct
- XR Safety Initiative (XRSI) ethical guidelines for developers, users, and organizations : https://xrsi.org/xrsi-code-of-conduct

4.3 Recommendations

4.3.1 Establish "digital subcommittees" in RECs

To address the challenge of understanding technical aspects, policymakers should create dedicated "digital subcommittees" within existing RECs or, if no RECs are competent, then establish dedicated "Digital Ethics Committees" (DECs). These bodies should combine XR technical experts with specialists in research ethics, AI regulation, and other related areas. Providing mutual learning time, appropriate training and resources to REC members will enhance the quality of ethics appraisal. Whenever there exists relevant sectorial or professional regulation, it should be taken into account, for example in the medical sector or in security applications of XR.

4.3.2 Ensure that AI-generated content in XR can be identified by users

To mitigate risks related to misinformation and manipulation, it is crucial to clearly distinguish between AI-generated and human-generated content, particularly regarding provenance and control of avatars in XR environments. Mandating the use of easily identifiable watermarks in all AI-produced outputs, including avatars, text, images, audio, and video used in XR environments, can promote transparency and inform users about the authenticity and source of the content. Establishing guidelines at the regulatory level will ensure consistent practices across platforms. Ethics experts should consistently check the application of this principle in research projects that

include content production by AI systems. Technical solutions are needed to ensure that provenance of XR content can always be identified.

4.3.3 Consider surveillance capabilities of XR, in particular in virtual work environments

As XR becomes integral to remote work and collaboration, privacy concerns arise due to the potential for increased surveillance capabilities. Policymakers should develop sectorial regulations to protect individuals' privacy and data in virtual reality, including virtual environments. Ethics experts and researchers should consider the possibility of surveillance in XR environments and analyze the implementation of limits on using data for surveillance. Consent documents should be adapted accordingly in order to safeguard user rights. Encouraging the adoption of privacy-enhancing technologies and best practices in data handling will further mitigate privacy risks associated with XR in the workplace.

5. Cross-cutting recommendations

5.1 Build appropriate scientific expertise in RECs, particularly in AI ethics

A common conclusion drawn from the study of the four selected technologies and discussions with experts is the need for ethics assessment processes to rely more on scientific expertise. While some RECs consider research ethics a matter of common knowledge, assuming it requires no special training and relies solely on moral intuition, **it is necessary for the ethical evaluation of a research project to be based on precise scientific and technical knowledge** related to the research or development being assessed. In essence, this highlights the importance of a reciprocal relationship between ethics and scientific expertise, promoting a more comprehensive assessment of complex scientific endeavors and fostering a deeper understanding of their ethical dimensions.

An outstanding example is the evaluation of projects in computer science and artificial intelligence. It has become clear from iRECS work that **there are not enough experts in AI ethics in Europe today** with sufficient knowledge of scientific and technological context (see Annex 1 and 2). Integrating AI experts in RECs is a pressing need across RECs. To effectively analyze ethical issues in AI-related projects, one possible strategy is to establish specialized digital ethics committees with a particular emphasis on AI expertise. Another, equally important aspect is the need for a self-evaluation procedure allowing ethics committees to evaluate their own scientific and ethical competence in a lucid and responsible fashion. To avoid overstepping their area of expertise, committees should develop a procedure to seek additional knowledge when needed, e.g., by **inviting external experts** or consulting with other ethics committees. Finally, training trainers remains a priority, particularly for AI ethics.

5.2 Move away from one-time compliance checks toward ongoing evaluation and ethics-by-design

Ethics committees frequently find themselves burdened with a heavy workload, leading to extended evaluation timelines for projects. They often struggle to perform medium-term or long-term monitoring of research projects they had previously assessed. At the same time, complex research projects in areas such as artificial intelligence frequently require regular ethical oversight during the lifetime of the project. The evolving landscape of societal changes and norms also necessitates continuous vigilance in monitoring research ethics. One-time compliance checks, especially in the domain of AI, may no longer mean that the result of the project is aligned with new regulation. In essence, the combination of administrative constraints with the dynamic nature of ethical concerns highlights the importance of ongoing ethics oversight.

Adopting an **ethics-by-design approach** is one possible solution, even if RECs typically lack training and resources to implement it. Ethics-by-design emphasizes early integration of ethical reflection in scientific research. It ensures that ethical considerations are not merely an afterthought but are woven into the fabric of the design process. This approach results in technologies and systems that are not only effective but also better aligned with human values and rights. By combining these strategies — embracing ethics-by-design and limiting purely legal compliance checks — ethics committees can effectively foster the culture of ethical excellence and integrity in science and technology. The implementation of this recommendation also

means that **the REC model will evolve from the committee form towards a permanent team or laboratory** devoted to research ethics.

5.3 Ethics experts should not merely scrutinize research projects but also advise on new, better reflected and anticipatory research directions

Ethics evaluation is often tasked with preventing or mitigating harm or transgressions while ensuring that scientific and technical endeavors remain within legal boundaries. As a consequence, ethics evaluation is often perceived as a “necessary nuisance” to research and RECs are seen as another body for “policing” science. This is obviously an exaggeration; however, such attitudes do exist across many disciplines and need to be addressed explicitly.

Ethics experts ought to produce reports that are focused on ethics, yet these reports may **contain scientifically interesting material**, e.g. suggestions concerning new open questions, advice on addressing ethical issues, etc. Proving that ethics is not only a matter of checks or controls, but can also inform scientists in an interesting way, is essential for keeping a good connection between research ethics and scientific enquiry.

Annex 1. Report from EUA leadership roundtable "Institutional approaches to research ethics and integrity"

The EUA leadership roundtable

The European University Association hosted on 31 May 2023 an online leadership roundtable. The event was entitled "Institutional approaches to research ethics and integrity: let's talk about new technologies," and open to rectors and vice-rectors from European universities. It was divided into two parts: a panel discussion with experts, followed by open discussions among participants.

A total of 26 participants were present at the meeting. They were all rectors or vice-rectors from universities in Albania, Andorra, Austria, Belgium, Cyprus, Czechia, France, Georgia, Germany, Ireland, Italy, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and Ukraine. Members of EUA secretariat and the iRECS project consortium attended the meeting as observers.

This section collects the main ideas voiced during the event, following the Chatham House Rule: "participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed."

Key messages and considerations

As a summary of the ideas gathered during the panel and breakout discussions, a list of key messages is presented below along with linked considerations to be made when tackling research ethics and integrity:

- Challenges posed by new technologies need to be constantly reconsidered, and their paradigm-changing consequences should not be underestimated. Universities should embrace such changes and re-define and re-assess the existing structures accordingly, both externally (through scientific research) and internally (university governance). For the latter, an example could be the exploration of XR and AI towards improving science communication.
    - Consideration 1: embrace technological change as an opportunity and explore its potential to solve their related challenges.

- Ethics and integrity should be understood as best practice within any research endeavor. Current risks regarding over-publication and the debates on authorship might have been increased by the development of AI and Natural Language Processing models, but they existed before and go beyond the use of AI. Structures and practices need to be re-assessed. Research Ethics Committees (RECs) can raise the alarm about malpractice, but getting to the root of a problem remains complicated both for RECs and university leaders alone, and additional legal support should be provided.
    - Consideration 2: understand integrity challenges as a whole and research their causes beyond the mere use of new technologies for malpractice.

- The structure and role of RECs varies not only between countries, but also at sub-national level and even at institutional level depending on the discipline.

Different regulatory levels apply, which might endanger academic freedom. It must also be noted that research ethics and integrity are not always separated within universities, and bodies in charge of them collaborate on a regular basis in some cases.

  - Consideration 3: Always consider academic freedom as an indispensable element of the academic and research endeavor, acknowledging the need of a balance with different levels of regulation and monitoring regarding research ethics and integrity. The ultimate responsibility of conducting ethical research lies with individual researchers and research teams, and positive reinforcement (e.g., "responsible AI" licenses) could be a useful tool.

- University governance bodies do consider the opinions of RECs. RECs are both mediators and enablers of research: transmitting general concerns to researchers and helping them adapt their research design accordingly. Additionally, in view of the growing ethical challenges and limited resources, RECs face a capacity limit problem.
  - Consideration 4: improve how research ethics procedures are communicated internally, along with making the role of RECs clear and understandable to the research community. RE&I is not a barrier to research but a channel of good practice.
  - Consideration 5: increase the support for RECs, not only in terms of resources, but also regarding administration and digitalization.

- The public is increasingly contesting the validity of scientific work. Several factors apply, but potential solutions include universities positioning themselves in cases of public misinformation, carefulness when sharing research results, and expectations management regarding scientific work.
  - Consideration 6: acknowledge science communication as part of research ethics efforts. There is a bridge-building role of researchers between academia and society. An ethical approach from researchers' side to communicating their scientific results must consider making such communication clear and easy to understand to the public, as well as wisely choosing the debates in which they take part according to their expertise. Training opportunities for researchers are needed in this respect.
  - Consideration 7: foster research on science communication, including the potential role of storytelling while keeping objectivity at its core, and empower universities to position themselves and take responsibility for adequately informing the public when fake information is spread.

- Research ethics training becomes a priority when talking about early-stage researchers. It is not only a matter of researchers' embracing ethical and responsible values, but also of managing their expectations towards research ethics assessment, as well as those of the university towards them.
  - Consideration 8: include anticipation skills in research ethics training, as well as practical details on the interaction with RECs and what to expect from research ethics assessment processes.

- Consideration 9: find a balance between mentoring, advising, and providing diversified training for early-stage researchers so that their core activity remains the conduct of research.

Annex 2. Report from the EUA focus group on research ethics and integrity

Introduction

The European University Association hosted on 13 November 2023 an online focus group in the context of the iRECS project (improving Research Ethics Expertise to Ensure Reliability and Trust in Science). The event was entitled "New Technologies and Training Needs for Research Ethics Committees," and open to university leaders, directors of research and innovation offices, members and chairs of research ethics committees, directors of doctoral schools, research ethics and integrity officers, research managers, open science delegates and researchers from European universities.

A total of 41 participants from universities in 19 countries were present at the meeting (Austria, Belgium, Croatia, Czech Republic, France, Germany, Ireland, Kosovo, Lithuania, Malta, Netherlands, Nigeria, Poland, Portugal, Spain, Switzerland, Turkey, Ukraine, United Kingdom). The focus group comprised members and chairs of research ethics committees, university leaders (vice-rectors) and heads of departments in charge of research ethics and integrity, support officers and advisers on research ethics and integrity. Members of EUA secretariat and the iRECS project consortium attended the meeting as observers. Three representatives of EUA members were also invited to share initial reflections and to prompt discussions on the draft recommendations:

- Filip Colson, Policy Advisor at the Flemish Interuniversity Council VLIR. As part of his portfolio, Filip deals with research ethics and integrity. He organised a seminar with experts on the possible use of generative AI in university policies.
- Senena Corbalán, Vice-Rector for Research, Professor of Biochemistry and Molecular Biology at the University of Murcia. Senena is a member of the EUA R&I Strategy Group, championing the research ethics and integrity dossier.
- Peter Hanenberg, Vice-Rector for Research and Innovation at the Catholic University of Portugal. Peter is a member of the Steering Committee of the EUA Council for Doctoral Education (EUA-CDE)

Invited reflections

Filip Colson, Policy Advisor at the Flemish Interuniversity Council VLIR

Filip Colson welcomed the proposed recommendations, appreciating that they are very well structured, balanced, thorough, and reflect the high level of expertise and experience of contributors in the four selected technologies. He presented a selection of basic principles developed by VLIR to support researchers and research groups when it comes to AI in research, generative AI in particular. Inter-university dialogue and institutional learning are key in this respect. Although those principles target individual researchers, they are also relevant in the institutional context, because there is an overlap in training needs:

- Transparency is essential when it comes to the use of AI, in particular generative AI. The correctness of output should be verified, to ensure correct sources.
- Researchers should respect copyright, personal data, and be mindful of undetected/unprotected IP.
- Researchers must be responsible for the output they publish. This includes awareness training regarding ethics in AI.

Filip Colson then identified two possible caveats in the recommendations:

- Synthetic data is not addressed – which mimics existing datasets. It has limitations, but these can be overcome. Care must be taken when evaluating these data for quality and biases. The output is highly dependent on the data quality.
- Sustainability: increasing energy demands for AI should be factored into ethical use (Nature Machine Intelligence recently published an article on this issue).

Finally, he mentioned the 'VLIR Mind the GAP (for Good Academic Practices)' initiative: English podcast on research integrity, with episode on AI (forthcoming, summer 2024). Filip Colson also shared extensive feedback in a separate document (provided in annex 1).

Senena Corbalán, Vice-Rector for Research, Professor of Biochemistry and Molecular Biology at the University of Murcia

Senena Corbalán congratulated the authors on this very complete and impactful document and shared her reflections on the proposed recommendations (her detailed feedback is provided in annex 2):

- The general message is that all recommendations (i.e. for the four technologies and cross-cutting recommendations) are extremely useful but their implementation in universities will not be easy. This would require extra effort that we need to consider. For instance, universities would need financial support. The experts should also be incentivised to contribute to RECs, because it is time consuming.
- The concepts of interest for RECs trainings are well defined, but in many cases, more than a full-day training course will be needed. In any case, since the topics are well defined, the extension of the course can be handled depending on the needs of each REC (this should be commented in the text).
- Digital Ethics committees as independent committees may not be able to address inter- and multi-disciplinary aspects of the research about or using these technologies. Data protection matters are also to be considered.
- To mitigate the risk of heterogenous evaluations, it is important for RECs to come to a uniform opinion, by working together and continuously learning together. Bigger committees at EU level could be helpful to solve the new issues that will arise.
- Biobanking: very good recommendations. Would be good to consider an EU-level standardised consent model, to be adapted.
- Genome editing: very appropriate recommendations.
- It is indeed necessary to build scientific expertise before evaluating.
- The idea of ethics-by-design makes sense but will complicate the functioning of the RECs, with continuous follow-up needed. This needs many resources, both time and financial. This statement should be included in the recommendation.

Peter Hanenberg, Vice-Rector for Research and Innovation at the Catholic University of Portugal

Peter Hanenberg shared key considerations on research ethics, in the context of doctoral education for early career researchers (ECRs):

- Maybe we should not consider ethics dumping but focus on ethics championing instead. AI is about human intelligence.
- Norms: necessary to have norms and regulations but it may not be enough. No need to wait for norms to start training. Need to raise awareness on those issues, beyond normative checklists. We need debate on these issues and to include ECRs in these debates. An integral and transversal approach to training is needed, for RECs but also by RECs themselves.
- RECs should be partners in research and not the police. They should be included as much as possible, as part of the whole research process, in all research groups. Having AI specialists in RECs may not be the solution. It is important to reflect on the purpose and not on the feasibility only.
- Embedding ethics process is a good approach.
- Mentorship by senior researchers can be a way to bring this awareness into life and to keep it alive.

Focus group discussion

Overall, participants welcomed the proposed recommendations. They highlighted the need for such comprehensive recommendations, appreciated the clarity of the document and noted that it will be impactful. This was further confirmed by the written feedback to a questionnaire sent to all participants, detailed in the next section.

Considerations

The following considerations were made:

- It might be worth defining what is meant by “AI experts”. Are they AI developers coming from IT disciplines, or more generally people with expertise in AI, including experts in the ethical and social impacts of AI?
- Whether AI specialists should be integrated in existing RECs or ad hoc RECs or dedicated subcommittees for AI should be built may be context-dependent. The first option is discussed in the recommendations, but not the second. In France, there is a separation between RECs dedicated to health (CPP) and RECs that deal with research that does not involve health (CER, etc.). Autonomous committees could be an option.
- Instead of dedicated committees, laboratories of digital ethics could be set up to help raise awareness and have a debate on those issues.
- The implementation of some recommendations (e.g. the integration of AI experts in RECs) may be challenging, because they are very busy and not necessarily motivated. The lack of AI specialists might create a problem, especially for interdisciplinary research. The implementation is also particularly challenging in smaller universities, with a limited pool of potential experts. How can they assess each other or themselves? What do we do when those experts are not available? What about other technologies – when there are no experts? How do we ensure that those who contribute to technology, if not expert in technology, can still provide feedback? External guidance and training on issues may be critical.
- The idea of establishing a pool of experts at EU level or even at international level was envisaged, using a cooperative approach between neighbouring universities. On the one hand, it was assessed positively, because in many cases, there is a unique reference at EU level. On the other hand, from a more

practical perspective, there may be some problems in terms of intellectual property (NDAs etc).
- To extend the pool of potential AI experts, they could also be considered as consultants, working in hospitals and in other settings.
- One of the main challenges for the future lies in the traceability of content (i.e. what is human vs. AI generated), and transparent communication about it. This is important for Recommendation 4.2. 'Ensure that AI-generated content in XR can be identified by users'.
- XR could be specific (compared to AI, Biobank and genome editing) in that some research in this area does not seem to (necessarily) involve heavy funding. Ethics-by-design could be more complicated to implement for small(er) projects.
- Issues related to AI/emergent technology research also arise outside of healthcare, so they should not be automatically considered in the context of bioethics. It may depend more on the institution and its REC structure.
- No one-size-fits-all approach, need to adapt to the needs of the university, and the structure of its committee(s).
- It is important to give sufficient bandwidth for RECs, to give them time and space to reflect.

Suggestions

The following suggestions were made:
- The target group(s) for those recommendations should be clearly identified: Are we speaking more to researchers, policymakers, etc.?
- The recommendation on unified criteria for reporting incidental findings to subjects could be extended beyond biobanking. This exercise would also be beneficial for researchers in SSH.
- In terms of training, best practices, special training, and recommendations (or even guidelines) are considered very useful. Several complementary options were discussed:
    - A "Train-the-trainer" initiative could be added to the recommendations, as a preamble or additional recommendation.
    - Peer to peer support can be an option for smaller universities. There is a need of researcher pioneers who can drive the ethical debate from the bottom up. At the University of Antwerp, researchers working on AI came together on the Antwerp Center of Responsible AI. This is a good example of the advantages of smaller scale organisations.

Questionnaire

The draft recommendations on training needs for research ethics committees were shared with focus group participants on the event platform. Participants were invited to complete a brief questionnaire to gather their feedback on the recommendations. The questionnaire was launched on 10 November and remained open until 15 November. 21 participants completed the questionnaire. The results are detailed below.

Are the proposed recommendations relevant?

21/21 YES, with the following additional comments:
- The cross-cutting recommendations are of special relevance.
- They target contemporary issues that RECs are facing.

- I think that the recommendations on four selected new technologies are helpful and highly relevant.
- The questions raised are important, and the proposals formulated are coherent. However, they raise important questions of feasibility.
- The recommendations are relevant considering the rapid evolution of technologies tested on plants, animals and humans that need expertise in RECs and scientific committees. These committees usually do not have expertise in digital technologies, nor do they have harmonised guidance.
- AI, biobanking, genome editing and XR experts are clearly needed to support ethical committees.
- The recommendations for establishing Digital Sub committees look very important to me, but also recognizing AI content. Also inviting external experts or consulting with other ethics committees is very much needed.

Are the proposed recommendations clearly formulated?

20/21 YES. The person who said NO specified as follows: “Probably, there is a need for some more specific recommendations in which way ethical expertise and expertise in AI, biobanking, genome editing and XR are interactively combined to reach valid judgements, recommendations and the like.”

Other comments are listed below:

- Yes, since they could help to the development of solutions preventing possible problems and establishment of good practise framework.
- They clearly articulated different complex issues in science and technology and how these could be managed by providing the needed expertise in RECs and scientific committees.

Are the proposed recommendations applicable in the short term?

14 YES / 7 NO, with the following comments from respondents who said NO:

- They need to be discussed and "democratized" within the institutions. And for those at EU level, everybody knows how slow these procedures are.
- I feel that there is a gap between the recommendations and actually applying them.
- The number of committees, and the availability of their members, do not always make it possible to combine ethical expertise with research specialization of the type that is expected here.
- We need a clear framework and standards for ethical clearance.

Additional comments are listed below:

- Cross-cutting recommendations no. 5 could be applicable in short term since they are related to Ethics committees acting on research organizations.
- Since ChatGPT and other generative AI found their way in late 2022, there has been lots of discussion and reflection leading to local and international immediate recommendations. The same concerns are topical for other medical devices that cut across plants, animals and humans.
- As the issues do be dealt with are there right now, the present recommendations are a welcome guide until more specific recommendations are being developed.

- It doesn't take so much time to form the sub-committees, and the inviting external experts or consulting with other ethics committees.

Are the proposed recommendations applicable in the medium term?

19 YES / 2 NO, with the following comments from respondents who said NO:

- Not sure I think some are however others are not.
- As stated before, more specific and perhaps extended recommendations should be developed in the medium term.

Additional comments are listed below:

- For some recommendations, the establishment of network of ethics experts and specialists could take some time.
- If states and institutions give RECs the means to achieve these ambitions.
- We hope the recommendations in the short term will provide directions for review and opportunity for medium-term recommendations.
- Move away from one-time compliance checks toward ongoing evaluation and ethics-by-design will be in the medium and permanent basis.

Are the proposed recommendations comprehensive? Would you add any elements?

17 YES / 4 NO, with the following comments from respondents who said NO:

- Rather vague at times.
- I think copyright and data protection issues need also be specifically addressed.

Additional comments are listed below:

- It can be assumed that some new recommendations will arise during implementation process.
- Some points raise questions, but the length of the document seems appropriate to me as it stands. Lengthening it would harm the possibility of it being read.
- Some examples and explanations.
- We need to add the following elements: 1. Developing ethics expertise (consultants) in the global South where international collaborative research between EUA/ EU and other continents (e.g. Africa) involves the implementation of the recommendations between committees that oversee such studies.

In your view, what are the most urgent or pressing recommendations?

Participants identified the most urgent or pressing recommendations. The three most selected recommendations are listed below and detailed scores are provided in the figure below:

- 5.1 Build appropriate scientific expertise before evaluating
- 3.3 Highlight policy differences between countries, including EU member states
- 2.1 Implement a standard consent model across EU member states

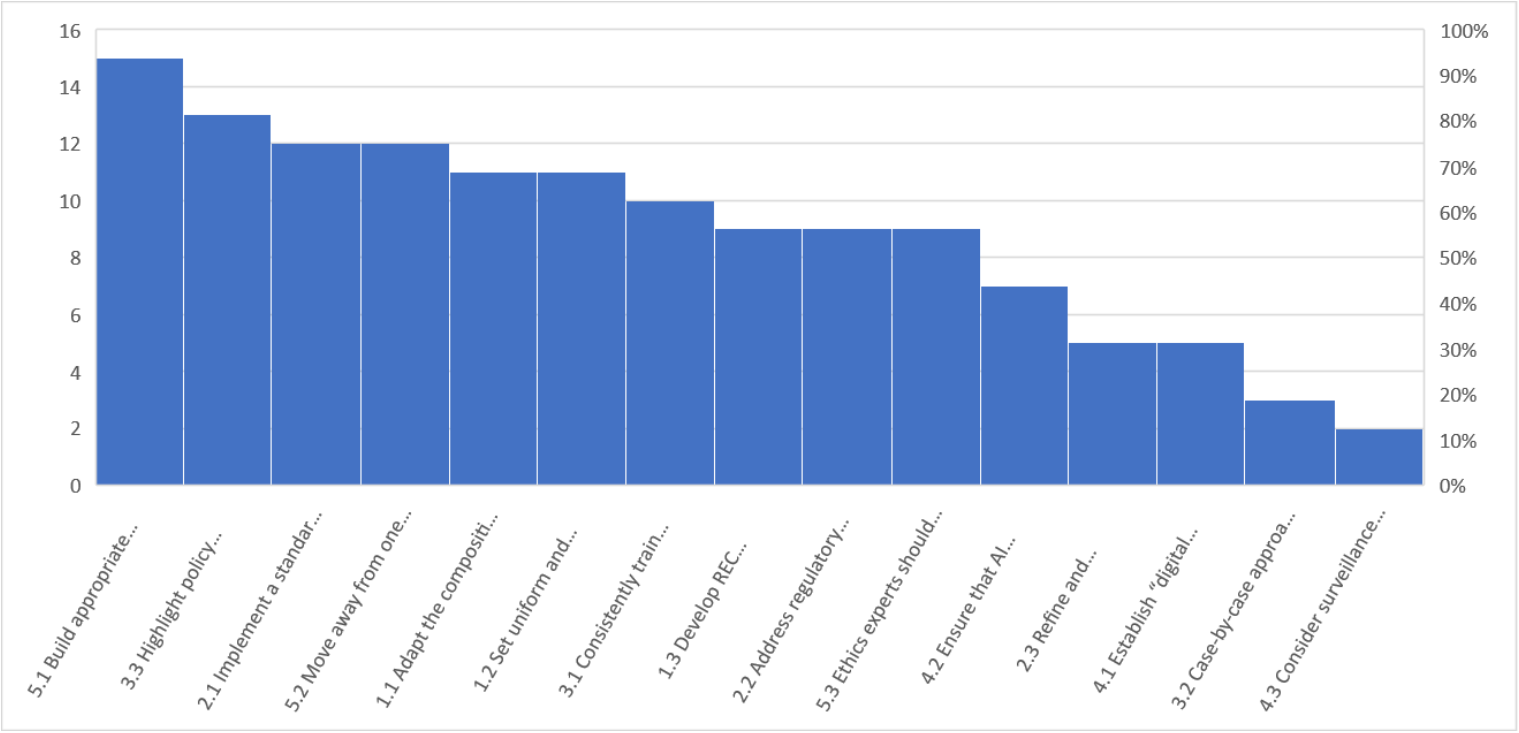


Figure 3: Chart of Priority Recommendations

Do you want to add any other comment on a specific recommendation? Please select the recommendation and use the text box to provide feedback.

- 1.1 Adapt the composition of RECs to include AI experts: (1) RECs should include AI & biobank ethics experts (consultants). These experts may not be limited to EU member states but internationally, where there is a possibility for multinational collaborative research involving AI, Biobanking, and gene editing/genome research across continents. (2) Depending on the frequency with which AI is encountered by a committee, and where resource is limited, it may be possible to alternatively have expert members who are called in when required?
- 1.2 Set uniform and coherent 'AI in healthcare' guidelines across EU member states: The idea of establishing specific Digital Ethics Committees (DECs) is clear but sounds like an independent committee and given the multi and inter-disciplinarity of these techniques, I think all experts should be working together in the REC to facilitate the continuous learning process.
- 2.1 Implement a standard consent model across EU member states (no feedback added)
- 2.3 Refine and homogenize the scope of reportable incidental findings: This question seems to me to go beyond the case of biobanking. I am not aware of any harmonization around the issue of incidental findings generally, but I may have missed something.
- 4.2 Ensure that AI-generated content in XR can be identified by users: The highlighted issue is important to adddress as touches coyright issues in many aspects.
- 5.1 Build appropriate scientific expertise before evaluating (no feedback added)

Anything else you would like to add?

- The focus in the recommendations seems to be only on healthcare. It may be more appropriate to focus on, for example, 'AI in research' as many Universities will conduct non-healthcare research where issues around AI also need to be considered.

Detailed feedback on AI and generative AI, from Filip Colson

Personal background: VLIR, Flemish Interuniversity Council, 5 research intensive universities + Institute of Tropical Medicine, + in our working groups: Institute of Biotechnology (VIB), imec (Interuniversity Microelectronics Centre), and other strategic research centres.
AI in research policy: topic of monthly debate at VLIR level:

- Research & Innovation WG (vice-rectors and research directors), and
- WG on Science, Ethics and Integrity (universities' ethics committees secretaries, and central services);
- VLIR Event in June 2023 on use of generative AI in research

Current version of recommendations: very well structured, balanced, thorough, and shows the amount of work, expertise and experience in these technologies of the people involved.
My main focus is the adequate support of researchers and research groups, and the interuniversity dialogue and institutional learning on evolving topics (such as AI)

- So, no critique on the Recommendations, just pointing out that this document is not aimed at (and therefore not useful for) individual researchers, who are usually my focus group and audience when it comes to capacity building exercises.
- But all well explained on p. 13 of the Recommendations, background: training needs for research ethics committees' members and EU ethics appraisal scheme experts.

With the above in mind, two caveats in the Recommendations: (1) synthetic data and (2) sustainability.
(1) Synthetic data: generation of synthetic data that mimic existing dataset (limitations such as privacy issues and confidentiality of real datasets can be overcome), but one has to carefully evaluate the generated synthetic data for quality and possible bias (as the output is highly dependent on the quality of the data on which the models are trained) + be transparent (mention explicitly, including reference)
Synthetic data is artificial data that is generated from original data and a model that is trained to reproduce the characteristics and structure of the original data. This means that synthetic data and original data should deliver very similar results when undergoing the same statistical analysis. The degree to which synthetic data is an accurate proxy for the original data is a measure of the utility of the method and the model.
The generation process, also called synthesis, can be performed using different techniques, such as decision trees, or deep learning algorithms. Synthetic data can be classified with respect to the type of the original data: the first type employs real datasets, the second employs knowledge gathered by the analysts instead, and the third type is a combination of these two. Generative Adversarial Networks (GANs) were introduced recently and are commonly used in the field of image recognition. They are

generally composed of two neural networks training each other iteratively. The generator network produces synthetic images that the discriminator network tries to identify as such in comparison to real images.
A privacy assurance assessment should be performed to ensure that the resulting synthetic data is not actual personal data. This privacy assurance evaluates the extent to which data subjects can be identified in the synthetic data and how much new data about those data subjects would be revealed upon successful identification.
Synthetic data is gaining traction within the machine learning domain. It helps training machine learning algorithms that need an immense amount of labelled training data, which can be costly or come with data usage restrictions. Moreover, manufacturers can use synthetic data for software testing and quality assurance. Synthetic data can help companies and researchers build data repositories needed to train and even pre-train machine learning models, a technique referred to as transfer learning.
Positive foreseen impacts on data protection:

- Enhancing privacy in technologies: from a data protection by design approach, this technology could provide, upon a privacy assurance assessment, an added value for the privacy of individuals, whose personal data does not have to be disclosed.
- Improved fairness: synthetic data might contribute to mitigate bias by using fair synthetic datasets to train artificial intelligence models. These datasets are manipulated to have a better representativeness of the world (to be less as it is, and more as society would like it to be). For instance, without gender-based or racial discrimination.

Negative foreseen impacts on data protection:

- Output control could be complex: especially in complex datasets, the best way to ensure the output is accurate and consistent is by comparing synthetic data with original data, or human-annotated data. However, for this comparison again access to the original data is required.
- Difficulty to map outliers: synthetic data can only mimic real-world data; it is not a replica. Therefore, synthetic data may not cover some outliers that original data has. However, outliers in the data can be more important than regular data points for some applications.
- Quality of the model depends on the data source: the quality of synthetic data is highly correlated with the quality of the original data and the data generation model. Synthetic data may reflect the biases in original data. Also, the manipulation of datasets to create fair synthetic datasets might result in inaccurate data.

(2) Sustainability

1. Harvard Business Review, Ajay Kumar and Tom Davenport, 20 July 2023 (https://hbr.org/2023/07/how-to-make-generative-ai-greener):
Almost all of the best-known generative AI models are generated by “hyperscale” (very large) cloud providers with thousands of servers that produce major carbon footprints; in particular, these models run on graphics processing unit (GPU) chips. These require 10–15 times the energy a traditional CPU needs because a GPU uses more transistors in the arithmetic logic units. Currently, the three main hyperscale cloud providers are Amazon AWS, Google Cloud, and Microsoft Azure.
If we try to understand the environmental impact of ChatGPT through the lens of carbon footprint, we should understand the carbon footprint lifecycle of machine

learning (ML) models first. That's the key to beginning to make generative AI greener through lower energy consumption.
2. Nature Machine Intelligence, Charlotte Debus et al., 10 November 2023 (https://www.nature.com/articles/s42256-023-00750-1) (Debus, C., Piraud, M., Streit, A. *et al.* Reporting electricity consumption is essential for sustainable AI. *Nat Mach Intell* (2023). https://doi.org/10.1038/s42256-023-00750-1)
The rise of artificial intelligence (AI) has relied on an increasing demand for energy, which threatens to outweigh its promised positive effects. To steer AI onto a more sustainable path, quantifying and comparing its energy consumption is key.
Even though current AI algorithms can tackle many applications with stunning results, we must ask what the cost of these achievements is in terms of consumed resources. Already, only a few companies and research institutions can provide the necessary compute resources to train, fine-tune and deploy state-of-the-art models, leaving behind most AI researchers, as well as small and medium enterprises. This hinders wide implementation of AI methods and points to a broader concern: especially in light of climate change and geopolitical resource availability, the price of AI advances in terms of their environmental footprint must be assessed. Substantial efforts are required to improve the energy efficiency of modern AI algorithms. Before energy consumption can be optimized, however, it must be quantified.
Here, we discuss recent efforts to monitor AI carbon footprint and energy consumption and issue an urgent call for action for the AI developer community to measure and report the environmental impact of methodological advances in a standardized, quantifiable and comparable manner to advance the goal of environmentally sustainable AI research.

Flemish universities' AI in research/education policies:
https://www.kuleuven.be/english/education/student/educational-tools/generative-artificial-intelligence

Tips and tricks for responsible use of GenAI (for students)

Be transparent about the use of GenAI: If the use of AI is allowed, you should be transparent about it. Read more specific information about this adapted to teaching staff, students or researchers.

Never import (privacy)sensitive or confidential information (including unprotected discoveries): Often, there is no insight in what the owners of AI applications do with imported data. In many cases, data saved on a non-European cloud is turned into applications that are not GDPR compliant. This is the case for personal data as well as new discoveries concerning scientific research. The entry of a discovery can be equivalent to disclosure and thus prevents the possibility of filing a patent for that discovery. So make sure you do not enter personal data or confidential information into these GenAI-applications. Check whether you have the necessary permission or license to enter copyrighted material. In case of doubt about the confidential nature of information, you can inquire about this with the information provider.

Make us of the 'opt out'-option of ChatGPT: Note that ChatGPT can link your information to you directly when it generates new texts (for others). It is thus possible that you - unknowingly - become a source of information for third parties by simply using the tool. ChatGPT does allow opting for "disable chat history and model

training" in settings (Data Controls FAQ), so that imported data cannot be used for the models' training and consequently not for generating new texts (for others). The possibility "to keep my history on but disable model training" also exists if you fill in a form for a "user content opt out request". In this last case, it is still possible to retrieve old conversations with ChatGPT. Attention: the opt out-possibility only ensures your entered data will not be used for the models' training but does not necessarily mean you should enter your privacy sensitive, IP-protected or copyrighted material. After all, entered info is often saved by the tool's owner and there is usually no transparency about what will happen with that data.

Verify GenAI: Use GenAI if permitted, but do not blindly trust technology. The more responsibility you place on the system, the more verification, control and justification is needed. Sometimes, AI output can seem very convincing, but it is perfectly possible that the answer is incorrect or even made up ('hallucinating AI'). In most cases it is impossible to retrieve the way algorithms have achieved a result and there is no transparency about sources used ('black box'). Check thoroughly what you use and look for existing source material you can cite. After all, you are the one responsible for the content of your delivered work.

Avoid plagiarism or any infringement of copyright: It is known that the generated references from the current version of ChatGPT and other text generating Ai-tools are sometimes fictitious. In GenAI's output, transparency about the used sources is sometimes absent, increasing your risk of plagiarizing. GenAI builds on work of others and a correct citation is always needed. The risk at copyright infringements is also apparent. The databases these tools use contain a lot of source material. So far, it is not clear if the authors have granted their permission for this or that copyright is being respected.

Double check the most recent state of affairs: The tools do not always use the most recent data available, resulting in outdated output. The free version of ChatGPT does not have access to information of recent years.

Be prepared for bias by GenAI: AI-applications are trained based on certain datasets, which sometimes are not representative. Transparency about the filters they apply does not exist. This raises a lot of ethical questions. With uncritical use, you risk further dissemination of incorrect information, certain stereotypes or prejudices.

Do not be satisfied with the first output: Asking a simple question rarely produces useful GenAI output. The more information and instructions you offer the tool, also called prompt engineering, the more useful the output becomes. On top of that, you should be aware of the output's bad reproducibility. Whatever ChatGPT (or similar tools) generate can differ with every attempt and lead to totally different answers. Another answer is also generated when you press "Regenerate response" after receiving an answer.

Give meaning to GenAI: When people hear a sentence, they link significance to it, connecting the utterance to reality in that way. A generative language model only has access to the form but can in no way establish the link to reality. As a result, you have no guarantee that the system's texts are indeed correct. The system's only concern is generating texts that seem as plausible as possible. Truth or reality count for nothing. By attaching meaning to GenAI's output, you create added value as a user.

Do not humanize GenAI tools: AI applications (chatbots in particular) are not human, even though it may seem so because of their interactive reactions. They are not influenced by personal experiences or their proximate environment. Via data they can be taught ethical principles. It is important to be aware at all times that the AI applications are mere technological resources. Refer to it as a thing ("it reacts"), not as 'he' or a 'she'.

Surpass GenAI: GenAI-application can sometimes be a resource for assignments (visual, writing and programming tasks). We expect students to add an extra layer: regarding argumentation or foundation, critical analysis, complete and correct citation, creative input, personal perspective or reflection, innovative character, connection to societal context ... As a student, you should be able to have a conversation or conduct a debate about your assignment.

Limit GenAI's energy usage: Do not forget that the energy costs of AI application's servers are very high. That is why you should only use them if they can add value.

VLIR Mind the GAP (Good Academic Practices): English podcast on research integrity, with episode on AI (summer 2024)

Detailed feedback on the implementation of the proposed recommendations, from Senena Corbalan

The document presents a very good study on the training needs for research ethics committees, concerning these 4 new technologies: AI in health and healthcare, biobanking, Genome-editing, and Extended reality. The gaps, challenges and grey areas have been detected for each technology. After the analysis, three recommendations have been proposed for each technology and another three cross-cutting recommendations.

Related to the concepts to study in the courses, I would say they are also well defined, but in many cases, more than a full-day training course will be needed. In any case, since the topics are well defined, the extension of the course can be handle depending on the needs of each REC (this should be commented in the text).
Concerning AI in health and healthcare, I agree that RECs need to include AI experts in the committee. The idea of establishing specific Digital Ethics Committees (DECs) is clear but sounds like an independent committee and given the multi and inter-disciplinarity of these techniques, I think all experts should be working together in the REC to facilitate the continuous learning process for all the members.
I find very difficult to recommend that to every REC since the infrastructure needed is complex and it might be very difficult to implement in many universities. This would increase the heterogeneity among RECs.

Because of that, the idea of setting uniform and coherent AI in healthcare guidelines across EU member states is fundamental, to address discrepancies and to advice in many of the cases that RECs are finding difficult to solve. The EU HLEG guidelines and the HLEG ALTAI check list are very useful, and I would suggest the High Level Expert Group should be reinforced to be the reference for the RECs in this matters.

The idea of ETHICS-BY-DESIGN makes a lot of sense but complicates a lot the working system of the RECs and implies a continuous follow-up that needs many resources, both time and financial. This statement should be included in the recommendation.

Related to Extended Reality, I think it is not very different from AI, in the issues to take into account for evaluation by the RECs, given the multi- and inter-disciplinary nature and the data protection matters.
Respect to Biobanking, I think the 3 recommendations make sense, given the actual situation. The standardization of the consent model across EU member states would enormously facilitate the process. However, the idea of dynamic might probably generate many delays. Perhaps, it is better to act in two pathways:

- One, preparing a consent model that specifies with details the implications of the donation of the samples for the patient. This can be updated annually.
- Second, the intervention of the REC is crucial to decide whether the research is appropriate or not, and this is given a security to the patients.

Refining and homogenizing the scope of reportable incidental findings is essential too and the gene list proposed is adequate, but it is important to include in the recommendation that the list should be annually updated.
Genome editing, the three recommendations are correct. Training the ethics evaluators is fundamental to reach a homogeneous evaluation. Due to the implication the case-by-case approach is important to minimize the potential adverse environmental effect. Unification of standards is necessary too.
Cross-cutting recommendations:

- Necessary to build the scientific expertise before evaluating.
- Ethics-by-design makes sense but will complicate a lot the functioning of the RECs, additional support is necessary. This should be mentioned specifically.
- Function of Advice by the RECs, not only at the time of the evaluation but also by designing continuous training for the committees and researchers.
- All four subjects are new matters still in development, so a centralized unit of analysis that also dictates recommendations and continuous training is crucial to have a standard way of acting based on science and experience. It should be complemented with the implementation of expert researchers in these areas by each REC, but they should have a standard reference to have homogenous decision-making.

General message: all recommendations are extremely useful but their implementation in the universities will need an extra effort that we need to consider to be able to design policies that help research ethics committees to accomplish all of them, mainly considering that it is a matter in continuous evolution.

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