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D2.4: Proposals for adaptation of ethics review processes

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

Lead authors	Vygintas Aliukonis (VU), Eugenijus Gefenas (VU), Vilma Lukaševičienė (VU)
	vygintas.aliukonis@mf.vu.lt, eugenijus.gefenas@mf.vu.lt, vilma.lukaseviciene@mf.vu.lt
Other contributors	Jurate Lekstutiene (EUREC), David Shaw (UM), Georgia Delliou (UM), Sandra Scholl (UBO), Daniela Proske (UBO), Maria Maia (KIT), Miltos Ladikas (KIT), Dirk Lanzerath (UBO)
Also contributed	Anais Resseguier (TRI), Borana Taraj (EARMA), Mariëtte van den Hoven (VUMC), Natalie Evans (VUMC), Miriam van Loon (VUMC), Vinciane Gaillard (EUA), Zhu Wei (FDU)

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Abstract

This deliverable aims at identifying the adaptation needs of the ethics review process of research involving four technologies selected in the irecs project: AI in health and healthcare, extended reality, biobanking, and genome-editing at the EU, Member State and non-EU state level, drawing on earlier findings (T2.2, T2.3). It also presents results of the survey of members of RECs and other ethics experts, which was distributed among members of ENERI, EUREC, EUA and EARMA, to collect data on experiences, needs, and gaps in the ethics review process and preferred methods of training, adding to the project knowledge base (WP4). The findings of the deliverable have been evaluated using SCORE analysis, focused on the EU and some non-EU countries, and will be integrated into the ENERI Classroom. The deliverable makes proposals for the adaptation of the ethics review process, focusing on the EC ethics self-assessment and existing guidance. to be trialled at pilot universities (T5.3).

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Task 2.2	Development of recommendations for addressing ethical challenges from research in new technologies

Task 2.3	Development of recommendations for addressing ethical challenges in technology research outside the EU
Task 5.3	Involve pilot universities

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Executive summary

Deliverable 2.4 is produced as part of Work Package 2 of the Horizon-WIDERA-2021 project irecs (improving Research Ethics Expertise and Competences to Ensure Reliability and Trust in Science). Through the SCORE analysis of the gaps in the ethics review process of research involving four technologies selected in the irecs project (AI in Health and Healthcare, Extended Reality, Biobanking, and Genome-Editing) at the EU, Member State and non-EU state level, the deliverable provides proposals on adaptation of the ethics review process drawing on the earlier T2.2, T2.3 findings.

First, the deliverable identifies the **cross-cutting challenges** related to ethics review processes common to all four technologies such as lack of transparency, lack of coordination, lack of specific guidelines, limitations of ex-ante review, resource constraints, lack of technical knowledge and expertise, difficulties in involving all relevant stakeholders and ethics review boundaries in data protection. It is proposed that

- transparency could be enhanced by publicizing review criteria, research ethics committee (REC) composition, and decisions.
- Improved coordination between RECs could be achieved by utilizing existing collaborative networks and organizing feedback sessions with researchers and stakeholders.
- Specific guidelines would be helpful for ethics review of new emerging technologies such as Artificial intelligence (AI) in health and healthcare, extended reality (XR), and genome editing (GE), alongside the adoption of a risk-based review approach to allocate resources efficiently.
- To address knowledge gaps ongoing training of REC members is needed, and/ or committees could be adjusted to include technical experts. Involving laypeople in reviews ensures diverse perspectives are represented.
- Furthermore, the role of RECs in data protection must be clarified to enhance collaboration with data protection bodies, ensuring General data protection regulation (GDPR) compliance while avoiding redundancy.

Regarding **AI in health and healthcare,** the deliverable gives several proposals to address ethical challenges, such as the lack of uniform and coherent guidelines across EU Member States, neglect of novel issues in AI in healthcare, the rapid advancement of technology, and ambiguities in the review process.

- To address the inconsistency of guidelines, it is suggested that collaboration between members of REC and experts be promoted to ensure a unified implementation of EU-level recommendations and ethical appraisal guidance.
- To tackle the neglect of emerging AI-related issues, it is proposed to involve AI experts in medical RECs or establish dedicated Digital Ethics Committees (DECs) specializing in the review of AI projects.
- In response to the fast-evolving nature of AI technology, involving RECs in the early stages of project development through "ethics by design" is proposed.
- Lastly, it is important to establish consistent and coherent AI guidelines across all EU member states to ensure ethical review consistency.

Regarding **XR research,** several challenges were recognized, including physical and psychological health risks, unclear data scope, social impact, and the ontological status of virtual objects. To address these challenges, proposed solutions include:

- establishing clear safety guidelines, setting ergonomic standards for XR hardware, and warning participants about content risks.
- Platforms should ensure inclusivity, create age-specific spaces and implement early issue detection with ongoing participant support.
- Data collection parameters must be clearly defined, with privacy features in place.
- Social impacts, especially on vulnerable groups, should be continuously assessed. AI-generated content must be clearly labeled with explicit permission to use personal data, while virtual crimes must be detected and addressed.

Concerning **biobanking (BB) related research** ethics review, the following specific challenges are addressed: difficulty in navigating biobank regulations, variations in ethics review, limitations in current broad consent policies, unclear policies regarding the return of individual health-related findings, and narrow legal definitions of biobanking.

- In response to the challenge of navigating biobank regulations, it is proposed to encourage networks of RECs and biobanks to share ethical and legal requirements using existing platforms, with the aim of promoting harmonization.
- For variations in ethics review, it is recommended to further research the importance of ethics reviews during biobank establishment versus research using biobank resources.
- To address limitations in current broad consent policies, it is suggested that the ethics review of biobank consent frameworks include an assessment of whether the consent model reflects the evolving nature of biobank research. This should include explanations of different types of research, commercialization, genome sequencing, objections to certain types of research, and ease of withdrawal.
- The possibility of adopting an IT-based consent model should also be explored.
- To clarify policies regarding the return of individual health-related findings, it is proposed that when biobanks consult RECs about the return of specific findings, RECs should engage with various experts, such as geneticists, psychologists, and other relevant specialists.

Finally, the deliverable addresses some specific challenges related to **GE research** ethics assessment.

- Responding to the difficulties in navigating the future of embryo research and heritable human GE, it is proposed to develop oversight and governance mechanisms to prevent altering embryo DNA for reproductive purposes.
- Regarding the lack of distinction in guidelines between somatic and heritable GE in some non-EU countries, it is proposed to evaluate the regulatory framework of genome editing in these countries in case of international research.
- To cope with the complexity of assessing somatic GE research, the proposal to prioritise ethics-by-design governance model is made. A lack of governance frameworks for experimental treatment involving somatic GE can be improved by setting up a patient ombudsman system.
- Challenges of animal GE potentially leading to human enhancement should be dealt with by RECs taking into account possible implications of such research to humans.
- Finally, the vagueness of ethical requirements and differences in non-human GE application regulations can at least partially be addressed by harmonization initiatives between the EU countries and developing a more detailed checklist of assessment criteria.

The proposals are also matched with the survey results among ENERI, EUREC, EUA and EARMA members on experiences, needs, gaps in the ethics review process and preferred training methods. The most important findings of the research ethics experts' survey results in all four technologies are followed by a summary of how the survey results fit the challenges to ethics review identified in the SCORE analysis. The findings of the deliverable focused on the EU and some non-EU countries will be integrated into the ENERI Classroom. The proposals for the adaptation of the ethics review process, focusing on the EC ethics self-assessment and existing guidance will be trialled at pilot universities (T5.3).

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List of acronyms/abbreviations

Abbreviation	Explanation
AI	Artificial Intelligence
BB	Biobanking
EC	European Commission
DPO	Data Protection Officer
EU	European Union
EUREC	European Network of Research Ethics Committees
GDPR	Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
GE	Genome editing
OECD	Organization for Economic Cooperation and Development
XR	Extended Reality
RECs	Research Ethics Committees
WMA	World Medical Association
SCORE	Strengths, Challenges, Options, Responses, Effectiveness

TABLE 1: LIST OF ACRONYMS/ ABBREVIATIONS

Glossary of terms

Term	Explanation
Artificial intelligence in	Artificial Intelligence (AI) in healthcare refers primarily to the application of machine learning to improve various aspects of

health and healthcare	healthcare and medical practices, e.g. diagnostics or remote consultation
Biobanking	Biobanking refers to collecting and storing biological materials and their associated data.
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.

TABLE 2: GLOSSARY OF TERMS

1. Introduction

1.1. Background

This document provides a SCORE analysis of the contents of the artificial intelligence (AI) in health and healthcare, extended reality (XR), biobanking (BB), and genome editing (GE) components of the irecs Task 2.2 Deliverable concerning ethical challenges of new and emerging technologies and ethics review processes. Based on the scoping and screening work in Task 2.1[1], the consortium was able to examine within Task 2.2[2] the relevant literature, which helped to define the most pertinent issues of concern for REC members and propose an analytical framework that was also used in Task 2.4 for the development of the quantitative survey. To address the specific ethical considerations related to the review of research conducted in non-EU countries, D2.4 draws upon the findings of D 2.3.

It also considers the strengths and challenges of ethics review processes on new technologies identified by previous relevant projects including Ada Lovelace Institute report[3], TechEthos project report[4], Sienna project report[5], and Panelfit project Governance report[6].

It first maps the key strengths of ethics review in this area, before describing the many challenges facing RECs concerning AI in health and healthcare, XR, BB, and GE, the various options for addressing these challenges, the potential external responses to those options if implemented, and finally the likely effectiveness of the chosen strategies given all the complex factors involved and their potential efficiency leading to actionable proposals addressing cross-cutting challenges as well as challenges relevant to specific technologies. Finally, the document provides the most important findings of the research ethics experts' survey results in all four technologies followed by a summary of how the survey results fit the challenges to ethics review identified in the SCORE analysis.

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[1] Resseguier, A., Naserianhanzaei, E., Mijatovic, A., Chatfield, K., Spyrakou, E., Proske, D., Aucouturier, E., Grinbaum, A. (October 2023) *Report on the case studies, irecs project D2.1.*

[2] Aucouturier, E., Grinbaum, A., et al. (November 2023) irecs D2.2 “Recommendations to address ethical challenges from research in new technologies”. Available at: https://irp.cdn-website.com/5f961f00/files/uploaded/Deliverable_2.2.pdf

[3] Ada Lovelace Institute (2022) Looking before we leap: Expanding ethical review processes for AI and data science research. rep. Available at: https://www.adalovelaceinstitute.org/report/looking-before we-leap/

[4] Seedall, C., Lindemann, T., Klar, R., Tambornino, L., (2023). Criteria for ethical review by RECs in emerging technology research. TechEthos Project Deliverable. Available at: www.techethos.eu. https://www.techethos.eu/wp-content/uploads/2023/11/TechEthos_D5.4.pdf

[5] Lisa Tambornino, Dirk Lanzerath. SIENNA D.3.3: Survey of REC approaches and codes for human enhancement (19th August 2019). https://zenodo.org/records/4066874

[6] Jurate Lekstutiene, Julia Maria Mönig, et al. PANELFIT D 5.3 Report on the governance of data protection ELI in ICT research and innovation (2021). Available at: https://www.panelfit.eu/other-outcomes/

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1.2. Methods

The methods employed to carry out the research presented in this report consisted of (a) the SCORE analysis of the ethical challenges and corresponding training needs for REC members and EU ethics appraisal scheme experts identified in Task 2.2 Deliverable, and (b) the online quantitative survey to understand how the REC members and other ethics experts approach the mentioned ethical challenges of emerging technology research in practice.

The SCORE analysis of the gaps in the ethics review process/the training needs and the online quantitative survey were conducted in parallel, which allowed us to match the results of the two methods in the end and assess whether empirical data corresponded to the data derived from earlier deliverables of the project.

The survey was developed following the analytical framework of the Task 2.2 deliverable and addressed both procedural/organizational issues of ethics review, such as ethics governance models used to assess different technologies as well as content-related issues of ethics review, for example, scientific/technical and ethics competencies of REC members and other ethics experts.

Regarding the SCORE analysis, the Task 2.2 materials were analysed in two rounds. Each technology was assessed by separate partners: four partners (UM, VU, EUREC and UBO) were responsible for the primary SCORE assessment of AI in health and healthcare, XR, BB, and GE. These partners of Task 2.4 and KIT also conducted the second round of analysis. Other partners of this task contributed to the dissemination of the survey.

1.2.1. SCORE Analysis

SCORE tool has been used to analyse irecs Task 2.2 and 2.3 deliverables concerning ethical challenges of new and emerging technologies and ethics review processes, focused on the EU, China, and Africa. A key difference from a more familiar SWOT method for basic strategy assessment is that, rather than just grouping concerns into four categories, SCORE creates a more interactive framework of different dimensions – an item in one dimension leading us to another item in one of the other dimensions. Also, in contrast to SWOT, SCORE can be used in more complex contexts such as multi-organisation partnerships, and adopt a more holistic perspective that allows to assess interactions between different factors. This helps to build a richer picture of more real-world strategic alternatives.

Score analysis dimensions are as follows:

- ***Strengths*** / *services* / *support*: existing capabilities and resources, and/or potential for new synergies
- ***Challenges*** / *constraints* / *capabilities needed*: concerns that indicate needed capabilities and resources
- ***Options*** / *opportunities and risks*
- ***Responses*** / *returns* / *rewards*: probable or emergent consequences of action or inaction
- ***Effectiveness***: related dimensions for impact on effectiveness in the context – efficient, reliable, elegant, appropriate, integrated

The SCORE analysis **emphasizes different *time-perspectives***:

- **Strengths and Challenges** address ***present/past time-perspective. These dimensions*** look at the legacy from the past or what is relevant today.
- **Option and Response** are oriented towards the ***future*, these dimensions** look at what is desired in the future or may impact us in the future.

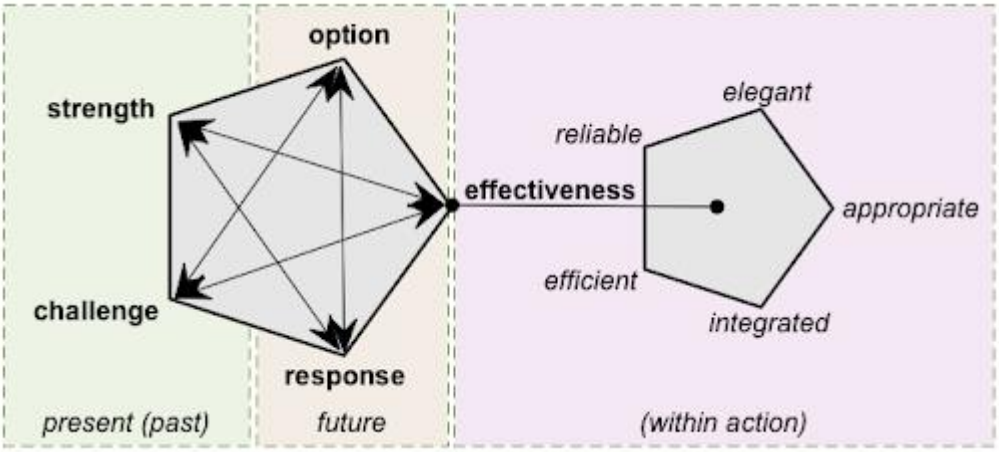

Figure. 1: Time perspective of SCORE (source: http://weblog.tetradian.com/2013/06/29/checking-the-score/)

- **Finally, effectiveness** (that is proposal for action being efficient, reliable, elegant, appropriate, integrated) looks at the implications and cross-dependencies as we put into action the bridge between present and future[7]. For Task 2.4 we use criteria of **SCORE Effectiveness** to draft concrete actionable **Proposals.**

1.2.2. The Survey

To understand how Research Ethics Committees (RECs) and ethics experts approach ethical reviews of emerging technology (AI in health and healthcare, XR, BB, and GE) research, an online survey was conducted from 2nd February 2024 to 2nd April 2024. The survey has been developed to match the main challenges identified by the SCORE analysis of Task 2.2 Deliverable.

Survey design and topics

The survey was designed to collect data on experiences, needs and gaps in the ethics review process and preferred methods of training. It contained several key sections, each for specific information from participants. Participants provided demographic information and professional background, including their country of work, years of experience in ethics assessment, main disciplinary background, and their roles in the ethics assessment process. This information helped contextualize the responses based on participants' backgrounds and expertise.

[7] Graves T. SEMPER and SCORE: enhancing enterprise effectiveness (2008)

The survey was designed to allow experts to select one of the initial multiple-choice questions relevant to the technology they work with. Those who did not select a specific technology were not asked questions related to it. In total, we received responses from 242 participants, out of which 149 completed the entire survey by selecting all the technologies.

In the biobanking section, participants were asked when an ethics review is required in their country. They self-assessed their competence in addressing ethical issues such as consent, data protection, data privacy, data sharing, return of individual health-related findings, involvement of children, and commercialization. Participants also shared their opinions on when ethical review is most necessary for biobank-related research.

In the AI in Healthcare section, participants evaluated their competence in addressing ethical issues, including consent, data protection, data privacy, data sharing, bias, justice and fairness, transparency/explainability, and responsibility for the consequences of AI applications. They also considered the criteria that determine when AI-related research falls within the scope of RECs.

Regarding extended reality (XR), some questions were similar to AI's: participants considered the criteria determining when XR-related research falls within REC scope. Also, they assessed their competencies in addressing ethical issues such as consent, data protection, data privacy, and data sharing. Some questions were specific to XR - like violence or abuse in XR environments, mental health issues, AI usage in XR research, involvement of children, and cybercrime. Experts self-assessed their understanding of XR technologies' inner workings and differences, including virtual reality, augmented reality, and XR using AI.

In the genome editing (GE) section, participants reflected on their competencies in addressing ethical issues related to somatic, germline, and non-human genome editing. For somatic genome editing, they considered issues such as consent, safety, accessibility, enhancement, and misuse. Similar ethical issues were addressed in germline genome editing, acknowledging the additional considerations due to heritable changes. For non-human genome editing, participants focused on safety, accessibility, enhancement, misuse, and protection of species.

The survey also explored cross-cutting ethical issues, where participants reflected on broader ethics governance and assessment practices across all technologies. They provided insights into the types of ethics governance applied—such as self-assessment, REC reviews before starting projects, and ongoing monitoring—and shared opinions on the sufficiency of current governance structures, offering suggestions for improvement. Key factors hindering effective ethics assessment were identified, including a lack of ethics expertise, insufficient scientific or technical understanding, inadequate guidelines, limited training opportunities, and scarce funding. Additionally, participants considered the feasibility of addressing broader societal impacts, like risks of discrimination and stereotyping, within research involving each technology. They reflected on the potential for implementing continuous ethics oversight, or "ethics by design," throughout the research lifecycle, beginning from the design stage.

The final section of the survey assessed training needs, evaluating participants' desires for additional training in each technology area. Participants selected the training content they believed would be most beneficial, and preferred modes of training and learning styles for online training were specified.

The survey target groups were the European Network of Research Ethics Committees (EUREC), the European Network for Research Ethics and Integrity (ENERI) e-community, the European University Association (EUA) Research & Innovation Strategy Group (Rectors or Vice-Rectors for Research) and the European Association of Research Managers and Administrators

(EARMA). Thus, the survey was disseminated among members of ENERI, EUREC, EUA and EARMA In addition, participants were recruited by other project partners who distributed the survey invitation with a link. The same recruitment strategy was implemented in the EU and non-EU countries.

The questionnaire was hosted online and managed by RAIT GROUP, an independent market research company, ensuring confidentiality and professional handling of the data.

Quantitative data were analyzed using descriptive statistics to identify trends and patterns among participants. We conducted additional analyses by categorizing participants into EU and non-EU groups and further segmented the data for specific regions, including the EU, China, Africa, and others. Where possible, statistical significance tests were performed to determine if observed differences between groups were meaningful.

Cross-tabulations were used to identify relationships between variables, and qualitative data from open-ended responses were analyzed to identify recurring themes, concerns, and suggestions.

This comparative analysis across different technologies and regions helped identify unique challenges and commonalities. A regional breakdown provided a better understanding of how ethical assessment practices and needs might vary in different parts of the world.

Challenges and limitations

A significant issue was the overrepresentation of participants from the European Union, which may have skewed results toward EU perspectives and limited the global applicability of our findings. The low number of participants from regions like Africa meant that specific regional insights were underrepresented, affecting the diversity of perspectives.

Response bias, including self-selection and social desirability bias, is a common issue with any survey and might have influenced the results. Participants with a particular interest in emerging technologies may have been more likely to respond, and some may have provided answers they thought were expected rather than reflecting their true opinions.

Data limitations included incomplete responses, resulting in varying sample sizes for different analyses. Self-assessments of competencies may not accurately reflect actual expertise, presenting potential inaccuracies.

Despite these limitations, the survey provided valuable insights into the current state of ethical reviews for emerging technology research and highlighted areas where further support and resources are needed.

The survey questionnaire (Annex 1) and the RAIT report (Annex 2) are **provided as attachments to this repor**t.

Profile of survey participants

Based on the analysis of respondents‘ demographics, a significant majority of participants in this study work within Europe (77%). Comparatively, a much smaller portion originates from China, comprising 12% of the sample, followed by Africa with 7%. The remaining 4% come from various other global regions.

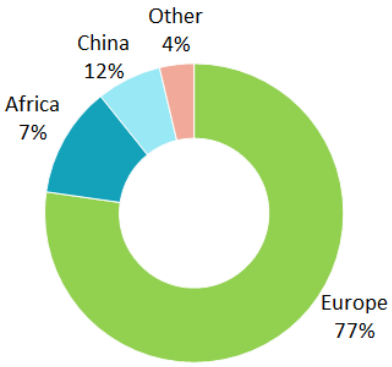

Figure 2: Demographics of survey respondents

From this point, all results shown are from European respondents.

The respondents' predominant disciplinary backgrounds are biomedicine/health science (32%), social sciences (22%), and life science (17%).

The largest segment of study participants comprises members of the research ethics committee (REC) (58%), followed by EU ethics experts (40%), and a bit more than a quarter are external ethics reviewers (not REC members) (27%).

Most of the study participants are involved in the ethical assessment of research projects centered on AI in health and healthcare (66%) and human biobanking (56%). The lowest number of participants dealt with germline and somatic genome editing (18% and 21%, respectively).

1.3. Structure of the report

After presenting a short background information about the project and its methods, Chapter 2 of this document provides a SCORE analysis of the contents of the artificial intelligence (AI) in health and healthcare, extended reality (XR), biobanking (BB), and genome editing (GE) component of the irecs Task 2.2 Deliverable concerning ethical challenges of new and emerging technologies and ethics review processes. The Chapter also includes an analysis of the survey results. Chapter 2 starts with the analysis of Cross-cutting strengths, challenges, options, responses, and actionable cross-cutting proposals on how to deal with the identified challenges. In addition, different sections of Chapter 2 on cross-cutting issues also integrate results from Deliverable 2.3 on ethical challenges from technology research outside the EU. The analysis of cross-cutting issues is also followed by presenting the research experts Survey results. The Chapter continues with a mapping of many technology-specific challenges facing RECs concerning AI in health and healthcare, XR, BB, and GE, the various options for addressing these challenges, the potential external responses to those options if implemented, and finally the likely effectiveness of the chosen strategies given all the complex factors involved and their potential efficiency, which leads into concrete actionable proposals for each technology. Each technology-specific section also provides the most important findings of the research ethics experts survey results in all four technologies, and a summary of how the survey results fit the challenges identified by the SCORE analysis. Finally, Chapter 3 provides an Overview of

proposals for adaptation of ethics review processes addressed to different stakeholders and Chapter 4 concludes the report.

2. SCORE analysis and survey findings

2.1. Cross-cutting strengths

2.1.1. Established REC review systems.

At most institutions worldwide, involved in health-related research, researchers have to submit their work to REC for ethics approval before conducting the study – typically at the early stages of the research lifecycle (e.g., planning stage or when applying for research grants). REC members provide an opinion on ethical issues relating to research. In many countries, RECs are also expected to advise researchers, produce guidance for how research should be conducted, and monitor instances of unethical behaviour. However, in terms of biobanking, there is also an acknowledgment of ethics oversight beyond REC review. There might be various bodies established like ethics committees or advisory committees by various biobanks for ethics advice and proposals beyond the REC review system. This reflects a proactive approach to handle ethical considerations in biobank activities.

2.1.2. Multidisciplinary composition of RECs.

The composition of RECs varies. In different countries, RECs requirements for the number and composition are established by laws or guidelines. Usually, RECs comprise an interdisciplinary board of people who bring different kinds of expertise to ethical reviews. Multidisciplinarity is one of the most important strengths of RECs in general, which can be of particular importance in the area of emerging technologies, such as AI in health and healthcare, XR, BB, and GE.
RECs may include professionals in the field of research protocols they review (physicians/ engineers/ social scientists, researchers, lawyers, ethicists, statisticians, etc.) as well as non-professionals (e.g., patients' representatives). A 'lay member' is in many medical RECs mandatory, but not often required in RECs of other disciplines. This ensures that perspectives from different disciplines and life experiences are taken into account when making a decision, including 'lay members' or patients' perspectives, ethnic and gender diversity.

2.1.3. Established ethical and legal framework

sets general requirements for research involving humans or their data. There are numerous international and national legally binding instruments as well as ethical guidelines regulating research with human or their data.
Besides instruments specific to research involving human or their data, international instruments related to data processing, such as the General Data Protection Regulation (GDPR) in EU countries, and global human rights instruments like the UN Universal Declaration of Human Rights[8], provide complementary frameworks that further contribute to the ethical conduct of research practices. There are also existing regulatory frameworks for the use of genome editing

[8] United Nations General Assembly. The Universal Declaration of Human Rights (UDHR). New York: United Nations General Assembly, 1948.

in humans. The WHO has issued guidelines for recommendations[9] as well as a framework for the governance of human genome editing[10]. There are also guidelines from the International Society for Stem Cell Research (ISSCR) regarding heritable human genome editing[11]. Human genome editing applications in the EU seem to generally follow relevant EU regulations and the regulations are being implemented and watched rigorously on a national level.

2.1.4. RECs tend to have substantial expertise

in assessing basic ethical issues such as informed consent, risk benefit assessment, privacy and data protection (both in terms of ethics and law) which are also highly relevant in terms of AI in health and healthcare, XR, BB, GE. For this reason, RECs also tend to focus on these issues when evaluating research projects. A clear focus helps researchers understand what to expect from ethics review and which ethical issues are most important for RECs to address. Another key strength of RECs in general is their main priority to protect the safety of patients, participants in research and society, and most RECs aim in achieving this by ensuring that they have the necessary expertise and processes for the evaluation of new and emerging technologies in place. RECs usually display a diverse expertise of their members which helps in delivering comprehensive ethical evaluations. This is a great benefit for evaluating new and emerging technologies that usually touch on various ethical and legal challenges. For example, while evaluating research associated with GE, RECs focus on specific ethical and legal issues including technical and safety risks such as off-target effects and mosaicism, justice and equality issues as well as gene drives and risks associated with genetically modified organisms and their relations with the ecosystem.

2.1.5. The support for researchers and ethics reviewers at the EU level.

Research projects funded by the European Commission involving emerging technologies often require a full review with a group of external experts, and many of such projects have independent ethics advisors, meaning that projects will receive expert review and oversight both before and during the research phase. High-risk projects undergo additional ethical reflection mechanisms, including the assignment of an ethics officer to provide guidance and perform intermittent ethics checks.
Also, technologies such as biobanking and AI in health and healthcare, GE are specifically listed in the ethics self-assessment tool, which helps researchers to identify and address ethical issues in the research projects involving these technologies.

2.1.6. Ethics by design approach

is already part of Horizon Europe ethics review framework. Ethics by Design is an approach for systematically and comprehensively including ethical considerations in the design and development process of new technological systems and devices. Historically its focus has been on the design of AI systems, however, this approach can be applied to any technology. Under the Horizon Europe ethics review procedure, compliance

[9] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. Human Genome Editing: Recommendations. Geneva: World Health Organization; 2021.
[10] WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. Human Genome Editing: a Framework for Governance. Geneva: World Health Organization; 2021.
[11] International Society for Stem Cell Research. ISSCR Guidelines for Stem Cell Research and Clinical Translation. 2021. Available at: https://www.isscr.org/s/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf

to AI research ethics standards is mandatory for AI projects, and the use of the EbD-AI approach is recommended[12].

2.2. Cross cutting challenges, options, responses, proposals, and survey results

2.2.1. Lack of transparency

Challenge: In some situations, RECs activities can lack transparency with their processes. This is particularly important for corporate RECs, which focus primarily on corporate values, legal compliance, and reputational risk. For example, private, commercial companies that wish to bring their project to market quickly might try to avoid ethics review, or review their projects with their own REC, raising concerns about independence and the quality of review. Some companies might want their project to be reviewed but have no relevant committee to consider their application. A related challenge for RECs in this area is that many ethics reviewers are involved in projects involving a specific new technology, and therefore have a conflict of interest that prevents them from being involved in reviewing those proposals.

Based on the findings of D2.3, other transparency related challenges are observed in non-EU countries where RECs may not be independent of government bodies, academia, or industry. While institutions themselves prefer to have their own ethics committees, many are actually known to suffer flaws in terms of expert qualifications and conflicts of interest, which undermines the ethical review process. Another related challenge noted in the D2.3 is that ethics review is often regarded as a mere bureaucratic formality, with the process being reduced to the completion of forms. Even more concerning are instances where researchers entirely overlook ethical and research integrity concerns to advance their studies. This can happen because some researchers still hold stereotypical misconceptions, like the belief that no boundaries should be set for research and that emphasizing the role of ethics hinders scientific progress.

A proportionate number of them still treat the ethical review as an unnecessary burden. It is not uncommon for researchers to choose to compromise the ethical soundness and prepare their research proposals in a way more likely to win approval from the ethics committees. Even more, some EU researchers may be engaged in unethical research by allowing their foreign counterparts to conduct studies in China which will not be approved in their own home countries. And this has been done in the guise of international cooperation.

In many non-EU regions, the reluctance of researchers to fully integrate ethics into their work is compounded by a lack of institutional support. Research may formally comply with ethical standards "on paper," but in practice, ethical oversight is inadequately enforced. To sum up,

[12] Dainow, B. and Brey, P. (2021) Ethics By Design and Ethics of Use Approaches for Artificial Intelligence. rep. European Commission. Available at: 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

there is a lack of an institutional or research culture that recognizes and values ethical considerations.

Option: Increasing RECs' transparency. Clear mechanisms for REC members to declare conflicts of interest abstaining from participating in the review of studies where they have conflicting interests should be implemented[13]. Access to previous REC submissions and decisions can inform REC policies and researchers, ensuring consistency and aiding in navigating novel ethical questions. Listing institutional policies and guidance promotes dialogue and ensures researchers understand the importance of responsible research.

As mentioned in D2.3, institutional support is a necessary resource for REC work and research in general. The issue is not only about the material support needed from the institution, in terms of funding, personnel, and infrastructure, but also the necessity of establishing a certain institutional culture that values and appreciates the work of RECs instead of seeing "this procedure as an obstacle in their way" in terms of working conditions and necessary infrastructure as well as institutional culture and support.

The proposals and recommendations identified for EU countries, such as clear guidelines on managing conflicts of interest and increasing transparency in REC activities, are equally relevant in non-EU contexts.

Response: Publicly releasing ethical review criteria and processes can enhance transparency, allowing stakeholders to understand the considerations behind corporate decisions. REC members should be required to declare any conflicts of interest and should be prohibited from participating in the review of any study in which they have a conflicting interest. Releasing transparency reports on rejected, amended, and approved studies can hold RECs accountable for their ethical practices and decision-making.

Proposals:

- RECs should have specific guidelines on managing conflicts of interest.
- RECs should publicly release (preferably in centralized repositories) ethical review criteria, the sources of REC funding, the composition of RECs, a list of institutional policies and guidance, report on previous REC submissions and decisions (approved, rejected, and amended studies).

2.2.2. Lack of coordination

Challenge: A related challenge deals with a lack of coordination between RECs evaluating AI in health and healthcare, XR, BB, and GE research (especially multi-site research involving diverse jurisdictions). This leads to variations in processes, decision-making, and outcomes.

As highlighted in D2.3, the non-EU countries face similar challenges. Due to the differences in administrative jurisdiction and the differences in their professional scope, institutions and departments have different work mechanisms, policies, and requirements for ethical review and supervision. Difficulties may inevitably arise when it comes to the setting of standards and

[13] World Health Organization (2023). WHO tool for benchmarking ethics oversight of health-related research involving human participants. Available at: https://www.who.int/publications/i/item/9789240076426

principles in real practice, particularly since interdisciplinary research is increasing, which necessitates cross-departmental reviews.
Experts identify challenges in the absence of mechanisms for monitoring adherence to existing guidelines in non-EU countries. Although some countries have relatively strong regulations, there is often no structured approach to ensuring compliance with these standards.

Options: create knowledge-sharing hubs for researchers and REC members, encourage more cross-institutional learning, and foster networking and collaboration between RECs using existing networks, such as EUREC. Centralized repositories can provide access to shared resources, news articles, literature, and lists of problematic cases fostering reflection on research ethics. It should be taken into account that maintaining and updating the repositories requires ongoing effort and resources, which may be challenging for institutions, especially if the hubs are not widely utilized. Therefore, careful consideration is required regarding governance structures and the practicalities of establishing the hubs at the institutional or national level. Sharing previous REC applications and decisions must be done considering privacy and confidentiality concerns. Regular feedback sessions with researchers about their experiences in the implementation of research and their thoughts about the ethical issues surrounding their work would be desirable. At the same time, stakeholder discussions (including the interested public, if possible) on the aims and impact of the specific research, are also vital in achieving reflection and anticipation.

Many of the challenges faced by non-EU countries can be addressed by adapting proposals from the EU context: the cross-institutional learning and knowledge-sharing hubs could be extended to non-EU regions, providing essential training for ethics boards, particularly in managing new technologies. Also, the emphasis on regular feedback sessions and transparency in declaring conflicts of interest could help strengthen institutional support (see section 2.2.1).

As identified by D2.3, there is the necessity of adequate monitoring or supervision of the review process for it to happen and to enable accountability. Government, industry and research institutions should take a more active role in developing policies in this respect.

Response: Establishing knowledge-sharing hubs fostering national networks and enhancing existing collaboration.

Proposals:

- RECs should be encouraged to utilize existing networks, and provide access to shared resources, news articles, literature, and lists of problematic cases.
- RECs should organize regular feedback sessions with researchers about their experiences in the implementation of research. Other stakeholders, including patients' representatives and external experts, could also be invited to share their thoughts about the ethical issues surrounding research on AI in health and healthcare, XR, BB, and GE.

2.2.3. Lack of specific guidelines

Challenge: There is a lack of clear and specific guidelines, particularly in the field of AI in health and healthcare, XR, and GE for researchers, RECs, and institutions on implementing ethical research. In addition, current general guidelines and regulations (e.g. on data protection in EU countries) are inconsistently implemented across different countries, disciplines, and departments within institutions.

For example, speaking about the human GE research there are currently no specific guidelines on human enhancement for REC members. Many REC members would welcome guidelines on human enhancement[14]. If guidelines aren't developed, RECs will be in a difficult position because they must make policy ad hoc.

Based on D2.3 findings, the lack of specific guidelines in non-EU countries mirrors the challenges seen in the EU, particularly in fields such as AI, XR, and genetic engineering. Even in the field of biobanking, despite the relatively good regulations and guidelines available in some countries, there is still a lack of an established mechanism for monitoring adherence to existing guidelines. Technological advancements occurring in high-income countries have become accessible worldwide almost immediately, but there is a significant gap in how these technologies are ethically managed. This lack of clear guidelines and training leaves many ethics boards unprepared to handle the complexities of emerging technologies. Some experts interviewed in D2.3 also emphasize that existing guidelines are often tailored to "data ethics" and fail to address broader technological applications, there is also a lack of consideration for research in the social sciences dealing with emerging technologies, a lack of focus on and regard for vulnerable communities and a very biased in terms of adopting specifically Western concepts. This is particularly important due to the increasing number of populations displaced by war, conflicts, and pandemics. These populations are highly vulnerable and there are practically no guidelines that are sensitive to realities, cultures, needs, vulnerabilities, especially of people in the South." (see also section 2.2.7)

Option: Develop standardised guidelines for AI in health and healthcare, XR, and GE research including ethics review protocol templates for RECs. These guidelines should be aligned with existing regulations like GDPR and include input from a variety of stakeholders (RECs; researchers; policymakers; funders; technology experts; and those likely to be affected by respective research).

Guidance should ideally be maintained by a permanent body such as a learned society or ethics organisation, regularly updated and distributed through REC networks to increase visibility. It should be noted that even with standardized guidelines, there may be variations in how institutions interpret and apply them, leading to continued inconsistency in ethical decision-making. Ensuring the involvement of underrepresented regions and communities in principle development is crucial, but there's a risk of their perspectives being overlooked or marginalized in the process. Another risk relates to the fact that technologies often advance faster than regulatory frameworks, meaning that RECs have to review projects that are not covered by existing legislation and regulation.

Response: Standardized principles and guidance can promote consistency in ethical decision-making across different RECs, reducing the risk of inconsistent decisions and enhance research integrity by providing clearer standards for addressing ethical challenges such as bias, privacy, and broader societal impacts. Involving representatives from different stakeholder groups and diverse nations ensures that the guidelines consider a wide range of ethical perspectives beyond Western societies, enhancing inclusivity and relevance. Engaging in a multinational effort, led

[14] Lisa Tambornino, Dirk Lanzerath. SIENNA D.3.3: Survey of REC approaches and codes for human enhancement (19th August 2019). https://zenodo.org/records/4066874.

by bodies like the OECD can facilitate the development of inclusive and globally applicable ethical guidelines.

The suggestion to create standardized guidelines that cover emerging technologies and are regularly updated by a central body would equally benefit non-EU countries. These guidelines could provide clarity in areas where policymakers lack sufficient knowledge to properly evaluate emerging technologies, ensuring that these guidelines are inclusive of vulnerable communities and incorporate perspectives beyond Western concepts would address concerns about bias.

2.2.4. Limitations of ex-ante review

Challenge: One-time REC review before starting the project (ex-ante review) cannot address all ethical issues that emerge at different stages of some types of AI in health and healthcare, XR, and GE research. Current review processes of research involving these technologies are often limited to this type of evaluation, but ethical and societal risks can emerge at various stages from idea to publication (for example, not only during a project, but also long after a REC has approved an application), posing challenges for assessment because the outcomes of data-driven research are unpredictable until data is processed.

The limitations of ex-ante review in non-EU countries, particularly for emerging technologies, are similar to those seen in the EU but are often more pronounced due to insufficient knowledge among REC members and a general lack of interest in ethics from researchers working in these fields. As highlighted in D2.3, research ethics considerations in science and technologies, especially in non-EU countries, are often reduced to filling forms, adhering to procedures, or doing routine activities. Lack of communication between research ethics committees and researchers and the need for a specific institutional or research culture was also identified as an obstacle to ethics review in non-EU countries by D 2.3 (see also Challenges 2.2.1 and 2.2.2).

Options: To follow a risk-based approach to determine cases when self-assessment of the project by the researcher himself/herself is sufficient or whether a one-time review, one-time review followed by monitoring, or ethics by design is required. The risk-based approach is also important for classifying risk levels and developing exemptions or expedited review procedures for low-risk projects. The extent of a REC's review varies depending on whether the project has any identifiable risks to participants or society. Many RECs apply a triaging process to identify research that may pose particularly significant risks. If projects meet certain risk criteria, they may be subject to a more extensive review by the full committee (full research ethics review). Lower-risk projects may be approved by only one or two members of the committee (expedited process). RECs may use a checklist that asks a researcher whether their project involves particularly sensitive forms of data collection or risk. During the review, RECs may offer researchers advice to mitigate potential ethical risks. Some RECs perform further checks when approval is granted (e.g. monitor SUSARs, periodic safety reports, review substantial modifications in clinical drug trials involving somatic GE or clinical investigations on medical devices including AI).

For gene drive experiments, there could be a case-to-case approach for RECs, as these kinds of experiments can cause extreme environmental effects depending on the purpose of the experiment and the type of genome editing used. If genetically modified organisms will be released into the wild, free, prior, and informed consent of the potentially affected communities should be obtained. For heritable genome editing in humans, there is a moratorium in place until the possible effects on future generations are better understood. For heritable genome editing

in animals, a case-to-case approach would be equally beneficial to better assess the possible risks of the experiments.

Assess the ethics-by-design approach, if applicable. D2.2 and D2.3 findings revealed that ethics reviews need a fresh perspective concerning new and emerging technologies. Not only knowledge of the state-of-art in many technologies is missing in RECs, but even more significantly, there is a widespread lack of interest in ethics among research scientists working in these areas. A possible solution to this conundrum could be the “ethics by design” approach. This means the embedment of ethics in the early stages of technological development, in tandem with researchers and developers. In this manner, ethics becomes a design principle for the technology product, avoiding future mishaps when people are faced with its implications. Ethics by design can be incorporated at a local level with guidance from local principles[15].

If research aims to develop a technology or create an application for a technology, request researchers to develop an ethics-by-design roadmap. This roadmap should specify how researchers will maintain ethical compliance. Researchers could reflect on the points listed in the “Specification of Objectives against Ethical Requirements” [16]. Where applicable, researchers should specify the populations likely to be impacted by this research and to seek community input on ethics-by-design roadmaps. However, this option is increasing the complexity of the review process, but it would also respond to the criticism that institutional support is lacking. In such an approach, the RECs would have a significantly more advisory role.

Responses. Follow a risk-based approach to determine the mode of ethics governance, such as ethics self-assessment, one-time “traditional” ex-ante ethics review, traditional review followed by monitoring, or ethics-by-design approach allowing for continuous re-examination and identification of risks.

The recommendation to adopt a risk-based approach and implement an "ethics by design" framework could be highly beneficial in addressing these challenges in non-EU countries. Where different ethical frameworks may be more appropriate, "ethics by design" can be tailored to reflect local cultures and perspectives, making it a flexible and practical solution. Adopting this approach would not only enhance the ethical oversight of emerging technologies but also promote a deeper commitment to ethics among researchers and stakeholders.

A case-to-case approach for gene drives would help minimize the potential adversary environmental effects when using gene drives because the risks can be assessed based on the specific type of genome editing chosen and the purpose of the experiment. Informed consent ensures that the people most affected by the gene drive experiment know the potential benefits of the experiment as well as the risks associated with it and can decide if they want this

[15] Miltos Ladikas, Claudia Brändle, Maria Maia. irecs D2.3 “Recommendations to address ethical challenges from research in new technologies” Recommendations to address ethical challenges from technology research outside the EU”

[16] Dainow, B. and Brey, P. (2021) Ethics By Design and Ethics of Use Approaches for Artificial Intelligence. rep. European Commission. Available at: 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

experiment to happen in their vicinity where it could potentially change their lives for better or worse.

The moratorium on heritable genome editing in humans should remain until the possible risks can be adequately assessed and it needs to be monitored to ensure that researchers obey it. This could lead to a delay in research on the treatment of heritable diseases in humans, but will also ensure that there won't be any uncontrollable dynamics in the germline of the human species.

A case-to-case approach for heritable genome editing in animals would make the evaluation of such procedures more bureaucratic for RECs, but will ensure that there won't be any uncontrollable dynamics in the germline of animals. Even if animals for research are often euthanized after the experiments, there is still the risk that a genetically modified animal can escape the lab and spread the altered DNA in populations outside the lab.

2.2.5. Resource constraints

Challenge: Many RECs are generally under-resourced in terms of budget, staffing, and member recognition, relying on voluntary, unpaid labour from institutional staff and due to limited resources are not able to compensate members for their time, provide timely feedback, and maintain necessary expertise. Insufficient resources can lead to delays in reviews and a negative impact on review quality.

Although these problems have existed to some degree since the development of RECs, this have become increasingly pressing in recent years, particularly with the advent of novel ethical dilemmas in research involving emerging technologies, which pose specific ethical considerations that are often distinct from traditional medical research. For example, if every particular research project has to be evaluated for every disease and patient population in human genome editing and for every organism, ecosystem and environment in non-human genome editing, this will increase the workload of RECs significantly and lead to longer waiting times until a REC finishes an evaluation. This can significantly delay research.

This could also lead to a gap between high-income countries and low / medium-income countries in terms of benefit sharing.

The resource constraints identified in non-EU countries, particularly in regions like the Global South, echo many of the challenges seen in the EU but are often more severe due to greater funding shortages and limited institutional support. While survey data suggests that funding is not always seen as the most significant obstacle, D 2.3 interview responses highlight that a lack of monetary resources and personnel remains a serious issue, particularly as research projects become more complex and involve emerging technologies. This gap becomes even more pronounced when compared to wealthier countries, creating a power imbalance between the Global North and Global South, where researchers in the South are often dependent on those in the North for funding and expertise.

Non-EU regions also face unique challenges, such as the lack of permanent, interdisciplinary RECs and insufficient resources for training, office space, and technology, particularly in African countries. Many RECs in these regions are established on an ad hoc basis to meet the demands of international collaborations, but they lack the ongoing support necessary to maintain independence and neutrality. Furthermore, RECs often depend on their host institutions for budget allocation and lack any means of income, making them vulnerable to political or financial conflicts of interest (see also section 2.2.1).

Options: increase funding and resources for ethical review (including XR, AI in health and health care, GE, and BB research). At the same time, certain risks should also be taken into account. RECs might become overly reliant on external funding, which could jeopardize their autonomy and impartiality in conducting ethical reviews or lead to prioritizing certain research areas over others. There may be concerns about the long-term sustainability of increased funding if it is not accompanied by sustainable mechanisms for resource allocation.

Applying a risk-based approach is also very relevant in the context of scarcity of REC resources as it helps to classify risk levels and develop exemptions or expedited review procedures for low-risk projects.

However, a standardized approach would not be helpful in cases where uncertainty about risks plays a big role. This applies to human genome editing as well as non-human genome editing.

RECs should evaluate the accessibility of new technologies for fair benefit sharing, especially if technologies are used in the Global South.

Responses: additional funding would address operational challenges faced by RECs, such as compensating members for their time and providing timely feedback, thereby improving the efficiency of the review process. Increased resources would enable RECs to maintain and enhance the necessary expertise on their boards, ensuring they are well-equipped to evaluate the ethical implications of research effectively. Funding for interdisciplinary ethics training initiatives would equip REC members with the knowledge and skills needed to address the complex ethical issues arising in research, fostering a more comprehensive approach to ethical reviews. Additional resources would allow RECs to expand their scope and remit to capture the unique risks and impacts associated with research, promoting trustworthiness and ethical conduct. Applying a risk-based approach helps to determine the modality of ethics review, such as multi-stage review, one-time ethics review with full or expedited procedure or to follow ethics self-assessment in case of exemption from ethics review for low-risk projects.

A case-based risk assessment would help RECs assess the individual risks of a procedure/clinical trial much better than a standardized risk assessment. This would help especially in cases where there is a huge uncertainty of risks associated with the procedure/clinical trial, e.g. when the germline is affected.

The suggestion to increase funding, apply a risk-based approach, and foster networking between RECs could help address these challenges in non-EU contexts. Additional resources would allow RECs to compensate members, provide timely feedback, and maintain the necessary expertise. Furthermore, fostering international collaboration and networking between RECs, similar to the EUREC model in Europe, could help non-EU countries access shared resources and expertise, ensuring more consistent and effective ethical oversight across different regions.

Proposals:

- Follow a risk-based approach in ethics review to determine the modality of ethics review to address limitations of the ex-ante review, and mitigate the scarcity of resources.
- Foster networking (such as EUREC) and collaboration between RECs to address challenges related to lack of coordination, specific guidelines, and lack of resources.
- To better address the interests of vulnerable communities in research ethics guidelines.

2.2.6. Lack of technical knowledge and expertise

Challenge: Many RECs lack the technical knowledge and expertise to understand novel challenges from new technology involving research, they face challenges related to the composition, expertise, and training of members which affects the quality and consistency of their reviews. Even fully functioning medical RECs with no general membership issues may nonetheless have no members with specific technology-related expertise. This in turn can make the evaluation of applications involving emerging technologies very difficult. If RECs lack expertise in any area, they may by default become more cautious than usual, putting barriers in place that prevent or delay approval of projects involving specific technology. The alternative is that they approve research but miss relevant technology-related ethical issues because of their lack of expertise, with potential reputational harm resulting if any approved study encounters issues as a result. Given this potential scenario, it is not surprising that RECs might prefer to be over-cautious. To make ethical analysis and work more reflexive and anticipatory, expertise from a broad range of disciplines would be beneficial. Due to structural problems, that might not always be the case which makes it difficult to evaluate new and emerging technologies adequately.

In non-EU countries, the lack of technical knowledge and expertise among REC members poses even more significant challenges for reviewing emerging technologies.

D2.3 findings show the lack of sufficient knowledge and lack of training about how to adequately review research projects dealing with emerging technologies. Not only for the technical review but for the ethics review and for experts who can see the significance of the relationship between the technical and the ethical issues. D2.3 also raises the topic of the differences in needs and approaches to technology between the global South and the global North. North had a longer time to adapt to new and emerging technologies through being part of their development, and thus were able to develop strategies on how to deal with the effects such technologies could have, e.g. through developing guidelines for their use and developing the concept of an ethics review for certain technological applications. This leads to a certain type of responsibility to offer training, sensitization, and knowledge transfer from North to South.

Options. One way to deal with this challenge would be to develop and provide training for current REC members in technology specific ethics review in order to create a larger pool of experts from which RECs can draw reviewers. It should be noted that such training activities require ongoing effort and resources to create and maintain training programs requires.

The need for training is widespread in every REC analysed in this project, whether European or not. There is no doubt that continuous training in new and emerging technologies should be the norm for a good functioning REC. But D2.3 review of non-European RECs shows a particular and urgent need to undertake capacity building on even the most basic functions of a REC. The fact that non-European RECs base their work on European or international guidelines that were made with different research contexts in mind, creates significant challenges in their adoption to the local context. As highlighted in D2.3, based on findings from Africa and China, there is a need for wider capacity-building efforts that can establish a culture of understanding of ethics. In this case, the need can be covered with the promotion of capacity building programmes on ethics, perhaps along with other existing capacity building programmes in Science & Technology areas. A biomedical capacity building programme or even an engineering programme could easily have an ethics part as add-on. Another important option is to adapt the composition of existing RECs to include relevant experts. Another way would be to recruit external experts for the review of individual projects involving different technologies. Finally, the third option (relevant mostly to AI in health and health care and XR research) is to establish technology-specific

subcommittees or committees (see section on AI specific challenges) to foster collaboration between technical experts and research ethics specialists enhancing the quality of ethics appraisal. The risk of this option is that dividing the ethics review process into sub-committees for different aspects could introduce complexity and potential inconsistencies in evaluation criteria and decisions.

The growing complexity of emerging technologies points out the importance of knowledge transfer from the Global North to the Global South, particularly in the form of training and sensitization programs. Universities and institutions in some non-EU countries have started to promote awareness among researchers, but most REC members still lack the necessary ethics training to evaluate emerging technologies adequately. This deficiency can significantly impact the quality and consistency of ethical reviews, especially when assessing technologies that may have unpredictable future risks and difficulty of assessing future benefits of this technology,

D 2.3 acknowledges the need for training and appropriate guidance documents that are necessary for REC members to adequately review and assess research projects featuring new and emerging technologies, especially in the case of research featuring AI technology. In this context, the necessity of technology-specific expertise to ensure an adequate review process. More expertise, either by bringing them in from the outside or by training REC members themselves.

Response. It is important to invest in ongoing training for REC members which looks like the most universal response. The choice of other alternatives (adapting the composition of existing RECs, recruiting external experts, establishing technology-specific subcommittees or committees depends on the local context, such as availability of resources and specificity of the research. Non-EU regions could adopt the proposals to invest in ongoing training for REC members or to adapt REC compositions by including experts with relevant technological expertise.

Proposals:

- Invest in training of REC members/ experts.
- Adapt composition of committees depending on the types of the reviewed research.

2.2.7. Ethics review boundaries in data protection

Challenge: D2.2 highlights the absence of clear guidance on the role of RECs in data protection, particularly in studies predominantly involving personal data, such as biobank research or research involving AI in health and healthcare in EU member states. The lack of clarity of the role of RECs in data protection may lead to heterogeneous practices. REC members may examine data processing issues with differing levels of detail. Consequently, there is a significant risk that the same research project could be assessed differently by different RECs or even by different members within a single REC17. The lack of clear boundaries regarding what to assess may lead to redundant efforts among RECs, DPOs, and DPAs, increasing the

[17] Jurate Lekstutiene, Julia Maria Mönig, et al. PANELFIT D 5.3 Report on the governance of data protection ELI in ICT research and innovation (2021). Available at: https://www.panelfit.eu/other-outcomes/

risk of contradictory advice and guidance[18]. Unclear REC's role in data protection may cause stakeholders to hesitate in addressing data protection concerns. For instance, RECs may believe that adhering to data protection laws is solely the responsibility of researchers, resulting in oversight of such matters in their reviews. Conversely, researchers may mistakenly assume that obtaining ethical approval means they have fulfilled their data protection obligations. This lack of clarity in roles could unintentionally weaken data protection efforts and put biobank participants as data subjects at unnecessary risk[19].

According to D 2.3, in non-EU countries, the scope of ethics review concerning data protection, particularly in cross-border research, is often also unclear. RECs in these regions face challenges in determining how deeply they should engage with data protection issues, leading to inconsistent reviews. Researchers may assume that obtaining ethics approval covers their data protection obligations, while RECs might view data protection as solely the responsibility of researchers or legal departments. This lack of clear boundaries creates gaps in oversight and poses risks, especially in projects involving vulnerable populations and international data sharing.

Another problematic issue raised by the experts interviewed in D2.3 is the cross-border sharing of samples and data in the context of biobanking research. In this context, researches often have to rely on general data protection regulations, which by some researchers and ethics experts is perceived as insufficient as they do not address the issues of benefit sharing, return of study findings for study participants, especially in cases when samples are shipped to high-income countries which benefit from the research and use of samples collected in resource poor settings from vulnerable communities**.**

Option: Enhance collaboration between RECs and data protection bodies. D2.2 suggests that RECs and data protection bodies should establish a better collaboration to ensure that data driven research is conducted in a way that respects both ethical principles and data protection requirements.

Response: One way to enhance collaboration between RECs and data protection bodies could be to assign RECs a role as ethics reviewers within the data protection framework. Another response could involve assigning the responsibility of addressing legal and ethical concerns stemming from the GDPR solely to researchers and research institutions, such as legal departments, research support units, and DPOs. Assigning RECs a role as ethics reviewers within the data protection framework might create redundancy to what is already done by DPOs/DPAs or other departments. To prevent redundancy and ensure efficient collaboration, the specific relationship between DPOs/DPAs and RECs must be clearly defined. However, it can be difficult to bring together two quite different communities and ensure leadership on this issue. Another solution - assigning the responsibility of addressing legal and ethical concerns stemming from the GDPR solely to researchers and research institutions might look as a simpler

[18] Jurate Lekstutiene, Julia Maria Mönig, et al. PANELFIT D 5.3 Report on the governance of data protection ELI in ICT research and innovation (2021). Available at: https://www.panelfit.eu/other-outcomes/

[19] Jurate Lekstutiene, Julia Maria Mönig, et al. PANELFIT D 5.3 Report on the governance of data protection ELI in ICT research and innovation (2021). Available at: https://www.panelfit.eu/other-outcomes/

solution. Under this arrangement, REC evaluations would primarily focus on assessing whether proposed protocols adhere to recognized research ethical standards and incorporate considerations such as risk/benefit ratios and confidentiality. In such a model, RECs could also facilitate the process by requesting statements from researchers confirming that their proposals have undergone assessment regarding personal data protection and comply with the GDPR (PANELFIT project, 2021). Considering that some RECs already engage in such practices, this would seem like a more easily implementable alternative.

To address this, non-EU countries could adopt the proposal to clarify the role of RECs in data protection. By defining the extent to which RECs are responsible for assessing data protection, the review process can become more streamlined and focused. Collaboration between RECs, DPOs, and DPAs could ensure that both ethical and legal aspects of data handling are considered without duplicating efforts

Proposal:

- To enhance collaboration between RECs and data protection bodies, clarify the role of RECs within the data protection framework. This role could be refined at least in several ways, such as assigning RECs a role as ethics reviewers within the data protection framework or assigning the responsibility of addressing GDPR-related legal and ethical concerns solely to researchers and research institutions, leaving RECs with only the duty of requesting statements from researchers confirming that their proposals have been assessed for GDPR compliance. To test which model is most suitable, among other factors (such as whether the REC operates at the institutional, regional, or national level), we suggest trying to include the DPO in the REC composition or creating another form of collaboration between the DPO and REC. This should also help these entities better understand each other's activities, overlapping and differing points, and ensure smoother collaboration with researchers.

2.2.8. Difficulties to involve all relevant stakeholders

Challenge: Representing all stakeholders in reviewing multidisciplinary research proposals that involve new technologies builds credibility and provides valuable insights. However, this could be complex in practice, and it could even be inefficient to include all stakeholders in the purview of REC review.

In non-EU countries, stakeholder involvement in ethics reviews is particularly important for addressing the needs of vulnerable populations, such as those displaced by war or conflicts. Experts highlight that current guidelines, often based on Western values, fail to account for the realities, cultures, and vulnerabilities of these groups. There is a need to formulate guidelines that are sensitive not only to the participants of the research but also to the communities involved. Involving laypeople in the review process, as proposed in the EU context, would help bridge this gap by ensuring that the guidelines are relevant to local cultures.

Option. Since not all stakeholders could be efficiently involved in the purview of the research involving new technologies, an option that could be implemented to improve trust, promote the public interest, and possibly foster credibility too, is the routine involvement of laypeople on RECs. Still, this involvement should not be symbolic, and it will be the responsibility of the rest of the RECs members to transfer the relevant comments received in a scientific way to the particular AI context.

There is currently no doubt that RECs must be constituted with a wide spectrum of disciplines represented. This has not always been the case, since the origins of RECs had a very narrow disciplinary approach that proved soon to be inadequate, since for instance, no research in the biomedical fields is void of social issues and biomedical professionals are not equipped to deal with such issues.

Response: Including a layperson in the RECs could provide the best possible representation of the public if this person could be a potential user/recipient of the technology in question. However, this may face some resistance from the other stakeholders of the research proposal, as this requires transparency and sufficient information to be widely published in advance in order to ensure that the appropriate layperson will be appointed.

As suggested in D 2.3, there should be a stronger focus on vulnerable communities, especially when they are directly involved in research.

Furthermore, approaches such as community engagement and citizen science have been growing in popularity to accommodate community consultation and gatekeeper permissions as alternative approaches for strengthening the informed consent process.

2.2.9. North-South divide

Challenge: As noted in D 2.3, the North-South divide in ethical review processes highlights significant differences in values and approaches between regions, particularly when Western guidelines, often rooted in individualism and utilitarianism, are applied in contexts with more communitarian or collective value systems, such as those in Africa and Asia. In Africa, the ethical concept of Ubuntu, which emphasizes community well-being over individual autonomy, plays a central role in decision-making. This contrasts with the Western focus on individual consent and autonomy, creating tension in informed consent practices. For instance, Ubuntu-based ethics might call for spousal consultation or community involvement in decision-making, which conflicts with Western models that prioritize individual consent. This misalignment raises concerns about the appropriateness of applying Western ethics frameworks in African and other Global South contexts, particularly in research involving vulnerable groups.

Similarly, in regions like China, the value of Harmony plays a key role in ethical decision-making, emphasizing balance and societal well-being over individual interests. This, like Ubuntu, does not align well with Western ethical principles, which complicates the adoption of ethical guidelines.

Option: There is a growing call for more region-specific ethical frameworks that can better account for these cultural differences and include voices beyond the scientific community, such as laypeople and community representatives, who are more in tune with local perspectives.

A key proposal that aligns well with these findings is the inclusion of laypeople in the ethics review process, as suggested in EU contexts. Involving community members and those directly affected by research can help bridge the gap between Western and local ethical frameworks, ensuring that local values are properly represented.

D2.3 analysis emphasises that RECs in the EU are not equipped to deal with non-European ethics approaches as they lack an understanding of local values, norms, and customs. The addition of anthropology in RECs would be a desirable step forward and an even better one would be the inclusion of experts from countries that the international collaboration under review, includes in. We must stress the point that this is not equivalent to requiring an additional REC

review from a local REC, since we have seen that local RECs face considerable challenges that have a direct impact in their abilities to review international research efforts. The ideal case is to incorporate non-European expertise in European interdisciplinary RECs. (see proposal in section 2.2.9)

Additionally, enhancing training for REC members to understand these regional ethical differences and fostering collaboration between North and South can also facilitate more balanced and inclusive ethics review processes.

Response: Rather than take a strict principlism approach; there is a need to accommodate more communitarian dimensions. Through this framework and others, there is a realisation that although the ethical principles remain the same, the way they are applied, including how respect, informed consent, and beneficence are used, must consider the local contexts. This view is also supported by guidelines such as the TRUST code, a global code of conduct for equitable research partnerships, which underscores the for promoting fairness, respect, care and honesty in conducting research to avoid ethics dumping and exploitation to support long-term equitable research relationships between partners in lower-income and high-income settings.

Proposals:

- Include laypeople and community members in the ethics review process to bridge the gap between Western and local ethical frameworks.
- Enhance training for REC members in the EU to better understand regional ethical differences and foster collaboration between North and South.

2.2.10. Survey results related to cross-cutting issues

The current model of ethics governance

The survey included identical questions for all technologies. One particular question aimed to assess the current model of ethics governance: *What type of ethics governance is currently applied in assessing the following technologies in your institution?*

The most common review process for research projects in EU countries involves obtaining approval from the research ethics committee (REC) before starting the project (traditional review). This is the case for over 70% of responses in BB, AI, and XR technologies and just over 63% in genome editing. The choice of review process varies between technologies, with the second most popular model for AI, BB, somatic, and germline genome editing being REC review before starting the research project, followed by monitoring after approval. Ethics self-assessment is the second most popular governing model for XR and non-human genome editing.

Later, it was asked whether the experts believed that the governance applied in evaluating the technology was sufficient. The answers show a difference of opinion comparing biotechnologies (biobanking and genome editing) and digital technologies (AI and XR).

In gene editing, more than half of the experts (53-59%) consider the existing governance sufficient, while in biobanking, the result rises to 69%. Governance was deemed insufficient by 11-15% of experts for all biotechnologies.

The assessment of digital technologies overlaps with each other but differs from biotechnology. Only 41% of the respondents rate the existing governance in both AI and XR technologies as sufficient. There is an even bigger difference among those with a negative governance assessment, where every fourth expert (25%) considers the current model insufficient.

After assessing the sufficiency of current ethics governance, the interviewees were asked an open-ended question: *How would you change it?* or *Do you have any suggestions on how to improve it?* Depending on whether the current governance is assessed as sufficient or insufficient.

A recurring theme in the responses is the need for guidance and training.

Hindering factors

Next, in the survey, we sought to determine *what factors hinder the ethics assessment of technologies the most*. The options were:

- lack of scientific/technical understanding;
- lack of ethics expertise;
- lack of guidelines;
- lack of training;
- lack of funding.

The primary factors that hinder the ethics assessment of technologies vary across different technologies.

A lack of scientific/technical understanding is the main factor driving challenges in AI (59%), somatic (34%), and germline (33%) genome editing. It is important to mention that if this factor is not in the first place in other technologies, its value remains very high everywhere and is only slightly inferior to other issues. Another important finding is that lack of scientific/technical understanding is significantly more important in digital technologies than biotechnologies.

Another obstacle that poses a significant problem for ethics review is the absence of guidelines. Lack of guidelines was noted as the most important factor in XR (49%), germline (33%), and nonhuman (32%) genome editing. Similar to scientific/technical understanding, the lack of guidelines also occupies a very high position in other technologies. For example, in AI, 46% of respondents chose this answer as an important factor.

Lack of ethics expertise was selected as an important aspect of all technologies but was not the most important aspect in any of them. The distribution is quite similar between technologies. In digital technologies, the need is a bit higher (44% in AI and 38% in XR), and in biotechnologies, the need is a little lower (22% in BB, 28-30% in GE).

The lack of funding was considered the least significant issue hindering the ethics assessment of every technology. However, a low number for this answer could be misleading, as the questionnaire wording was about "funding," and the responses might not encompass issues like human resources.

In addition to the need for guidelines, many experts emphasized that a better ethical evaluation requires additional training. The results show the greatest overall desire for training among digital technologies (AI 41% and XR 36%). The need for training in biotechnology is a bit lower and very similar between different technologies (28-31%).

To summarize this issue, it is observed that in digital technologies, all surveyed aspects are considered more important in hindering ethical review than in biotechnologies. In biotechnologies, the responses are distributed very similarly for all questions. The only exception is the lack of funding, which was almost equally mentioned as the least important aspect of all technologies.

The survey collected opinions on whether it's feasible to consider the broader societal impacts of different technologies. Most experts found it feasible for all technologies, with only 6 to 9% disagreeing. Unlike the previous questions, there's no apparent difference between digital and biotechnology. The "agree" option was most popular for AI (72%) and biobank technology (79%). For XR and genome editing, 56-61% chose "agree," while 31-35% chose neither "agree" nor "disagree."

Finally, it was assessed for the feasibility of applying continuous ethics oversight starting from the design stage of research and including ethics review and monitoring throughout its lifecycle (ethics by design).

The findings were consistent with the broader social impact assessment. AI (73%) and biobanks (79%) received the most favorable evaluations, while XR and genome editing were viewed more cautiously (61-67%), with a larger number of respondents neither agreeing nor disagreeing (26-32%). The percentage of those who disagreed with the options was low across all the technologies (6-8%).

Questions about experts' perceived competence were directed to each technology separately. Therefore, they are reflected in the sections of the report on different technologies. However, some of the questions overlapped, allowing us to compare how self-perceived competencies on the same issues differ in respect to different technologies. Upon cross-checking, it was found that experts rated their competence highest when assessing consent in all technologies.

When assessing data-related competency questions, the responses were quite similar. In the case of biobanks, 62-67% of respondents felt competent in data protection, data privacy, and data sharing, while for AI, the percentages were 58-64%, and for XR, they were 58-70%.

The survey included an open-ended question to determine when AI and XR technologies research should be subject to ethics review. The most commonly cited reason for both technologies is research involving people or personal data. It is important to note that in AI technology, the responses often go beyond working with people; they also consider the potential impact on society, justice, and decision-making.

Desired training

The survey tried to determine what training the experts would like.

Experts consider training in digital technologies the most pressing need, with 80% requiring training in AI and 85% in XR. In biotechnology, the need for training is between 57% and 66%.

Ethics experts consider the ethics assessment of technology research and development to be the most helpful training content (85%).

Participants ranked their preferred training methods in the following order: self-directed online training (34%), group workshops online (33%), in-person group workshops (18%), and downloadable workbooks (14%).

The most preferred learning styles for online training are listening to presentations (54%) and watching videos (50%). The least preferred is group chat (20%).

The survey results seem to strongly support most of the proposals to address the cross-cutting challenges to ethics review. For example, responses to the survey questions about ”factors hindering the ethics assessment of technologies the most” revealed the importance of proposals to address the lack of specific guidelines and lack of technical knowledge and expertise. A lack of scientific/technical understanding is the main factor driving challenges in AI and genome editing, while the lack of guidelines was noted as the most important factor in XR and had nearly similar numbers as the lack of scientific understanding in genome editing. Even if none of these two factors were ranked as most important, their value remained very high for every technology.

The survey participants answered the questions on the feasibility of applying continuous ethics oversight and considerations of the broader societal impacts. Findings were consistent for both questions, with more than 60 % of responders seeing these options as feasible and only less than 8 % disagreeing. These findings support proposals for addressing limitations of ex-ante ethics review and the involvement of appropriate stakeholders, particularly in the ethics review process. On the other hand, the survey results do not entirely correspond to the challenge of resource constraints, which needs further analysis.

Comparison of survey results between EU and non-EU countries

The survey results highlight both similarities and differences between ethical review processes in EU and non-EU regions, though it is important to note that the response rate from non-EU countries, especially Africa, was relatively low, which may affect the representativeness of the conclusions for non-EU contexts.

Both EU and non-EU countries recognize the need for continuous ethics oversight. This shared understanding supports the proposals for adopting ethics-by-design and risk-based review approaches. These methods are particularly effective in ensuring that ethical challenges are addressed dynamically throughout the research lifecycle.

There is also agreement between the regions on the importance of training REC members to improve their technical knowledge and ability to assess emerging technologies. This aligns with the proposal to invest in REC training and involve external experts where needed. Enhancing REC expertise would help ensure more consistent ethical evaluations, reducing gaps in technical understanding that might otherwise hinder effective oversight.

However, there are some differences. Non-EU countries face a greater lack of funding, particularly in Africa, which impacts the effectiveness of REC operations and limits their capacity of ethical review. The proposal to increase funding could help both regions build more sustainable REC systems, ensuring adequate support for REC members, proper compensation, and maintenance of the expertise required for quality ethical evaluations. However, if increased funding is not feasible due to resource constraints, establishing knowledge-sharing hubs could also alleviate some of the resource burdens in Africa. By promoting the exchange of information, best practices, and expertise, these hubs could help maximize resource use efficiency, thereby reducing the reliance on direct funding. Hubs could also be instrumental in addressing the lack of specific guidelines—a challenge that is significantly more pronounced in Africa compared to other regions. These hubs could serve as platforms for sharing updated guidelines, providing centralized access to international standards, and disseminating best practices. This could help bridge the gap between Africa and the rest REC’s.

A notable difference between EU and non-EU countries is the reported prevalence of traditional ethics reviews compared to post-approval monitoring (Figure 2). Traditional ethics reviews appear to be more established in Europe, whereas non-EU regions more frequently report the use of post-approval monitoring processes. This finding is unexpected, particularly considering that expert interviews revealed that ethics review in non-EU countries is insufficiently funded and rather often regarded as a bureaucratic formality. Thus, these survey findings should be approached with caution, as there is a possibility that the reported monitoring may be occurring rather superficially or formally, without representing effective ethical oversight in practice.

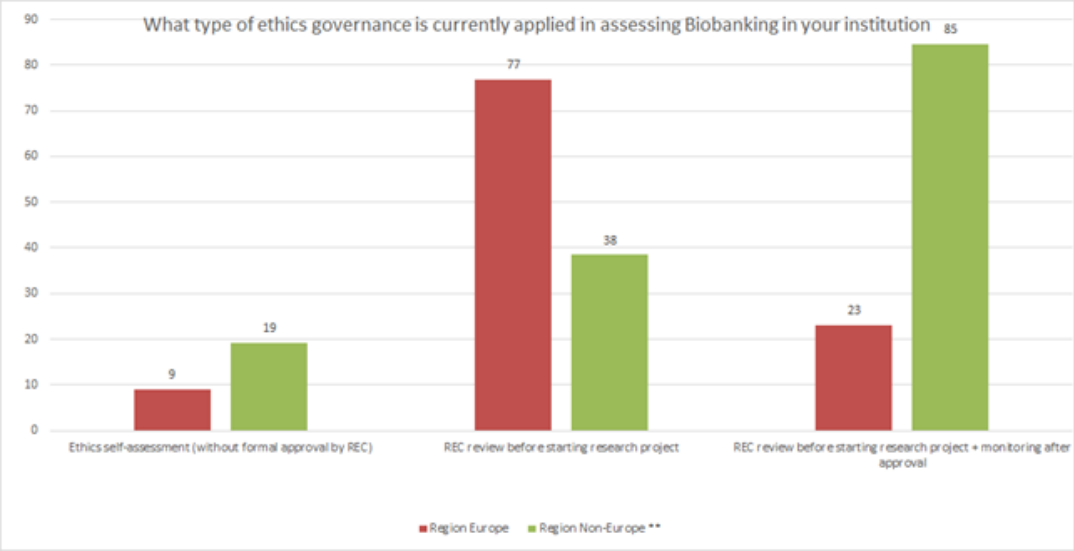

Figure 3: Different types of ethics governance

2.3 Ethics review involving AI in health and healthcare: specific challenges, options, responses, proposals, and survey results

2.3.1. Lack of uniform and coherent 'AI in healthcare' guidelines across EU member states

Challenge: The area of AI is evolving in many directions at a high speed. This could lead to a lack of the specific technical or ethical expertise needed in the particular research areas reviewed by RECs.

A potential option is to set uniform and coherent 'AI in healthcare' guidelines across EU member states so as to align review processes and avoid divergence. This would ensure consistency between RECs and streamline international collaboration. One risk here is that a drive towards consistency might lead to more bureaucracy. Also, there is likely to be some resistance to any attempt at harmonisation of REC procedures between countries, with governance organisations in different jurisdictions wishing to assert independence.

Response: The resistance can be reduced using the EU level recommendations as well as ethics appraisal scheme guidance[20] that provides recommendations to address key ethical issues involved in research on AI, specifically:

(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.

Proposal:

- Foster collaboration between REC members and experts to ensure common responsibility for unified implementation of the EU level recommendations and the ethics appraisal scheme guidance.

2.3.2. Neglecting specific issues in AI in health and healthcare

Challenge: While the previously mentioned EC recommendations and guidance on ethical issues in AI research do provide some guidance for REC members without experience in AI, they nonetheless concern issues that reviewers are not familiar with, making it difficult for them to reliably detect where they are present in proposed new projects. The novelty of the area may have the result that RECs might overfocus only on the identifiable AI issues that match the members expertise, such as consent and privacy issues, neglecting other important issues in AI. This particularly applies to novel issues that are not part of the core concepts of research ethics (such as discrimination and bias, safety and liability, transparency and algorithmic bias).

Option: The most important option is to adapt the composition of medical RECs to include AI experts. Given the major challenges RECs face in recruiting members generally and experts in AI specifically, this is a clear opportunity for improvement of ethics review of AI projects. The only associated risk is failure to achieve this goal. An alternative option is to develop dedicated "digital ethics committees" (DECs) specialising in review of AI projects. (However, that would involve finding experts from non-AI areas for these new committees).

Response. There may be some resistance from those working on RECs or the institutions to any suggested change to REC make-up and mechanisms, potentially including the addition of AI experts.

Proposal:

- Include AI experts as part of the composition of medical RECs or develop dedicated "digital ethics committees" (DECs) specialising in review of AI projects.

2.3.3. Fast evolving technology

[20] 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).

Challenge: AI development is likely to continue to outpace even updated regulatory frameworks, meaning that RECs may need to continue to review projects without specific legislation being in place. RECs may also continue to experience issues in reviewing areas where there is significant uncertainty, such as efficacy and accuracy, safety and risk, excessive trust (overtrust) in AI systems, bias, and explainability.

Option. An option is to (further) develop REC methodologies beyond compliance. Rather than being a "once off" review authority, RECs should be involved in "ethics by design" of projects at the development stage (see section 2.2.4). This would help researchers engage in ethical reflection and evaluation. Going further, RECs could adopt an "embedded ethics" approach, continuing to be involved in projects once they are up and running. This is particularly important when projects may involve risks that only emerge during the research itself.

Response. There are potential attempts by the industry to circumvent ethics review; this will remain a potential response to any new review mechanisms.

Proposal:

- Involve RECs in "ethics by design" of projects at the development stage to engage in ethical reflection and evaluation.

2.3.4. A "grey area" of the review

Challenge. Some AI-healthcare research does not fall under the purview of medical REC review due to different definitions being used in different jurisdictions. This is because REC review structures diverge between different European countries. If a particular AI study falls out with the definition of biomedical research in a given jurisdiction, it may be assessed according to the standards of a non-medical REC (which are likely to be more diverse still) or not be evaluated at all.

Option. A potential option is to set uniform and coherent 'AI in healthcare' guidelines across EU member states so as to align review processes and avoid divergence. This would ensure consistency between RECs and streamline international collaboration. One risk here is that a drive towards consistency might lead to more bureaucracy.

Response. There is likely to be some resistance to any attempt at harmonisation of REC procedures between countries, with governance organisations in different jurisdictions wishing to assert independence. Medical RECs are already criticised in some quarters for impeding research with unnecessary bureaucracy; there may therefore be resistance to increasing the level and quality of review of AI research.

Proposal:

- Ensure consistency by setting uniform and coherent 'AI in healthcare' guidelines across EU member states.

2.3.5. Survey results: AI in healthcare related research

Respondents were asked to rate their competence in various issues related to AI-related research in healthcare.

Experts rated their competence best in the issue of consent, with 72% of respondents considering themselves competent and 8% non-competent.

Competence in data-related issues (data protection, data privacy, data sharing) was evaluated less favorably. Between 58 and 64% of the respondents considered themselves competent, but a sharp increase in the number of experts who consider themselves incompetent (14-18%) is observed. The rest rated themselves as average.

Specific AI competencies such as bias, justice and fairness, transparency/explainability, and responsibility for the consequences of application were also evaluated. The number of experts with a positive self-evaluation almost did not differ concerning different AI-specific issues. Only slightly more than half (51-53%) of the respondents considered themselves competent.

However, the number of negative responses varied by question. Experts considered themselves the least incompetent in assessing responsibility for consequences (12%), a bit worse in the assessment of justice, fairness, and transparency/explainability (16-18%), and worst in bias assessment, where more than one in five (21%) considered themselves incompetent.

The findings of the survey strongly support most of our initial findings in the SCORE analysis in relation to AI in healthcare. 41% of participants thought that the current ethics governance of AI (including RECs) was insufficient, supporting our recommendation to involve RECs in “ethics by design” of projects at the development stage to address the challenge of ”fast-evolving technology’.

According to the survey findings, one of the main challenges mentioned in AI-related research in healthcare is the lack of scientific/technical understanding (identified by 59% of respondents), which implies that this specific expertise (AI) is missing from the committees’ members. This finding particularly supports the Challenge of ”Neglecting novel issues in AI” in the SCORE analysis. In addition, this challenge is supported by the finding that the RECs feel least competent in being unbiased, responsible for application consequences, and justice and fairness. Finally, challenge emphasizing the ”Lack of uniform and coherent ‘AI in healthcare’ guidelines across EU member states” is supported by a high number of respondents complaining about the lack of relevant guidelines.

In the research findings, AI in healthcare has been recognised as one of the two most desirable areas for training (together with XR) among all the research areas of the project. However, the resistance to changes in many levels, already mentioned in our initial findings in SCORE analysis as potential Responses (Responses no.1-no.3), is confirmed by the survey participants through their specific suggestions for improvement, which propose ‘This field is developing so quickly it is hard to stay abreast. The safest approach may be a conservative one for now until a better understanding of the technology can be obtained’ and ‘Strict ethical review standards’. Suggestions like these could be argued to compromise any attempt to deliver current and comprehensive ethical evaluations relevant to AI. This approach has already been identified in our initial Challenge no.2 ('RECs might prefer to be over-cautious') and can lead to our initial Challenge no.3 ('RECs will focus only on the identifiable AI issues that match the member's expertise and leave other important issues neglected’).

2.4. Ethics review involving XR: specific challenges, options, responses, proposals, and survey results

2.4.1. Risks to physical and psychological health

Challenge: Extended Reality (XR) poses potential risks to physical and psychological health: it can trigger physical issues such as seizures and cybersickness or may cause difficulties transitioning back to the physical world after extended use, leading to disorientation. Additionally, immersive technology could worsen addictive behaviors and dissociative disorders in psychotherapeutic settings.

Options. To cope with this challenge, clear safety guidelines for developers and users can be established, outlining best practices to minimize physical risks (e.g., tripping hazards) and psychological harm (e.g., ensuring content is appropriate and not excessively distressing). It is also important to design XR hardware and interfaces with user ergonomics in mind to reduce the risk of physical strain or injury. This includes adjustable equipment that can accommodate different body sizes and shapes and minimize motion sickness through design optimizations. This option is related to some risks: designs may not accommodate all users equally, leading to exclusion or discomfort for those with specific physical needs or disabilities and might significantly increase the price of technology.

It is also important to provide users with clear warnings about the content and the potential risks it may pose, allowing them to make informed decisions about their engagement, and work closely with healthcare professionals, regulatory bodies, and industry stakeholders to develop standards and regulations that ensure the safe use of XR technologies. The risks of this option are that regulatory processes can be slow, and there may be a lack of consensus on standards, leading to uneven implementation of safety measures across the industry.

Response. Safeguard the rights of subjects involved in XR studies. Create support systems for participants that offer guidance and assistance before, during, and after the study, addressing any concerns or adverse effects experienced as a result of their participation in XR research, particularly for studies that may have psychological impacts, to ensure their well-being after participation and to address any long-term effects. Active engagement with research participants, seeking their feedback on their experiences, and incorporating their insights into future research designs and ethical considerations.

Proposals:

- REC members should have clear guidelines or ensure that researchers submit a self-assessment checklist with well-defined safety criteria covering physical and psychological harm risks.
- XR hardware should adhere to ergonomics standards to minimize physical strain or injury.
- Participants must have clear warnings about XR content risks and reporting mechanisms for harassment or inappropriate content.
- Mechanisms to identify and address potential issues early in the research process and support systems for participants before, during, and after XR studies should be established.

2.4.2. Unclear data scope

Challenge: It is unclear what specific data can be collected using XR and to what extent. Biometric data such as facial and eye muscle movements can be recorded, which may reveal more information than users intended.

Option: clearly define XR data collection parameters: e.g., visual, auditory, biometric, behavioral. This includes specifying the scope of data collection, what aspects of user behavior or interaction are recorded, and the level of detail required. However, it should be taken into account that narrowly defined objectives might limit the scope of research, potentially overlooking important data or user experiences. Overly specific aims could also restrict the applicability of findings to broader contexts.

Response. Establishing clear parameters for XR data collection, which should include visual, auditory, biometric, and behavioral aspects. This approach can help ensure that the collected data is relevant and appropriate while maintaining the research scope and applicability.

Proposal:

- XR data collection parameters, such as visual, auditory, biometric, and behavioral aspects, must be clearly defined. Proposals must provide appropriate privacy settings, blocking features, and reporting mechanisms.

2.4.3. Unclear social impact

Challenge: XR tech can have an unclear social impact. XR platforms can subtly influence user interactions, particularly affecting young users through behavioral nudges. Furthermore, XR presents risks of dignity violations, including harassment, exposure to inappropriate content, bias, discrimination, and manipulation, alongside serious concerns of virtual violence, such as sexual assault against avatars. Using avatars, including those representing deceased individuals, raises significant ethical questions about identity, autonomy and consent.

Options:

- develop inclusive and safe XR platforms by designing accessible interfaces for diverse users and creating age-specific virtual spaces with effective age verification systems to protect minors and ensure a discrimination-free environment for everyone. This option provides users with privacy settings, blocking features, and reporting mechanisms to empower them to control their experience and report incidents of harassment or inappropriate content.
- regularly assess the social and psychological impact of XR technologies on users, especially vulnerable groups like minors and individuals with mental health concerns, to identify potential issues early and adjust strategies accordingly.
- Instruct researchers to include a social and environmental impact statement on their research when submitting XR research protocols to RECs.
  At the same time, it should be taken into account that the development of age-specific spaces and accessible interfaces increases the technical and design complexity, potentially leading to higher costs and longer development times for XR platforms. Implementing effective age verification systems may require collecting personal information, raising privacy concerns and the risk of data misuse. Reporting mechanisms might not be as effective or responsive as needed. If reports of harassment or inappropriate content are not promptly or adequately addressed, it could lead to a loss of trust in the platform. Finally, implementing broader societal impact assessments, particularly monitoring of

ongoing projects, may require significant resources and infrastructure, posing challenges for research institutions. There is a risk of subjectivity in evaluating societal impact statements, as interpretations of potential harms and benefits may vary among researchers and RECs. Researchers may feel discouraged from pursuing certain research avenues if they perceive that potential societal impacts could lead to rejection by RECs, potentially stifling innovation and exploration.

Response. Create safe and inclusive XR platforms with accessible interfaces for diverse users. Integrate privacy settings, blocking features, and responsive reporting mechanisms. Assess social and psychological impacts on vulnerable groups and provide broader societal impact statements that would enable researchers to reflect on the potential positive and negative consequences of their work beyond traditional methodological considerations. This would foster accountability and transparency in research practices, ensuring that researchers are aware of and address potential risks and benefits. Understanding and documenting potential societal impacts could lead to the development of technologies that are more suitable for their intended purposes, ultimately enhancing the quality and effectiveness of research outcomes. A specific checklist for XR research could be included in the EU grants ethics self-assessment document.

Proposals:

- Include social and environmental impact statements outlining how potential issues will be identified and addressed during the research process.
- Continuously assess the social impacts of XR technologies on users, with particular attention to vulnerable groups.
- Platforms should be inclusive and safe for diverse users, with age-specific virtual spaces and effective age verification systems in place.

2.4.4. Ontological status of virtual objects

Challenge: There is a need to determine whether ethical guidelines that apply to human-created content also apply to AI-generated content. For example, should the consequences for actions taken against a human avatar be the same as those taken against an AI-generated avatar? Additionally, there is concern about how virtual crimes should be acknowledged as actual crimes in the physical world.

Options:

- Develop a clear legal framework that differentiates between actions taken in virtual environments and those in the physical world while also recognizing the psychological and social impact of virtual crimes. However, creating separate standards might inadvertently minimize the perceived seriousness of virtual crimes, potentially allowing harmful behaviors to proliferate under the guise of virtuality.
- Tiered response system for virtual actions, where consequences are proportionate to the severity of the action and its impact on the virtual and real-world well-being of individuals. This could involve warnings, temporary suspensions, or bans for offenses, with distinctions between offenses against human avatars versus AI avatars.
- Conduct ongoing research into the impacts of interactions with AI-generated content and avatars, using findings to continuously update ethical guidelines and legal frameworks. However, continuous research and evaluation require

significant resources and may face challenges in keeping pace with rapid technological changes, leading to gaps in understanding and policy.

Response. AI-generated content recognition. Introduce mandatory labelling for AI-generated content, making it easy for users to distinguish between human-created and AI-generated materials. This could help manage expectations and user engagement with content. For content that involves personal data or likeness (e.g., deepfakes or avatars), develop consent protocols that require explicit permission from the individuals whose data or images are being used to generate or interact with AI content. Regularly assess the social, psychological, and cultural impacts of AI-generated content. Continuous monitoring can inform adaptive strategies to mitigate emerging and evolving risks.

Proposals:

- AI-generated content must be clearly labelled.
- If data or images are used from individuals, explicit permission is required. Virtual crimes must be detected and addressed appropriately.

2.4.5. Survey results: XR related research

Assessing the competencies of experts in the field of XR. The experts rated their competencies best in the issue of consent, where 70% of the respondents consider themselves competent and 9% not competent enough.

In data related issues (data protection, data privacy, data sharing). Between 58 and 70% of the respondents considered themselves competent, with the best assessment of preparation in data privacy and the worst in data sharing. Meanwhile, the experts consider themselves to be insufficiently competent almost equally in all questions (12-14%)

XR-specific issues: violence/abuse, mental health issues, AI usage in XR, involvement of children, and cybercrime issues are significantly less familiar to experts. A low number of the respondents consider themselves competent in any of these categories (23-40% marked as competent). The lowest number of people who considered themselves competent was in the area of violence/abuse, where only 23% considered themselves to have sufficient knowledge. Also, many experts in these questions (33 to 42%) felt incompetent.

In addition to questions about competencies, experts were also assessed on how they understand the inner workings and differences of XR technologies using virtual reality, augmented reality, and XR using AI.

The responses are concerning because only slightly more than a third of experts (33% and 37%) view themselves as competent in these areas. Similarly, the same percentage of experts (33% and 37%) consider themselves incompetent.

Survey results showed that experts do not understand the inner workings and differences of XR technologies - only slightly more than a third of experts (33% and 37%) view themselves as competent in these areas, and an equivalent percentage (33% and 37%) consider themselves incompetent. Additionally, a substantial part (85%) of experts expressed a desire for further training in XR, and more than half (57%) indicated an interest in deepening their knowledge of the scientific aspects of the technology. Regarding data-related issues, such as data protection, privacy, and sharing, 58% and 70% of respondents rated themselves as competent. The highest self-assessed competence was in data privacy, while the lowest was in data sharing.

Such results support our proposals from the original SCORE analysis for Risks to physical and psychological health and Unclear data scope, which state that REC experts should have clear guidelines and a self-assessment checklist with well-defined safety criteria for physical and

psychological harm. In addition, XR data collection parameters, such as visual, auditory, biometric, and behavioral aspects, must be clearly defined as without a sufficient understanding of how the technology works, there is a significant risk of overlooking potential risks to research participants' health or the potential for excessive data collection and sharing.

When it comes to XR-specific issues, such as violence/abuse, mental health concerns, AI usage in XR, the involvement of children, and cybercrime, experts demonstrate significantly less familiarity. A few respondents (23-40%) consider themselves competent in these categories, with the lowest competence reported in violence/abuse (23%). Additionally, many experts (33-42%) felt incompetent in these areas. Such results justify our SCORE analysis proposal to include social and environmental impact statements, outlining how potential issues will be identified because new and rapidly changing technology is challenging to predict, and even ethics experts have very limited knowledge in this area.

The survey also indirectly justifies the challenge of determining the ontological status of virtual objects. With limited knowledge about AI usage in XR (40% of experts felt competent and 33% felt incompetent) and even less knowledge about cybercrime (only 35% felt competent and 42% felt incompetent), experts have little ability to properly assess the differences between human and AI-generated actors, as well as the responsibilities that apply to their actions.

2.5. Biobanking related challenges, options, responses, proposals, and survey results

2.5.1. Difficulty to navigate biobank regulations

Challenge: Unlike the case of AI and XR, biobanks and scientific research involving them are quite comprehensively regulated both at the international and national levels. However, the regulatory framework governing biobanks is rather complex and multi-layered. There are several international and regional regulatory instruments specifically developed to safeguard the rights of biobank participants and ensure responsible biobank practices. These instruments include the WMA Taipei Declaration (2016), CIOMS guidelines (2016), the Council of Europe Recommendation on Research on Human Biological Material (2016), and OECD guidelines (2009). These instruments are advisory in nature but typically carry significant influence. On the other hand, there are complementary instruments that are legally binding, partially overlap with biobank-specific instruments mentioned earlier and that extend beyond the scope of biobanking (such as the GDPR). Additional complexity arises from existing national regulations. While some countries have specific national regulations for biobanks, many apply general regulations that are not specific to biobanking activities. This makes it difficult for both researchers (especially international ones) and supervisory bodies to navigate and interpret existing legal and ethical requirements, including the requirements for the proper ethics review. Difficulties in finding and properly interpreting regulatory framework could result in improperly designed biobanking activities. This could lead to harm to biobank participants and sanctions from supervisory authorities for non-compliance with relevant regulations.

Option: establish a more harmonized and collaborative research environment. Sharing information about ethical and legal requirements for biobanking, including the ethics review requirements, across different countries could help to create a more harmonized and collaborative research space. This could encourage to aim for more consistency in the ethics oversights of biobanks across different biobanks and which could be enhanced by updated national, regional and international regulatory frameworks**.**

Response: this option most probably requires a certain platform in which homogeneity of information and its regular update are ensured. The first steps towards a more extensive mapping of European REC practices and legal landscapes for ethical approval have already been taken. For example, the Task Force REC, as part of the ELSI Services of BBMRI-ERIC, has taken the initiative to conduct a survey for this purpose[21]. The TRREE project is also updating old and creating new national training models, which integrate questions and requirements for biobanks, including ethical review requirements. Both initiatives known to us, initiated by BBMRI and TRREE, have the potential and are suitable for creating a more harmonized and collaborative research environment to share legal and ethical requirements for biobanking. Firstly, because these projects are not new, they already have years of experience in sharing experiences with different biobanks or offering international and national training modules in the field of health ethics and law. However, there remain certain risks in both cases - updating information requires regular coordination of the platform and a commitment from representatives of countries to constantly update this information, which is not always easy to ensure. Therefore, in developing such environments, it is important to consider motivational measures to make such environments work effectively and be beneficial to various biobank stakeholders.

Proposals:

- European networks of research ethics committees and biobanking should be encouraged to create a more harmonized and collaborative research space to share information about ethical and legal requirements for biobanking, including the ethics review requirements, across different countries by utilizing already existing platforms and initiatives led by their own as well as external ones like TRREE (Training and resources in research ethics evaluation). When creating and maintaining this space, it is important to implement motivational measures for national contributors to ensure that the information is continuously updated**.**

2.5.2. Variations in ethics review

Challenge: Despite the presence of international and regional regulatory instruments specifically tailored for biobanking, there are variations in the proposed scope of REC review. For example, the OECD guidelines mandate an ethics committee (or an equivalent supervisory body) to review the planned specific research study and determine its alignment with previously given consent. The WMA Taipei Declaration, on the other hand, expands the scope of ethics review by requiring ethics committees to assess not only the need for additional protection measures to protect research participants when conducting specific research studies, but also to assess the planned and ongoing biobank (research) activities. Strech even argues that it may be more important to conduct an ethics review in the initial stage of biobank creation when consent, incidental finding policy, and access procedures need to be established, as later on, only a few research-related risks remain, which can be addressed sufficiently by the biobank's

[21] Casati, Sara, Bridget Ellul, Michaela Th Mayrhofer, Marialuisa Lavitrano, Elodie Caboux, et Zisis Kozlakidis. « Paediatric Biobanking for Health: The Ethical, Legal, and Societal Landscape ». Frontiers in Public Health 10 (2022): 917615. https://doi.org/10.3389/fpubh.2022.917615.

internal access committee[22]. The same variations in ethics review can be reflected in the practices of various biobanks. Following D2.2, some RECs are only involved in approving biobank research projects, while others also play a role in approving the establishment of biobanks. Moreover, RECs may have additional obligations beyond those mentioned. For example, some RECs are mandated to review the transfer of biobanked samples and health-related data to other biobanks or research studies carried out abroad. This diversity reflects the complexity of ethical governance structures across Europe as well as complicates international collaboration. In addition, having very different ethical review models in different countries can lead to different protection of biobank participants.

Option: Research the importance of having an ethics review when a biobank is being established compared to the ethics review of biobank research. Considering that RECs are more commonly involved in the ethics review of biobank research, but at the same time, considering that some scientists argue that ethics review is important, or even more important when establishing a biobank, it is suggested to explore what ethics review model would be most appropriate for biobank activities**.**

Response: Exploring the ethical review practices for biobanking in different countries and searching for the best model of ethical oversight for biobanks is one of the tasks of the irecs project. Currently, it seems that different responses could be proposed depending on the future results from irecs project: 1) ethics review is only necessary when establishing the biobank 2) ethics review is only necessary when conducting specific biobank studies 3) ethics review is necessary in both cases. Proposing these models does not imply in any way that the biobank lacks or cannot have other elements of ethical oversight - for example, ethics advisory boards, which in some biobanks already assist and could contribute to addressing ad hoc emerging ethics issues or contribute to the development of the biobank ethics framework. It may also be important to note that while exploring ethics review practices, it might also be relevant to investigate circumstances under which biobank research could be exempt from ethical review.

Proposal:

- Scientists together with practitioners should conduct theoretical and empirical research to explore the significance of instituting an ethics review during the establishment phase of a biobank in contrast to the ethics review process for research conducted using biobank resources. The research should also include the investigation of specific circumstances (if any) under which biobank research might be exempt from ethical review.

2.5.3. Limitations in current broad consent policies

Challenge: D2.2 highlights the complexities of the broad consent currently most often applied in biobanking, particularly considering: 1) formulation of future research in a way, that seemingly allows any biobank research to be carried out, 2) the evolving nature of biobank research,

[22] Strech, Daniel. « Ethical review of biobank research: Should RECs review each release of material from biobanks operating under an already-approved broad consent and data protection model? » European Journal of Medical Genetics 58, no 10 (1 octobre 2015): 545-49. https://doi.org/10.1016/j.ejmg.2015.09.008

encompassing areas like innovation that go beyond traditional biomedical research, 3) the use of more privacy-invasive research methods, such as whole-genome sequencing, and 4) the challenges of assessing consent over time, especially in ethically more sensitive research areas (e.g., research involving commercial partners). It raises questions about the voluntary nature of consent and informedness. Difficulties for RECs in assessing whether consent is truly informed and voluntary, and conducting potentially ethically sensitive research without providing additional information to biobank participants, could result in decreased trust in biobanks.

Option: Implement a standard consent model. D2.2 emphasizes the importance of developing an effective consent framework during the creation stage of a biobank. It particularly stresses the need to evaluate early on the feasibility of implementing IT-based consent models such as dynamic consent. Additionally, it highlights the importance of enabling biobank participants to express objections to specific research areas and ensuring clarity regarding the scope of future research. This clarity can be achieved by specifying research areas for sample and data usage, such as cardiovascular disease or cancer, as demonstrated by UMC Utrecht (2020)[23] and Manchester Cancer Research Centre (2022)[24], or by providing a sample list of diseases for investigation, as seen in the UK Biobank (2010)[25]. Additionally, to promote cross-border sharing of biobank resources and enhance transparency in their international use, it is important to work towards standardizing consent models across EU member states and globally.

Response: At least two approaches to consent models were proposed: improving broad consent currently prevalent in many biobanks or implementing a new web-based consent model such as dynamic consent.
Both directions either to improve broad consent or implement dynamic consent might be plausible. Improving the broad consent model can be pursued in several directions: 1) increasing public and biobank participant awareness of biobank activities (this can be done not only by biobanks and supervisory bodies, but also through organizations conducting research with human biological samples and health data stored in biobanks, scientific societies, public health agencies, and patient advocacy organizations); 2) improving the consent document provided to potential biobank participants (providing a list of sample diseases that can be investigated or specifying research areas, when possible); 3) enhancing the consent process itself (more emphasis on what people are concerned most). To improve the broad consent model, both personnel and financial resources are needed for both the biobank, and all involved in increasing public awareness about biobanks. Considering that biobanks typically have very limited budgets and operate on project-based funding, it would be difficult to expect that this could be done from funds allocated to biobanks. This response also looks simpler at least from the technical point of view. On the other hand, implementing the dynamic consent model may require even more resources, including additional technical expertise (at least in the short term). Both approaches may also require certain legal document changes at the national level.

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[23] UMC Utrecht, "Procedure for sub-biobank review by the MREC in parallel to WMO review", https://assets-eu-01.kc-usercontent.com/25b20d25-d13c-01de-3f74-7ca92fec5e2f/1aa7192e-7b40-421e-bd81-a438ce4ad412/Procedure%20for%20MREC%20review%20of%20sub-biobanks%20and%20points%20for%20attention%20v%20dd%205-11-2020_EN.pdf, 5 November 2020.
[24] Manchester Cancer Research Centre, „MCRC Biobank Access Policy", https://www.mcrc.manchester.ac.uk/wp-content/uploads/2022/11/MCRC-Biobank-Access-Policy-Version-13.0.pdf, 4 July 2022.
25 UK biobank, „Information leaflet", https://www.ukbiobank.ac.uk/media/ei3bagfb/participant_information_leaflet-baseline.pdf, 21 April 2010.

Proposals:

- Biobanks (with the help of RECs) should regularly review the biobank consent frameworks especially those utilizing broad consent. Based on review suggestions, they should evaluate how the framework can be further improved and develop a strategic plan for implementing these improvements. This proactive approach ensures that consent practices remain robust, transparent, and responsive to evolving ethical standards and participant/public expectations.
- While reviewing biobank consent frameworks, biobanks and RECs should ensure that the consent model reflects the evolving nature of biobank research. This involves assessing whether it clearly specifies the types of research to be conducted or excluded (for instance, providing examples of specific diseases or research areas), addressing issues such as commercialization and genome sequencing (if relevant to the biobanking activities), enabling participants to object to specific types of research, and incorporating an easily accessible way to withdraw consent. Overall, they should evaluate whether an IT-based consent model, like dynamic consent, would be suitable and feasible for implementation considering both short- and long-term risks and benefits, or if it would be preferable to maintain a broad consent approach with certain improvements.
- Considering that the current EC appraisal scheme requires confirmation from a biobank that consent has been obtained but does not require an explanation of the specific consent model used, nor does it provide guidelines on how the model should be explained in the country, adding clarity would be beneficial. It could include a request for essential elements of the consent model, addressing not only procedural aspects (whether one-time or continuous consent is required) but also certain content-related elements such as the scope of future research and circumstances under which donors need to be recontacted.
- Biobanks should also pay specific attention to the enrolment procedure for biobanking, addressing concerns raised by potential participants, such as societal concerns like data protection and uncertainties about the scope of future research or individual concerns like fear of blood sampling.
- Biobanks should also be encouraged to be involved in increasing public awareness about biobanking activities. Having a strategy for how both the biobank itself and the organizations conducting biobank research can contribute to awareness efforts might be helpful.

2.5.4. Unclear policies regarding the return of individual health-related findings.

Challenge: D2.2 identifies challenges stemming from unclear policies and legal regulations regarding the return of individual health-related findings. One major issue is the ambiguity surrounding which individual health-related findings should be returned. Inconsistencies in the interpretation of what useful findings may occur not only across different countries but also within the same country. This may mean that biobank participants may expect very different findings. Furthermore, considering that some biobanks still do not offer individual health-related findings, participants of certain biobanks may not expect anything. Another layer of complexity in assessing the returnable findings stems from the potential gaps in expertise among REC members. For example, in the context of emerging technologies like AI-driven polygenic risk scores, RECs may lack sufficient understanding of the ethical implications associated with disclosing health-related findings to biobank participants. Therefore, they may assess the return of such findings either overly critically or overly favourably. This may lead to unfair return practices towards biobank participants in different or even the same country.

Option: establish a more coherent approach for defining the utility of findings. Given the considerable diversity in the criteria used to define useful findings, it is important to create an international/European framework for assessing various utility approaches, especially when dealing with complex diseases. Refining the international/European framework can provide clearer guidance and promote consistency in their interpretation. In the near term, one potential solution could involve refining the scope of reportable findings by utilizing the already existing gene lists, or by adhering to a set of general criteria.

Response: The literature outlines various methods for determining the utility of findings (mostly coming from genetic tests). These methods differ on their focus and how they determine "useful" findings: 1) medically actionable genes (MAG) approach: this method prioritizes identifying genetic predispositions to highly penetrant, single-gene disorders with available preventive or treatment options. The American College of Medical Genetics and Genomics (ACMG) recommendations exemplify this approach. A similar, but slightly different, approach proposed by Berg et al. (2016)[26] emphasizes tools for evaluating the clinical "actionability" of specific gene-disease combinations rather than relying on a fixed list of actionable genes. 2) patient actionable genes (PAG) approach: This method, developed by Ploug and Holm (2017)[27], emphasizes considering patients' preferences by shifting the focus from purely medically actionable findings to "patient actionable genes". This approach includes untreatable conditions that might be relevant for reproductive decisions, expanding the scope beyond only the medically actionable genes approach. 3) Direct-to-Consumer Genetic Testing (DTC GT) approach: unlike the previous methods, most DTC GT companies prioritize user curiosity and exploration of ancestry, genealogy, and various aspects of health, including not only single-gene disorders but also multifactorial ones. This approach focuses less on identifying actionable findings and more on user interest and information provision. While the DTC GT approach might be the most effective motivator for participating in biobanks, it also appears to be the most misleading. This approach can mislead consumers by implying that medically relevant information will be provided to all or most participants. In contrast, the MAG and PAG approaches are unlikely to be as motivating due to the low percentage (1-3.5%) of individuals receiving actionable findings (Evans et al., 2013[28]; Bochud et al., 2017[29]). However, these two approaches differ in their emphasis on personal autonomy. The PAG approach prioritizes individual preferences regarding the usefulness of findings, placing greater weight on them compared to the MAG approach.

[26] Berg, J. S., Foreman, A. K., O'Daniel, J. M., Booker, J. K., Boshe, L., Carey, T., et al. (2016). A semiquantitative metric for evaluating clinical actionability of incidental or secondary findings from genome-scale sequencing. *Genetics in medicine: official journal of the American College of Medical Genetics*, *18*(5), 467–475. https://doi.org/10.1038/gim.2015.104.

[27] Ploug, T., & Holm, S. (2017). Clinical genome sequencing and population preferences for information about 'incidental' findings - From medically actionable genes (MAGs) to patient actionable genes (PAGs). PLoS ONE, 12(7), e0179935. https://doi.org/10.1371/journal.pone.0179935.

[28] Evans JP, Berg JS, Olshan AF, Magnuson T, Rimer BK. We screen newborns, don't we?: realizing the promise of public health genomics. Genet Med Off J Am Coll Med Genet. 2013 May;15(5):332–4.

[29] Bochud M, Currat C, Chapatte L, Roth C, Mooser V. High participation rate among 25 721 patients with broad age range in a hospital-based research project involving whole-genome sequencing - the Lausanne Institutional Biobank. Swiss Med Wkly. 2017;147:w14528.

Regardless of the chosen approach, implementing the policies of returning individual health-related findings requires addressing various challenges beyond ethical ones [30]. These challenges, which include financial, logistical, social, and legal aspects, warrant further analysis to ensure the practical application of the return of health-related findings, not just its theoretical value.

Proposals:

- Given the diversity in approaches for determining the utility of findings, particularly from genetic tests, it is crucial to establish an international/European framework for assessing these various approaches, especially in the context of complex diseases. In the short term, biobanks (with the assistance of RECs) could establish their own strategies for handling health-related findings and be able to justify them ethically, especially those biobanks that adhere to a non-return strategy. Those considering the return policy may be advised to define the scope of reportable findings by using existing gene lists or adhering to a set of general criteria as suggested by Berg and colleagues.
- Biobanks (with the help of RECs) should regularly assess their strategy for returning individual health-related findings to biobank participants to ensure the framework is still ethically justifiable. This ongoing assessment should ensure that the approach to returning findings remains ethically sound, up-to-date with best practices, and aligned with the rights and expectations of participants.
- When biobanks seek REC consultation related to the return of specific health-related findings, it is important that the REC engages with different experts (e.g., geneticists, psychologists, and others outside the REC, if needed) when advising on this issue.

2.5.5. Narrow legal definitions of biobanking

Challenge: Reviewing policies related to the establishment of collections of human biological samples and health-related data as well as research proposals involving samples and data often presents challenges due to national rules with limited definitions of "biobanks." Additionally, there's not enough clear guidance for RECs on how to ethically assess collections similar (or even the same) to biobanks, such as those originally gathered for non-research purposes or created during a specific research study in a different country than the one where the samples and data were collected. This lack of clarity of how to treat collections similar or identical collections to biobanks can hinder proper ethical review and raise concerns about the protection of research participants.

Option: develop clear guidance for RECs on ethically assessing collections similar to, or even identical to, biobanks.

Response: one of the responses, which could be sought in countries with narrow definitions of biobanks, is to consider expanding the definition of a biobank to include various types of collections that, while meeting the essence of biobanking, may not formally fall under biobanking

[30] Lekstutiene J, Holm S, Gefenas E. Biobanks and Individual Health Related Findings: from an Obstacle to an Incentive. Sci Eng Ethics. 2021 Aug 11;27(4):55.

regulations. However, it is important to establish requirements for such collections based on their associated risks. Expansion of the definition of biobanks, in any case, requires changes in legal documents, and the establishment of requirements for such collections based on their associated risks may also require a comprehensive examination of different collections and their risks, which is typically a lengthy and time-consuming process. Considering that such risk typologies do not exist at the European and international levels, it may be quite challenging to implement this response in practice. Nevertheless, despite this, if the decision to implement such a response is made, it may be possible to rely on examples of integrating certain collections into biobanks from other countries. For instance, Finnish[31],[32] and UMC Utrecht[33] suggested examples on how to integrate old collections into biobanks, which might be worth considering.

Proposal:

- National governments should encourage the development of clear guidance for RECs on ethically assessing collections similar to, or even identical to, biobanks. Using existing examples, such as the Finnish model, on how to integrate old collections into biobanks might be worth considering.

2.5.6. Regulatory disparities between biobanking and other data initiatives

Challenge: Biobank regulations are generally stricter, and ethics reviews remain prevalent in various European countries. In contrast, European and national secondary data use initiatives appear to have less stringent ethical review policies. Ethics review of any biobank research (even those where researchers work with anonymous data) may be redundant and lead to unjust overprotection of biobank participants as compared to data reuse initiatives. However, too little protection of the interests of data subjects whose data are reused following secondary data use initiatives might also be an issue. D2.2 suggests that there may be gaps in the oversight of secondary data use initiatives, which could undermine the overall ethical framework for research related to data and result in informational harm to data subjects and trusts in participating of such initiatives.

Option: Implement a coordinated and consistent approach to ethical review for various data initiatives at the national and international levels.

Response: The first step to respond to regulatory disparities between biobanks and other initiatives that involve the secondary use of data could be to explore and establish specific criteria to guide these regulatory distinctions, if any. However, in the long term, it might be important to implement a coordinated and consistent approach to ethical review for various data initiatives at the national and international levels. A regional or European project could help to conduct a systematic review of biobanks and other secondary data use initiatives. However, no

[31] Finland, Biobank Act, 688/2012. https://www.finlex.fi/en/laki/kaannokset/2012/en20120688.pdf
[32] Auria Biobank, “What are old samples?”, https://www.auria.fi/biopankki/en/kansalaisille/.
[33] UMC Utrecht, “Biobank Regulations”, https://assets-eu-01.kc-usercontent.com/546dd520-97db-01b7-154d-79bb6d950a2d/ae4726d2-b6eb-407b-a576-db1a5c63a139/Biobank_Regulations_UMCUtrecht.pdf, 19 June 2013.

such initiatives that would explore this specific regulatory aspect are currently known for irecs consortium.

Proposal:

- Research funders should initiate calls to explore biobanks and other secondary data use initiatives, including their regulatory distinctions and justifications for these distinctions. They should also assess whether similarities can lead to a coordinated and consistent approach to ethical review for various data initiatives and biobanks at both national and international levels.
- In ethical reviews, it must be considered whether patients who provide biosamples or health data have the opportunity to benefit from the research results for better treatment (access and benefit sharing).

2.5.7. Survey results: BB related research

The survey findings align with our initial results from the SCORE analysis on biobanking. For example, in Challenge 2.5.2 "Variations in ethics review," the survey highlighted some variability in ethics review processes in biobanking. Specifically, in Europe, 62% of respondents noted that an ethics review is required when establishing a new biobank, 65% when conducting a specific study, and slightly fewer (47%) when amending an approved project.

While searching for the best ethical oversight model for biobanks, similar models were identified in the SCORE analysis: ethics review required only during biobank establishment, only when specific study is planned, or in both cases. The survey results showed strong support (74%) from ethics experts for the third model, which advocates for ethics review during both biobank establishment and specific scientific studies. Despite this majority endorsement, further research is necessary to survey a broader range of stakeholders and to analyze the advantages, disadvantages, and applicability of these models to biobanks.

Additionally, the survey findings support other initial results from the SCORE analysis related to biobanking. For instance, one of the main strengths of ethics review identified in the SCORE analysis (2.1.4 Strength on RECs expertise) as well as in the survey is ethics experts' competence in consent when reviewing both the establishment of biobanks and biobank research, with over 80% of respondents feeling competent in this area. Similarly, respondents evaluated their competence in data protection, data privacy, and data sharing with a reasonably high level of confidence, with over 60% feeling competent. However, in contrast to consent, more respondents felt incompetent in these areas, with over 10% as compared to 2% in consent. The lack of competence in the area of data protection might also be explained by the unclear role of REC in data protection (cross-cutting Challenge 2.2.8 Ethics review boundaries in data protection).

The survey respondents rated their competence lowest in issues related to the commercialization of research results, with 39% feeling competent and only 24% indicating they were not competent. Therefore, it is not surprising that consent documents do not always address this aspect (Challenge 2.5.3 "Limitations in current broad consent policies").

So, the obtained data show that regardless of the stage at which the biobank is being created or the evaluation of a specific study, the main problems in expert competence are very similar. The data agree between different regions in almost all criteria, except for commercialization, where representatives of African countries indicated a substantially lower level of competence.

2.6. Genome editing related challenges, options, responses, proposals, and survey data

2.6.1. Navigating the Future of Embryo Research and Heritable Human GE

Challenge: regarding human germline GE, lack of effective oversight and governance mechanisms to prevent altering embryo DNA for reproductive purposes. Although there is broad consensus that altering embryo DNA for reproductive purposes should remain forbidden[34]: a 2020 study showed that 75 of 96 surveyed countries have banned it. In the USA, the use of funds by the FDA to review 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 to export their research to evade constraints established in their home jurisdictions.

As regards embryo research regulation[35], an extension of the 14-day rule for embryo research (which is legally binding in some countries) has been under discussion for many years. The International Society for Stem Cell Research (ISSCR) relaxed its guidelines 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[36]).

Option: International organizations may be able to deal with this issue and provide guidelines on these issues. 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.

Response: There could be another legal instrument on the European or worldwide level dealing with embryo research to find a common international normative basis for research on human embryos. If a new instrument can find a common international normative basis for research on human embryos, this would help to harmonize the regulations on this issue. Even if a consensus won't be reached, there is a chance that a significant number of countries will support the instrument which would already be helpful for minimizing the disparities between the existing regulations.

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[34] The Lancet. Human genome editing: ensuring responsible research. Volume 401. Issue 10380. P877 (18th March 2023). https://doi.org/10.1016/S0140-6736(23)00560-3.

[35] Adashi EY, Cohen IG. Who will oversee the ethical limits of human embryo research? Nat Biotechnol. 2022 Apr;40(4):463-464. doi: 10.1038/s41587-022-01274-6. PMID: 35361998.

[36] The International Society for Stem Cell Research (ISSCR). Guidelines for Stem Cell Research and Clinical Translation. 2021. Available at: https://www.isscr.org/guidelines.

Proposals:

- Initiate discussion to draft international guidelines and develop oversight and governance mechanisms to prevent altering embryo DNA for reproductive purposes;
- Dialogue between different RECs to exchange experiences and to create awareness of possible problems.

2.6.2. Lack of distinction in guidelines between somatic and heritable GE

Challenge: In some non-EU countries, there is a lack of distinction in guidelines between somatic and heritable editing[37]. If these two types of editing aren't distinguished properly, allowing one procedure related to somatic editing can lead to a slippery slope which can lead to the permission of heritable editing. As these two types of genome editing have different risks and benefits, a clear distinction between the types is advisable. Regulatory vacuums can furthermore lead to premature commercialization of purported therapies and to prevent this outcome, ethical principles need to inform and be connected to regulatory frameworks. A lack of distinction in guidelines makes establishing a regulatory framework more difficult.

Option: Policy differences in different countries should be highlighted because genome editing is regulated on both a European level as well as a national level. This leads to a lack of policy alignment between countries. Ethics experts should be aware of the differences and of the risk of ethics dumping. If possible, REC members should apply a unified standard science-based approach and inform researchers and policy makers about regulatory discrepancies.

Response: There might be resistance from various stakeholders to find a clear distinction between somatic gene editing and heritable genome editing. Various stakeholders might try to establish a distinction that fits their individual worldview and aims best which will lead to conflicts between stakeholders with different world views and aims. This is especially the case in questions related to the beginning of human life, embryo research regulations, and reproductive techniques which are connected to the technology of gene editing.

Proposal:

- Regularly evaluate the regulatory framework of genome editing in other countries in case of international research.

2.6.3. Complexity of somatic GE ethics governance

Challenge: one of the main issues for European RECs will most probably be risk assessment regarding somatic genome editing. Bittlinger et al. (2022)[38] conducted an expert interview study to investigate the demands for a structured risk assessment approach to gene therapy/genome

[37] Millett, Piers et al. Somatic Genome Editing Governance Approaches and Regulatory Capacity in Different Countries (28th February 2023). https://dx.doi.org/10.2139/ssrn.4375726.
[38] Bittlinger M., Hoffmann D. et al. Risk assessment in gene therapy and somatic genome-editing: An expert interview study. Gene and Genome Editing, Volumes 3–4, 2022, 100011, ISSN 2666-3880, https://doi.org/10.1016/j.ggedit.2022.100011.

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 the validity of relevant animal models and long-term risks), is a suitable approach. 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).

Option. The complexity of risk assessment and the necessity to take into account the participatory aspect in genome editing research leads to the discussion on an appropriate ethics governance model. In particular, it is still under discussion whether a one-off assessment (traditional one-time prior review) or a continuous assessment of this type of research (ethics by design) is more appropriate.

Response. Taking into account the uncertainty of outcomes and social implications of GE intervention, the ethics-by-design approach of ethics governance might be prioritized. It should, however, be taken into account that 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.

Proposals:

- Evaluate risks of human genome editing on a case-to-case approach to better assess possible risks;
- Prioritise ethics-by-design ethic governance model;
- The EC ethics self-assessment document should be better tailored to genome editing interventions.

2.6.4. Lack of governance frameworks for experimental treatment

Challenge: There is a lack of distinction in guidelines between research and treatment in human genome editing[39], that 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. Establishing governance frameworks for experimental treatment in somatic human genome editing on a local or national level is currently often seen as not feasible because there aren’t many cases and a national monitored governance system would not have much to do. This might change in the future, but the frameworks would be helpful for RECs and researchers.

[39] Millett, Piers et al. Somatic Genome Editing Governance Approaches and Regulatory Capacity in Different Countries (28th February 2023). https://dx.doi.org/10.2139/ssrn.4375726.

Option: International organizations such as EMA, WHO and OECD could play an important role in evaluating experimental treatment and they could set up a patient ombudsman system.

Response: If international organizations set up a patient ombudsman system, that would help RECs because complaints from patients would all go to the ombudsman and can then be made available for the RECs. This would make it less difficult for RECs to find complaints that patients had about a specific procedure.

Proposal:

- set up a patient ombudsman system.

2.6.5. Implications of animal genome editing for human enhancement

Challenge: By approving enhancement procedures in animals for research purposes, RECs may have to pave the way for human enhancement as well. If a REC approves a procedure that aims to enhance certain traits in animals without any obvious medical advantage, one could argue that by approving this procedure, it also opens the door for a later enhancement application in humans through a slippery slope, even if human enhancement is not stated as an aim in the research proposal. Additionally, there are concerns for dual use of such applications that should be taken into account. A risk is that the REC could only focus on the animal welfare aspects of such a proposal without seeing it as a gateway for later proposals involving human enhancement.

Option: Genome editing in animals with the goal of enhancing their specific traits that is not exclusively aimed at using the animals as model organisms for later human applications should not only be evaluated for animal suffering and later applications in animals, but also with regard to possible later applications on humans to avoid starting a slippery slope towards an application in humans. There is also the concern of dual use for such applications. Furthermore, RECs should refrain from taking an exclusively anthropocentric approach in their evaluation of nonhuman applications as the dignity of non-human living beings might be affected by the applications and therefore should be considered. It could be helpful to engage with stakeholders for the evaluation as well as consulting experts from the fields of other disciplines. The risks and benefits should be communicated transparently and honestly to local stakeholders.

Response: If RECs evaluate genome editing in animals with the goal of enhancing certain traits with regard to a possible later application on humans and with regard to the possibility of dual use, this would make going down the slippery slope less probable and dual use less likely to occur. If RECs refrain from taking an exclusively anthropocentric approach in their evaluation of nonhuman applications of genome editing, this would make their assessment more likely to be accepted without complaints, especially when relevant experts and stakeholders were consulted before the decision. Additionally, consulting with experts would also help gain acceptance in local communities that could be affected by the experiments, especially when gene drives are tested in the wild. If local communities prefer other measures for the same purpose, this should be respected.

Proposal:

- While evaluating animal GE research projects RECs should take into account possible implications to humans.

- Consulting with experts would help gain acceptance in local communities that could be affected by the experiments.

2.6.6. Vagueness of ethical requirements and differences in their implementation

Challenge: There are existing regulatory frameworks for the use of genome editing in animals and plants. The EU directive 2001/18/EC regulates under which conditions genetically modified organisms (GMOs) may be released into the environment. Directive 2009/41/EC deals with legal problems concerning the contained use of genetically modified organisms. Also, The UN Convention for Biological Diversity (which is, in principle, legally binding for the countries which signed it) dealt with gene drives[40] in 2018[41]. However, existing ethics requirements are often vague and their effectiveness depends on national implementation and oversight. If the requirements are too diverse, this can lead to difficulties in international cooperation if different national regulations exist. This generally affects all applications of genome editing, however, non-human application regulations are generally less implemented on a national level and have a greater diversity.

Options, In general, harmonization of regulations for gene editing in different countries and clearer ethics requirements for RECs are needed. More specifically, for research on plants or gene drives, the EU ethics self-assessment checklist is rather short even if it mentions possible effects on humans and on the environment that the research could have. Therefore, more details on the type of research being carried out to ensure that adequate measures are taken to protect the environment and humans from possible negative side effects of the research are needed. This especially applies to research on gene drives and plants that are going to be planted outside a lab.

Response: There might be resistance to harmonise the different regulations for gene editing in different countries and to give clear ethics requirements to the RECs. While this would make international collaborations easier, it is to be anticipated that many countries don't want to change their regulations because it is a time-consuming process and possibly because they believe their regulations correspond to their country's cultural tradition. The same would apply to ethics requirements.

Proposal:

- EU ethics self-assessment checklist should include more detailed questions on the type of research being carried out and possible negative side effects of the research.

[40] Gene drives are being used to alter the genome of a population rapidly by increasing the heritability of a certain gene. All descendants of an organism treated with gene drives will carry the gene in question.
[41] Convention on Biological Diversity. Decision approved by the conference of the parties to the convention of biological diversity, 14/19. Synthetic Biology. Sharm El-Sheikh: UNCBD 2018.

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2.6.7. Survey results: GE related research

The survey's genome editing questions were further divided into three categories: somatic gene editing, germline gene editing, and non-human gene editing.

When assessing the experts' competencies, parts such as the issue of consent (which does not apply to non-humans), safety, accessibility, enhancement, and misuse were evaluated. In the non-human part, competencies for protecting species were additionally evaluated.

In both somatic and germline gene editing categories, experts rated their competence in obtaining consent as high (71-79% considered themselves competent). However, in the germline category, more experts rated themselves as incompetent (4% vs. 10%) in the same question.

Regarding somatic gene editing, safety, accessibility, enhancement, and misuse competencies were evaluated quite favorably; between 71% and 79% considered themselves competent, and around 10 % - felt incompetent. However, in germline gene editing experts indicated lower confidence in their competencies in accessibility (52%) and enhancement (57%).

Comparing different parts of gene editing: experts in nonhuman gene editing chose the competent answer very similarly to those in germline editing. However, noncompetent answers were chosen less often, more often opting for the neutral option (3 points on a five-point Likert scale).

The survey findings support proposals on genome editing technology. Up to 1/3 of experts believe that the most significant hindering factor in the genome editing part is the lack of guidelines - which justifies the propositions arising from challenges 2.6.1, 2.6.2, and partially for 2.6.4.

Also, data support challenge 2.6.3 (prioritize ethics-by-design ethical governance model) as more than 60 percent of experts believed that continued ethics oversight starting from the design stage of research is feasible when applying it to genome editing (regardless of its modality), and only less than 10 % believed that such an offer was not feasible.

Very similar results can be seen for the opportunity to consider the broader societal impacts (more than half of experts agree, and less than 1 in 10 disagreed with this statement); such findings correspond well with proposals from challenges 2.6.5 and 2.6.6. It is important to mention that up to 29% of the experts considered themselves incompetent in assessing the issue of enhancement, which further strengthens the proposal arising from challenge 2.6.6.

3. Overview of proposals for adaptation of ethics review processes

Chapter	Challenge	Proposals
Cross-cutting issues		
2.2.1	Lack of transparency	1. RECs should have specific guidelines on managing conflicts of interest.

		2. RECs should publicly release (preferably in centralized repositories) ethical review criteria, the sources of REC funding, the composition of RECs, a list of institutional policies and guidance, report on previous REC submissions and decisions (approved, rejected, and amended studies).
2.2.2	Lack of coordination	3. RECs should be encouraged to utilize existing networks, and provide access to shared resources, news articles, literature, and lists of problematic cases. 4. RECs should organize regular feedback sessions with researchers about their experiences in the implementation of research. Other stakeholders, including patients' representatives and external experts, could also be invited to share their thoughts about the ethical issues surrounding research on XR, AI in health and healthcare, BB, and GE.
2.2.3 2.2.4	Lack of specific guidelines Limitations of ex-ante review	5. Follow a risk-based approach in ethics review to determine the modality of ethics review to address limitations of the ex-ante review, and mitigate the scarcity of resources.
2.2.5	Resource constraints	6. Foster networking (such as EUREC) and collaboration between RECs to address challenges related to lack of coordination, specific guidelines, and lack of resources. 7. To better address the interests of vulnerable communities in research ethics guidelines.
2.2.6	Lack of technical knowledge and expertise	8. Invest in the training of REC members/ experts. 9. Adapt the composition of committees depending on the types of the reviewed research.
2.2.7	Ethics review boundaries in data protection	10. To enhance collaboration between RECs and data protection bodies, clarify the role of RECs within the data protection framework. This role could be refined at least in several ways, such as assigning RECs a role as ethics reviewers within the data protection framework or assigning the responsibility of addressing GDPR-related legal and ethical concerns solely to researchers and research institutions, leaving RECs with only the duty of requesting statements from researchers confirming that their proposals have been assessed for GDPR compliance. To test which model is most suitable, among other factors (such as whether the REC operates at the institutional, regional, or national level), we suggest trying to include the DPO in the REC composition or creating another form of collaboration between the DPO and REC. This should also help these entities better understand each other's activities, overlapping and differing points, and ensure smoother collaboration with researchers.
2.2.8	Difficulties to involve all relevant stakeholders	11. Include laypeople and community members in the ethics review process to bridge the gap between Western and local ethical frameworks.

2.2.9	North-South divide	12. Enhance training for REC members in the EU to better understand regional ethical differences and foster collaboration between North and South.
AI related issues		
2.3.1	Lack of uniform and coherent 'AI in healthcare' guidelines across EU member states	13. Foster collaboration between REC members and experts to ensure common responsibility for unified implementation of the EU-level recommendations and the ethics appraisal scheme guidance.
2.3.2	Neglecting novel issues in AI in health and healthcare	14. Include AI experts as part of the composition of medical RECs or develop dedicated "digital ethics committees" (DECs) specialising in the review of AI projects.
2.3.3	Fast evolving technology	15. Involve RECs in "ethics by design" of projects at the development stage to engage in ethical reflection and evaluation.
2.3.4	A "grey area" of the review	16. Ensure consistency by setting uniform and coherent 'AI in healthcare' guidelines across EU member states.
XR related issues		
2.4.1	Risks to physical and psychological health	17. REC members should have clear guidelines or ensure that researchers submit a self-assessment checklist with well-defined safety criteria covering physical and psychological harm risks. 18. XR hardware should adhere to ergonomics standards to minimize physical strain or injury. 19. Participants must have clear warnings about XR content risks and reporting mechanisms for harassment or inappropriate content. Mechanisms to identify and address potential issues early in the research process and support systems for participants before, during, and after XR studies should be established.
2.4.2.	Unclear data scope	20. XR data collection parameters, such as visual, auditory, biometric, and behavioral aspects, must be clearly defined. Proposals must provide appropriate privacy settings, blocking features, and reporting mechanisms.
2.4.3.	Unclear social impact	21. Include social and environmental impact statements outlining how potential issues will be identified and addressed during the research process. 22. Continuously assess the social impacts of XR technologies on users, with particular attention to vulnerable groups. 23. Platforms should be inclusive and safe for diverse users, with age-specific virtual spaces and effective age verification systems in place.
2.4.4.	Ontological status of virtual objects	24. AI-generated content must be clearly labelled. 25. If personal data or images are used, explicit permission is required. Virtual crimes must be detected and addressed appropriately.
BB related issues		

2.5.1	Difficulty to navigate biobank regulations	26. Networks of RECs and biobanking should be encouraged to share ethical and legal requirements using existing platforms like TRREE, ensuring continuous updates through motivational measures for national contributors, and aiming for harmonisation.
2.5.2.	Variations in ethics review	27. Scientists and practitioners should further research the importance of ethics reviews during biobank establishment versus for research using biobank resources, including when exemptions might apply.
2.5.3.	Limitations in current broad consent policies	28. Biobanks (with the help of RECs) should regularly review biobank consent frameworks, especially those utilizing broad consent, and implement necessary changes whenever appropriate. 29. The review should include an assessment of whether the consent model reflects the evolving nature of biobank research including the explanation of different types of research, commercialization, genome sequencing, objection to certain research, and ease of withdrawal. The possibility of using an IT-based model should also be assessed. 30. Essential elements of the consent model, addressing procedural aspects (one-time or continuous consent) and content-related elements such as the scope of future research and recontact circumstances, might be added as a requirement alongside confirmation by a biobank that consent has been obtained. 31. Biobanks should pay specific attention to the enrolment procedure, addressing societal and individual concerns (e.g., data protection, future research scope, etc.). 32. Biobanks should help increase public awareness about biobanking activities, with a strategy for how they and research organizations can contribute.
2.5.4.	Unclear policies related to return of individual health-related findings	33. Given the diversity in approaches for determining the utility of findings, particularly from genetic tests, it is crucial to establish an international framework to assess these approaches, especially for complex diseases. In the short term, biobanks should create and ethically justify their strategies for handling health-related findings, using existing gene lists or criteria for reportable findings. 34. Biobanks (with the help of RECs) should regularly assess their strategy for returning individual health-related findings to biobank participants to ensure the framework is still ethically justifiable. This ongoing assessment should ensure that the approach to returning findings remains ethically sound, up-to-date with best practices, and aligned with the rights and expectations of participants. 35. When biobanks seek REC consultation related to the return of specific health-related findings, it is important that the REC engages with different experts (e.g.,

		geneticists, psychologists, and others outside the REC, if needed) when advising on this issue.
2.5.5.	Narrow legal definitions of biobanking	36. National governments should encourage the development of clear guidance for RECs on ethically assessing collections similar to, or even identical to, biobanks. Using existing examples, such as the Finnish model, on how to integrate old collections into biobanks might be worth considering.
2.5.6.	Regulatory disparities between biobanking and other data initiatives	37. Research funders should initiate calls to explore biobanks and other secondary data use initiatives, including their regulatory distinctions and justifications for these distinctions. They should also assess whether similarities can lead to a coordinated and consistent approach to ethical review for various data initiatives and biobanks at both national and international levels.
GE related issues		
2.6.1.	Navigating the Future of Embryo Research and Heritable Human GE	38. Initiate discussion to draft international guidelines and develop oversight and governance mechanisms to prevent altering embryo DNA for reproductive purposes. 39. Dialogue between different RECs to exchange experiences and to create awareness of possible problems
2.6.2.	Lack of distinction in guidelines between somatic and heritable GE	40. Regularly evaluate the regulatory framework of genome editing in other countries in case of international research.
2.6.3.	Complexity of somatic GE ethics governance	41. Evaluate risks of human genome editing on a case-to-case approach to better assess possible risks; 42. Prioritise ethics-by-design ethic governance model; 43. The EC ethics self-assessment document should be better tailored to genome editing interventions.
2.6.4.	Lack of governance frameworks for experimental treatment	44. Set up a patient ombudsman system.
2.6.5.	Implications of animal genome editing for human enhancement	45. While evaluating animal GE research projects RECs should take into account possible implications to humans. 46. Consulting with experts would help gain acceptance in local communities that could be affected by the experiments.
2.6.6.	Vagueness of ethical requirements and differences in their implementation	47. EU ethics self-assessment checklist should include more detailed questions on the type of research being carried out and possible negative side effects of the research.

4. Conclusion

The overarching objective of the deliverable 2.4 was to analyse ethics review processes and to develop proposals for their adaptation**,** with a particular focus on the EC ethics self-assessment and existing guidance. Accordingly, some of the proposals in this report aim to address the identified needs for specific guidelines or to tackle issues that require attention within the existing guidelines (see Chapter 3, Proposals: 7, 16, 17, 36, 38, 40, 44).

However, taking into account the needs of RECs identified in this report and that proposed adaptations will have to be trialled at pilot universities (T5.3), the majority of proposals are targeted to the needs of RECs assessing research on emerging technologies. In this report, we present at least two types of proposals for RECs: those that require procedural changes to make the ethical review process more focused on tech-related research and the need to evaluate it, and those that involve content-related changes to ensure that evaluations take greater account of the technology itself and the challenges it raises. This would ensure a more thorough evaluation, going beyond what is typically done in evaluating traditional biomedical research.

Some of these proposals, especially those related to content, are important for EC ethics appraisal experts, who also assess such research.

Additionally, while preparing this report, it became clear that certain changes can only occur with the involvement of other stakeholders—such as REC networks, researcher networks focused on specific technologies, research-performing organisations, research-funding organisations, and policymakers. These actors play a crucial role in fostering an ethics-sensitive institutional culture, shaping the up to date requirements for conducting research, and promoting ethical and responsible governance of tech-related research, ensuring that ethics remains central to scientific excellence.

It is important to note that these proposals are primarily based on the literature review and informal conversations with various stakeholders, as presented in the 2.2 deliverable, as well as the REC survey conducted as part of task 2.4. Therefore, it is crucial that these proposals for the adaptation of the ethics review process, especially those directly applicable to REC members, are tested in practice. This will be done later in the irecs project, in task 5.3, where pilot universities will use these proposals as part of the pilot materials.