D5.1: Report documenting elements to open and complement operational guidelines for research ethics committees

[**WP5** – The consortium's proposals]

Lead contributor	Lisa Tambornino; Dirk Lanzerath; Philipp Hoevel; Tom Lindemann European Network of Research Ethics Committees (EUREC Office gUG) tambornino@eurecnet.eu
Other contributors	Konrad Siemaszko; Maciej Kalisz, Helsinki Foundation for Human Rights (HFHR)
	Amal Matar; Mats Hansson, Uppsala University (UU)
	Anais Resseguier; Rowena Rodrigues, Trilateral Research (TRI)
	Philip Brey; Anna Drozdzewska; Yasemin Erden; Eliana Bergamin, University of Twente (UT)
	Annex 1 written by Maciej Kalisz (HFHR); annex 2 written by Elmar Doppelfeld (chair of EUREC); annex 3 written by Maria Alexandra Ribeiro (member of the EUREC Board and Vice-President of the National Ethics Committee for Clinical Research in Portugal); annex 4 prepared by EUREC Office gUG
Reviewers	Jantina de Vries, University of Cape Town (UCT) and Robert Gianni, Maastricht University (UM)

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Abstract

Research ethics committees (RECs) are well established to review health-related research projects. Nowadays, ethical assessments by RECs are requested not only for research projects in this field, but also beyond. However, standards and procedures for RECs outside the health-related research fields are still unclear or vague. Therefore, the question arises if and to what extent guidance documents and guidelines for RECs from the health-related field could be helpful to review research projects in other fields. In this report this question was analysed with a special focus on ethical reviews of research projects in the field emerging technologies.

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Information in this report that may influence other SIENNA tasks

Linked task	Points of relevance
Tasks 2.3, 3.3, 4.3	In tasks 2.3/3.3/4.3 a search for guidance documents and guidelines was conducted. Task 5.1 builds on the finding relevant for RECs.
Task 6.3	Task 6.3 will build on task 5.1. For task 6.3 a generalised approach for developing guidance documents for RECs in the field of emerging technologies will be developed.

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Executive Summary

In this report four guidance documents relevant for RECs were analysed and applied to hypothetical cases beyond their usual remit of application. All four documents were developed for health-related research fields and all encourage the involvement of a REC before, during and after research with humans is conducted. The documents in focus refer to principles and obligations researchers need to follow and contain detailed information on how a REC should be constituted, how a REC should assess research projects and how a REC should be organized in general. It could be concluded that guidelines developed for the health-related field are useful, but not sufficient on their own, to review research projects in the field of emerging technologies. This is because research projects working on new emerging technologies are often different compared with clinical trials or other health-related research projects involving humans. Therefore, the existing guidelines need to be complemented with additional information engaging with the specific ethical challenges associated with emerging technologies.

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List of acronyms/abbreviations

Abbreviation	Explanation
AI&R	Artificial Intelligence & Robotics
ALTAI	Assessment List for Trustworthy AI
ANCEI	National Association of Research Ethics Committees
CDBI	Steering Committee on Bioethics
CIOMS	Council for International Organizations of Medical Sciences
D	Deliverable
EMA	European Medicines Agency
ERCIC	Ethics Review Committee Inner City faculties
ERCPN	Ethics Review Committee Psychology and Neuroscience
ERCPN	Ethics Review Committee Psychology and Neuroscience
EU	European Union
FHML-REC	Ethics Review Committee Health, Medicine and Life Sciences
GCP	Good Clinical Practice
HET	Human Enhancement Technologies
HG	Human Genomics
HRA	Health Research Authority
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IRB	Institutional Review Board
LEA	Law Enforcement Agencies
METC	Medisch Ethische Toetsingscommissie
NEC	National Ethics Committee
NEM	The National Committee for Medical and Health Research Ethics
NENT	The National Committee for Research Ethics in Science and Technology
NESH	The National Committee for Research Ethics in the Social Sciences and the Humanities
REC	Research Ethics Committee
REK	Regional Committees for Medical and Health Research Ethics
SATORI	Stakeholders Acting Together On the ethical impact assessment of Research and Innovation

Abbreviation	Explanation
SIENNA	Stakeholder-informed ethics for new technologies with high socio-economic and human rights impact
SOPs	Standard operating procedures
WHO	World Health Organization
WMA	World Medical Association
WP	Work package

Table 1: List of acronyms/abbreviations

Glossary of terms

Term	Explanation
Artificial intelligence	The science and engineering of machines with capabilities that are considered intelligent (i.e., intelligent by the standard of *human* intelligence).
Autonomy	The value of a person's ability to decide and act on their own desires and preferences, without being unduly influenced, coerced or manipulated by others.
Human enhancement	A modification aimed at improving human performance and brought about by science-based and/or technology-based interventions in or on the human body.
Informed consent	The formal process whereby a research participant confirms their willingness to participate in a particular study, on a voluntary basis, without undue influence and after having been given sufficient information. Participants can only give informed consent, after having been informed of all aspects of the research that are relevant to the person's decision to participate.
Institutional Review Board (IRB)	See Research Ethics Committees
Investigator	The person that is responsible for the conduct of a study. A leader of a team that conducts a study is a principal investigator.
Protocol	A document that describes the objectives, methodology and organisation of a trial. Also called research protocol.
Research Ethics Committees (REC)	Committees that review research applications, give opinions about whether research is ethically sound and ultimately give approval for the research to proceed.

Table 2: Glossary of terms

1. Introduction

1.1 Background

In the health-related field, research ethics committees (RECs) are established to assess if and how a research project can be conducted without violating the rights, safety, well-being and dignity of persons potentially involved in the research. Ethical assessment of a research project is often challenging, since many different aspects of a research project need to be considered, like voluntariness of research participants and informed consent procedures, fair selection of participants, risks and benefits assessment and protection of privacy, dignity and autonomy of the involved persons. In order to help RECs in their work, some guidance documents and guidelines have been developed for health-related research with humans. In this report, we focus on four crucial documents, namely the Declaration of Helsinki[1], the guideline for good clinical practice E6(R2)[2], the CIOMS International Ethical Guidelines for Health-related Research Involving Humans[3] and the Guide for Research Ethics Committee members from the Steering Committee on Bioethics[4]. These documents are well-known by RECs assessing research projects in the health-related field. Nowadays, ethical assessments by RECs are requested not only for research projects in the health-related field, but also beyond. However, standards and procedures for RECs outside the health-related research fields are still unclear or vague. Therefore, the question arises if and to what extent guidance documents and guidelines for RECs from the health-related field could be helpful to review research projects in other fields.

1.2 Objectives

The main objective of this report is to examine if guidance documents, and guidelines used by RECs in the health-related field could be helpful to review research projects in the field of emerging technologies.

1.3 Structure of the report

The main body of the report consists of the three parts following this introduction (section 1) and the section on methodology (section 2). Section 3, "History, role and function of RECs", gives an overview of the development of medical RECs in the 20th century and describes the role of RECs in biomedical research with humans and which role they could potentially have in non-health-related research. Section 4, "Guidance documents and guidelines for RECs and their usability to review research projects in the field of emerging technologies", contains a detailed summary and analysis of the four mentioned guidance documents for RECs, as well as a summary of the results from the breakout sessions of the

[1] World Medical Association (WMA), "WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects", 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[2] European Medicines Agency (EMA), "Guideline for good clinical practice E6(R2)", 2016, p. 10. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

[3] Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO), "International Ethical Guidelines for Health-related Research Involving Humans", 2016. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

[4] Steering Committee on Bioethics (CDBI), "Guide for Research Ethics Committee Members", 2012. https://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/Guide/Guide_EN.pdf

online workshop. Section 5 aims to give a conclusion and response to whether existing guidance documents could be useful to review research projects in the field of emerging technologies. Annex 1 of this report contains a summary of European and national legislation in selected countries with regard to legally binding and non-binding provisions for the work of RECs. Annex 2 is written by the chair of EUREC and annex 3 by a EUREC board member. In these two annexes the reader can find more detailed information on two of the most relevant documents. Annex 4 presents results of our search for guidance documents and guidelines for RECs in a table.

1.4 Scope and limitations

In Task 5.1, we focused on existing guidelines and guidance documents for RECs in the health-related field and explored how these could be extended to review research projects in the field of emerging technologies. This scope is clearly defined by the terms of the SIENNA Description of Action (DoA). As outlined above, four guidance documents in particular are relevant when it comes to the ethical review of health-related research projects. As mentioned in the DoA, these documents demonstrate the development and application of ethical and scientific standards for the conduct of health-related research involving human subjects. Adherence to these documents helps RECs ensure that the dignity, rights, safety and well-being of research participants are promoted and that the research produces reliable results.

The restriction to guidelines or guidance documents for RECs from the health-related field automatically implies that we could not take a closer look at general ethics guidelines for AI or other fields of emerging technologies. For the AI field, already a number of general ethics guidelines exist – e.g., the guidelines developed by the High-Level Expert Group on Artificial Intelligence[5], the guidelines developed by the Institute of Electrical and Electronics Engineers (IEEE)[6] and the recommendations of Council on Artificial Intelligence of the OECD[7]. These general ethics guidelines are not developed as guidance for RECs. The existing general ethics guidelines could be partially incorporated into research ethics guidelines, but this is not the scope of this task. This is done within the scope of another SIENNA task, namely in task 5.4. The results are reported as “Research ethics guidelines for AI&R” and will be published as annex 4 of D5.4 soon.

Moreover, some organisations developing or working with emerging technologies have established ethics boards or committees in their institutions and have developed statements on how to deal with ethical issues, for instance, Microsoft and Google. Documents from such ethics committees are also not part of this task. It is important here to distinguish between “research” ethics committees (RECs) and such other ethics committees and ethics bodies. Within the scope of this report, we looked at ‘research ethics committees’ and not at ethics committees or ethics bodies in general. This also means

[5] AI HLEG, *Ethics Guidelines for Trustworthy AI*, 2019. https://ec.europa.eu/futurium/en/ai-alliance-consultation/guidelines#Top

[6] The IEEE Global Initiative on Ethics of Autonomous and Intelligent Systems, *Ethically Aligned Design: A Vision for Prioritizing Human Well-being with Autonomous and Intelligent Systems*, First Edition, IEEE, 2019. https://standards.ieee.org/content/ieee-standards/en/industry-connections/ec/autonomous-systems.html

[7] OECD, *Recommendation of the Council on Artificial Intelligence*, 2019. https://legalinstruments.oecd.org/en/instruments/OECD-LEGAL-0449.

that we could not focus on ethical guidelines developed for instance for computer and information technology. These guidelines exist (usually with a strong focus on privacy and data protection issues). However, they do not provide guidance for RECs.

Another limitation is that it was not possible in the allocated time for Task 5.1 to analyse if the guidance documents from the health-related field could be helpful to review research projects beyond medicine in general. The decision was made to focus on research projects in emerging technologies only, since this scope fits most closely to the three SIENNA areas, namely human genomics (HG), human enhancement technologies (HET) and artificial intelligence and robotics (AI&R).

2. Methodology

Based on previously completed SIENNA work (mainly tasks 2.3/3.3/4.3), we searched for guidance documents for RECs in the health-related field and in the field of new technologies. The main results of this search are documented in Annex 4 of this document. In our search for guidance documents and guidelines for RECs, we found more relevant documents than just the four we analysed. As these other documents relate to these four, we focus only on these in this report. Other documents, such as standard operating procedures (SOPs) developed for national RECs, do not bring any new insights. We also searched for existing guidance documents for RECs in the field of new technologies. The result was that they do not yet exist in this form. However, there are some relevant documents that provide guidance on setting up ethics committees or ethics advisory panels in specific technology areas, e.g. AI and computer science, but these do not include information for setting up 'research' ethics committees. One exception is a document on "Establishing Data and AI Ethics Advisory Boards", which we present at the end of Section 4.

In October 2020, a two-day online workshop was organized by EUREC. Participants were REC members from the EUREC network and other stakeholders. The workshop aimed to examine the scope of existing guidance documents for RECs in the health-related field and to investigate if and how these documents could be helpful to review research projects in the field of emerging technologies. On the first workshop day (26 October 2020) four invited experts gave talks on:

- Experiences with the acceptance of guidelines for medical RECs in the health-related field
- Experiences with non-medical RECs in Norway
- The model of networking of non-medical RECs in the Netherlands
- The ethics-self assessment tool for Artificial Intelligence & Robotics developed by the SIENNA project

On the second workshop day (27 October 2020), in a first step, REC members presented which specific guidelines they consider particularly valuable in their daily REC practice, and to what extent these guidelines could be useful to review research projects in the field of emerging technologies.

In a second step, the participants were divided into three working groups. Each working group discussed a given example of a research project and answered the following questions:

- Based on the common guidance documents for RECs, would you be able to review the research project appropriately?

- What guidance is needed to review the research project appropriately?

Working group 1 discussed a research project from HG, working group 2 one from HET and working group 3 one from AI&R. All three research projects were related to the field of emerging technologies.

As preparation for the workshop the participants had studied the research proposals and, furthermore, familiarized themselves with the four guidance documents in focus.

In a last step, we analysed the results of the online workshop, did some further research on guidance documents for RECs, the role of RECs and ethical assessment in the field of emerging technologies, and, finally, synthesized the results in this report.

3. History, role and function of RECs

After summarizing the history of medical RECs in the 20th century briefly, this chapter describes the role of RECs in health-related research with humans. Thereafter, a short overview of RECs outside the health-related field is given.

3.1 Historical aspects

Discussions about research with humans and ethical standards and principles for clinical trials emerged only in the 20th century. The Nuremberg Code of ethics[8] published in 1947 and the Helsinki Declaration published in 1962 were the first attempts to curb unethical research practices, which were still fairly common in their years of publication. Both documents spell out ethical principles, including the need for voluntary consent, avoiding harm of research subjects, and weighing risks against potential benefits.

In 1966, Henry K. Beecher published a landmark article on ‘‘Ethics and clinical research’’. In this article he identified many questionable research cases carried out by doctors and scientists in renowned universities and published in high ranked journals. Beecher’s article opened the debate on ethical standards and principles in research ethics, and paved the way for the establishment of RECs and other ethics bodies[9]. Besides the experiments on Jews during the Nazi regime, one of the worst questionable research projects was the so called “Tuskegee Syphilis Study”[10], a clinical study conducted between 1932 and 1972 in the United States with the aim to observe the natural evolution of untreated syphilis. In a nutshell, African American men infected with syphilis were told they were receiving free health care from the federal government of the United States, although actually none of them were treated with penicillin (the antibiotic was widely available and had become the standard treatment for syphilis), and many of them died because they were denied treatment. The study was stopped immediately, when an article by the journalist Jean Heller was published in the New York Times on 26

[8] National Institute of Health, “Nuremberg Code”, 2007. https://web.archive.org/web/20071029120713/http://ohsr.od.nih.gov/guidelines/nuremberg.html
[9] Beecher, H.K., “Ethics and clinical research”, The New England Journal of Medicine, Vol. 274, No. 24, 1966, pp. 1354-1360.
[10] Heller, Jean, “Syphilis Victims in the U.S. Study Went Untreated for 40 Years”, The New York Times, 26 July 1972. https://www.nytimes.com/1972/07/26/archives/syphilis-victims-in-us-study-went-untreated-for-40-years-syphilis.html

July 1972. The Tuskegee trial was a major violation of ethical standards and principles, and has been cited as "arguably the most infamous biomedical research study in U.S. history."[11]

In reaction to this scandal "the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research" was established in 1974 to develop ethical principles for research on humans. This first US bioethics commission has produced a whole series of reports. Most of these reports deal with specific questions related research on humans, such as research on foetuses, children or prisoners. The so-called Belmont Report, which the Commission published in 1979[12], addresses a broader topic, however. The aim of this report was to identify basic principles and to present a conceptual framework for the analysis of ethical issues arising during research with humans. The Belmont Report identifies three fundamental ethical principles:

- respect for persons,
- beneficence, and
- justice.

Based on these three principles, standards for the implementation of research projects with human beings were formulated, which are, among others, informed consent, careful risk/benefit assessment, a fair selection of research participants[13].

Tom Beauchamp and James Childress have further developed this approach of ethical principles. In their book "Principles of Biomedical Ethics" they add a fourth principle, the principle of no-harm (nonmaleficence)[14]. Furthermore, they use the principle "autonomy" instead of "respect for persons". The four principles postulated by Beauchamp and Childress, namely autonomy, beneficence, non-maleficence and justice, are accepted as standard principles for research ethics since many years. Most guidance documents for research ethics refer to these four principles, while some add further principles or values. In the last years, discussions on research ethics have revolved around approaches beyond principles. Some authors argue that principles should be a basis for research ethics and ethical decision making, yet emphasize that something beyond mere principlism is needed.[15]

[11] Katz, Ralph V., B. Lee Green, Nancy R. Kressin, S. Stephen Kegeles, Min Qi Wang, Sherman A. James, Stefanie L. Russell, Cristina Claudio and Jan M. McCallum, "The Legacy of the Tuskegee Syphilis Study: Assessing its Impact on Willingness to Participate in Biomedical Studies", *Journal of Health Care for the Poor and Underserved*, Vol. 9, No. 4, November 2008, pp. 1168-80.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2702151/

[12] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research", 1978.
https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

[13] Ibid.

[14] Beauchamp, Tom L., and James F. Childress, Principles of Biomedical Ethics, Oxford University Press. 8th Edition, 2019.

[15] See for example the following article: Rességuier, Anaïs., and Rowena Rodrigues, "AI ethics should not remain toothless! A call to bring back the teeth of ethics", Big Data & Society, Vol 7, No. 2, 22 July 2020.
https://doi.org/10.1177/2053951720942541.

3.2 Role of RECs

The central role of a REC is to review research projects involving human beings. [16] A REC needs to assess if a research project can be conducted without violating the rights, safety, well-being and dignity of persons potentially involved in the research. However, protecting the potential participants in the research is not the only responsibility of RECs, they must also take into account potential risks and benefits for the community in which the research will be carried out, since the ultimate goal is to promote high ethical standards in research for health[17]. According to the World Health Organisation (WHO), "research ethics committees review proposed studies with human participants to ensure that they conform to internationally and locally accepted ethical guidelines, monitor studies once they have begun and, where relevant, take part in follow-up action and surveillance after the end of the research. Committees have the authority to approve, reject or stop studies or require modifications to research protocols."[18]. The members of RECs normally come from different disciplinary backgrounds and need to be independent.

According to the Steering Committee on Bioethics:

> "RECs provide independent advice on the extent to which a biomedical research proposal complies with recognised ethical standards. The REC must be satisfied about the scientific quality of the research proposal and of its conformity with national law; scientific quality and conformity with law may be assessed by the REC per se or by other competent bodies. RECs therefore play a central part in the research process. In addition to their role in the protection of participants, they specifically help to ensure that research is soundly based and trustworthy, and consequently that medical interventions and treatments prescribed to patients have been assessed adequately. In this way, RECs help ultimately to improve the quality of health care."[19]

The central goal of involving RECs thus is to protect the interests of research participants and, at the same time, to ensure that research is conducted ethically. To that end, a REC gives an opinion on whether research is ethical and fair.

RECs can be established at different levels, e.g. on the local, regional or national level. "They may be appointed by institutions or by regional or national authorities and are increasingly provided for by law. Their scope as a local, regional or national REC is defined by the appointing authorities."[20]

- Local RECs are linked to research performing institutions, such as universities and hospitals, and assess research activities within these institutions.
- Regional RECs are instituted by different regional bodies (regional authorities, medical associations, etc.) and assess research activities within a certain geographical area.

[16] In the USA RECs are mainly known by a different name, they are called "institutional review board" (IRB).
[17] World Health Organization (WHO), "Research ethics committees. Basic concepts for capacity-building", 2009. https://www.who.int/ethics/Ethics_basic_concepts_ENG.pdf
[18] Ibid, p. 11.
[19] Steering Committee on Bioethics (CDBI), "Guide for Research Ethics Committee Members", 2012, p. 8. https://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/Guide/Guide_EN.pdf
[20] Ibid, p. 15.

- National RECs supervise local and regional RECs, assess specific types of research activities, and may serve as appeal bodies.[21]

Besides this there are also associations of RECs, some of which have the status of a national body, like for instance the National Association of Research Ethics Committees (ANCEI) in Spain.[22]

There is a difference between national RECs on the one hand and national ethics committees or bodies on the other. An example of the latter is the German Ethics Council[23]. Unlike national RECs that assess research on a national level, national ethics committees mainly offer ethics guidance for researchers. However, in some countries the distinction between national RECs and national ethics committees is blurred because there are bodies that perform both functions. The Norwegian National Committee for Research Ethics in the Social Sciences and the Humanities (NESH), for example, does both conduct ethics reviews of research projects and functions as a national ethics committee. [24]

Depending on the regulations in different countries, the scope of REC activity varies. Most RECs have been established in medicine, social and behavioural sciences. A few RECs have been established for fields like AI&R.

3.3 Power of RECs

Whether or not a positive opinion by a REC is required depends on international and national law and standards. In some countries, ethical review of research projects is for some professions required by law. In Germany, for instance, doctors need to get ethics approval before carrying out research with humans or human materials. Besides, ethical review is also required if researchers aim to publish their results in a journal which will not publish articles based on research without ethics approval. Many journals are following such a rule. Furthermore, ethical review may be needed if a researcher wants to get funding from an institution or a public authority.

The main role of a REC is to assess a research project before it starts. The procedures and regulations vary from country to country and from discipline to discipline. If researchers must or want to get ethics approval for their research project, they need to send a research protocol to the responsible REC. In most countries standard application forms exist that researchers are encouraged to use. Normally the research protocol needs to entail information on the person responsible for the study, what qualifications this person has, a description of the experiment, and the expected benefits achieved by the experiment, a project plan and documentation ensuring the consent of the participants.[25] Besides the assessment of research proposals, RECs are also involved when the study design changed or when in the event of unusual occurrences. RECs may also have a role after the research project is conducted,

[21] SATORI, "Policy brief: Improving the organisation of research ethics committees (RECs)", January 2017, p. 4. https://satoriproject.eu/media/SATORI-policy-brief-_2017_Improving-the-organisation-of-RECs-_26-06-2017.pdf
[22] National Association of Research Ethics Committees (ANCEI), "Home", 2020. https://ancei.es
[23] The German Ethics Council, „The German Ethics Council", undated. https://www.ethikrat.org/en/the-german-ethics-council/
[24] SATORI, "Ethics assessment and guidance in different types of organisations. Research Ethics Committees", 2015, p. 5. https://satoriproject.eu/media/3.a-Research-ethics-committees.pdf
[25] Ibid, p. 16.

for instance with regard to the publication and dissemination of research results. In some circumstances it is also expected that RECs give an opinion whether research has a social value and this can only be achieved if research results get published.

In appendix 1 of this report a short overview of the most relevant European law with regard to ethics review performed by RECs is given. Furthermore, some national legislation requiring approval or opinion from RECs in order to initiate research activities is summarized.

3.4 RECs outside medicine

Obtaining the favourable opinion of a REC is a standard procedure for medical researchers involved in research with human subjects. In the health sector many RECs are established on national, regional and local levels. However, positive opinions by RECs could also be desirable or even necessary in other research fields. More and more researchers doing research in social sciences and other research fields are also being asked to submit their proposals to RECs. In the scope of this report, it is not possible to give a detailed overview of all research fields and their specific need for ethical review by RECs. Nevertheless, some insights to ethical assessments by RECs in the non-health sector should be given.

> "During the last years, however, RECs expanded their scope to many other fields of R&I such as the engineering sciences and computer science. This rapid expansion is accompanied by a growing need for guidance and harmonisation of practices of RECs. Additionally, it presents a need for improved training of REC members and quality assurance."[26]

The SATORI project developed a list of different research fields and published it in the CWA part 1.[27] The following research fields are distinguished:

- The natural sciences
- The engineering sciences and technological innovations
- The medical sciences
- The life sciences
- The computer and information sciences
- The social sciences and the humanities

SATORI listed general and field-specific ethical principles that need to be taken into account for ethical reviews in each of these fields. RECs have not yet been established in all the listed fields. While there are a lot of medical RECs and also a number of RECs for the social and behavioural sciences, only a few RECs have been established in the field of emerging technologies. However, quite a number of ethics bodies other than RECs focuses on the field, especially for research in AI&R – for instance the High-Level Expert Group on Artificial Intelligence (AI HLEG).

[26] SATORI, "Policy brief: Improving the organisation of research ethics committees (RECs)", January 2017, p. 4. https://satoriproject.eu/media/SATORI-policy-brief-_2017_Improving-the-organisation-of-RECs-_26-06-2017.pdf

[27] European Committee for Standardization (CEN), "Ethics assessment for research and innovation - Part 1: Ethics committee", Workshop Agreement CWA 17145-1, May 2017, p. 20. ftp://ftp.cencenelec.eu/EN/ResearchInnovation/CWA/CWA1714501.pdf

In the online workshop on 26 and 27 October the situation for non-medical ethics assessments in Norway and the Netherlands was in focus and should also briefly be described here.

Experiences with non-medical RECs in Norway

The Norwegian National Research Ethics Committee is the central ethics body in Norway. Its main objective is to ensure that all research is conducted in accordance with recognized research ethical norms. To fulfil this objective, the committee established different sub-committees and commissions, namely[28]:

- The National Committee for Medical and Health Research Ethics (NEM)
- The National Committee for Research Ethics in the Social Sciences and the Humanities (NESH)
- The National Committee for Research Ethics in Science and Technology (NENT)
- The National Commission for the Investigation of Research Misconduct

Furthermore, there are seven independent regional committees for medical and health research ethics (REK). [29]

All these committees are advisory bodies. However, their task is also to assess research proposals. This means the committees do not only provide overall guidance, but also give concrete advice. Therefore, they combine elements of a national ethics committee and a REC. For research ethical issues in medicine and health sciences, a researcher needs to contact NEM. For research ethical questions in the fields of science and technology a researcher can ask for advice by NENT. For research ethical issues in the social sciences and the humanities, including law and theology, NESH is the right contact. Members of the different committees are researchers from different disciplines and institutions and also lay people's representatives.

The work of all the Norwegian committees is based on the Helsinki Declaration, in addition to the Health Research Act. However, NEM, NESH and NENT have also developed subject-specific research ethics guidelines and additional area-specific guidelines and guides.[30]

A guideline for Research ethics in science and technology was developed by NENT in 2007 and revised in 2015.[31] In this guide, NENT outlines 23 guidelines in nine categories, which are:

- The obligations of research to society
- Scientific integrity, truthfulness, and accountability
- Uncertainty, risk, and the precautionary principle
- Protection of research subjects
- Protection of animals used in research
- The relationship between research and other knowledge-bearers and forms of knowledge

[28] The Norwegian National Research Ethics Committee, "Who are we and what do we do?", 8 June 2019. https://www.forskningsetikk.no/en/about-us/who-are-we-and-what-do-we-do/
[29] Ibid.
[30] Ibid.
[31] The National Committee for Research Ethics in Science and Technology (NENT), "Guidelines for Research Ethics in Science and Technology", 2016. https://www.forskningsetikk.no/globalassets/dokumenter/4-publikasjoner-som-pdf/60126_fek_guidelines_nent_digital.pdf

- Commissioned research, openness, and conflicts of interest
- Whistleblowing and ethical responsibility
- Dissemination of research to the general public

The model of networking of medical and non-medical RECs in the Netherlands
At the online workshop on 26/27 October participants were informed about the REC system in the Netherlands, especially how RECs from the health sector and other sectors are connected. Two members of the "Ethics Review Committee Psychology and Neuroscience (ERCPN)" from the University of Maastricht presented their experiences at the workshop.

Ethical assessments of research proposals involving either human participants or personally identifiable data is done by several ethical review committees within the University of Maastricht. Medical research projects need to be reviewed by the accredited review committee METC (Medisch Ethische Toetsingscommissie), and this is mandatory. For other research projects, ethical assessment is carried out by the relevant ethics committee. Most important are:

- Ethics Review Committee Inner City faculties (ERCIC)
- Ethics Review Committee Psychology and Neuroscience (ERCPN)
- Ethics Review Committee Health, Medicine and Life Sciences (FHML-REC)

Reviews are conducted using the assessment criteria and guidelines laid down in the Code of Ethics for research in the Social and Behavioural Sciences involving human subjects. The Medical Research Involving Human Subjects Act and the Code of Ethics for research in the Social and Behavioural Sciences involving human subjects are in compliance with the overarching UM Integrity Code of Conduct.

Review of non-medical research is not mandatory by law, but by the faculty of the University of Maastricht.

4. Guidance documents and guidelines for RECs and their usability to review research projects in the field of emerging technologies

4.1 Introduction

As outlined above, the central role of a REC is to assess if a research project can be conducted without violating the rights, safety, well-being and dignity of persons potentially involved in the research, and to ensure that research is carried out in accordance with national and international law. This is a challenging task, and to fulfil it appropriately guidance is needed. RECs need guidance on different levels or rather answers to various questions, for instance:

- Who should be the members of a REC?
  - Which disciplines, groups, stakeholders need to be represented in a specific REC? What do REC members need to know (expertise) and what do they need to learn (training)?
  - Should laypersons be members?

  - Should the community be engaged? Who is the relevant community?
- On what basis should RECs assess research projects?
  - What principles and values need to be taken into account?
  - How can principles be applied?
  - What needs to be considered regarding informed consent?
  - What needs to be considered regarding vulnerable groups?
  - How can a fair selection of participants look like?
  - What needs to be taken into account regarding risks and benefits assessment?
    - Risks and benefits for the involved participants?
    - Risks and benefits for the society as a whole?
    - Risks and benefits for the environment?
    - Long- and short-term risks and benefits?
- Should ethical assessments by RECs be mandatory or voluntary?
- How should RECs be organized?
- How can RECs work together with other ethics bodies and other involved institutions (harmonization)?
- Who is paying for the work of RECs?

These are a lot of important questions. For RECs in the health sector there are some guidance documents and guidelines that give answers to some of them. As outlined in the introduction, this report focuses on four relevant guidance documents or guidelines for RECs, which are, to our knowledge, considered as useful by RECs, namely:

1. WMA Declaration of Helsinki – ethical principles for medical research involving human subjects
2. CIOMS International Ethical Guidelines for Health-related Research Involving Humans
3. ICH Guidelines for Good Clinical Practice E6 (R2)
4. Guide for research ethics committee members developed by the Steering Committee on Bioethics (CDBI) of the Council of Europe

These four documents will be described and for each document it will be analysed if and how they could also serve as guidance for ethical assessments of non-health research projects. Thereafter, observations from our online workshop in October are summarized. In working groups, participants discussed the usability of the four guidance documents to review research projects in the three SIENNA fields. Finally, we refer to two documents that point out important points when setting up RECs for the AI field.

4.2 The Declaration of Helsinki from the World Medical Association

In 1964 the World Medical Association (WMA) developed the Declaration of Helsinki as "a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data"[32]. This is widely regarded as the cornerstone document of human research

[32] World Medical Association (WMA), "WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects", 2013, article 1. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

ethics. Since the first Declaration in 1964, seven revisions have been carried out – the last revision was adopted by the 64th World Medical Association in Fortaleza, Brazil in October 2013. The current version and all former versions of the Declaration of Helsinki are available online. The Declaration is not legally binding but has in many countries a major impact on national legislation, e.g., in Germany the declaration is binding for medical doctors. This is spelled out in the professional Code of Conduct for the German medical Profession. § 15 IV of the code states: "In research involving human subjects' physicians shall respect the ethical principles for medical research on human subjects set out in the Declaration of Helsinki by the World Medical Association."[33]

In general, the declaration "is addressed primarily to physicians"[34]. However, the WMA encourages others who are involved in medical research involving human subjects to adopt these principles[35]. In the version from 2013, there are 37 articles grouped in different sections. The first section outlines general principles, for example the ones also Beauchamp and Childress focus on, that is, autonomy, non-maleficence, beneficence, and justice[36].

> "It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent."[37]

The next section answers questions on how to assess risks against benefits and burdens before conducting a research project. "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects."[38].

> "All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher."[39]

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[33] German Medical Association, „(Muster-) Berufsordnung für die deutschen Ärztinnen und Ärzte [(Model) Professional code of practice for German physicians]", 14 December 2018, p. 5. https://www.bundesaerztekammer.de/recht/berufsrecht/muster-berufsordnung-aerzte/muster-berufsordnung/ (German)

[34] World Medical Association (WMA), "WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects", 2013, article 12. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[35] Ibid.

[36] Beauchamp, Tom L., and James F. Childress, Principles of Biomedical Ethics, Oxford University Press. 8th Edition, 2019.

[37] World Medical Association (WMA), "WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects", 2013, article 9. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[38] Ibid, article 16.

[39] Ibid, article 17.

Furthermore, there are sections on "vulnerable groups and individuals", on "scientific requirements and research protocols": "The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol."[40].

A section which is important within the scope of this report is the section on RECs. Article 23 says:

> "The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. (…) After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions."[41]

Furthermore, there are sections on "privacy and confidentiality" and detailed guidance on "informed consent", "use of placebo", "post trial provisions", "research registration and publication and dissemination of results" and "unproven interventions in clinical practice".

As outlined above, the declaration of Helsinki is well accepted as guidance document for ethical assessments in the medical fields or even in the whole health-sector. Within the scope of this report, it is important to clarify the usefulness of the declaration of Helsinki for RECs in other research areas. The declaration is addressed primarily to physicians, and the WMA encourages others who are involved in medical research involving human subjects to adopt these principles. The question arises if others who are not involved in medical research but in other research involving human beings could also adopt the outlined principles.

The declaration gives special advice to "physicians" on how to treat "patients" within "medical research". In that respect, it seems to be clear that using the declaration as guideline for RECs outside the medical field would not make much sense. However, if some special medical terms are replaced, there might be a chance that the declaration could be useful to review research projects beyond medicine. More concretely, "patients" could be replaced with "participants" or "persons involved in the research project" and "medical research" with "research" and "physician" with "researcher". The principles outlined in the declaration might be useful to review all research projects involving human subjects. The general principles outlined in the declaration and also the principles regarding, risks, burdens and benefits, informed consent, privacy and confidentiality, vulnerable groups and individuals can serve as basis for the ethics assessment by RECs not only in the medical science, but also for research trials in other fields, especially for projects in the social sciences and the humanities. However, especially for research projects that are not involving participants directly, there might be less use of the declaration. In the field of emerging technologies research projects are often conducted without research participants and nevertheless, they can be seen as research with humans. For

[40] Ibid, article 22.
[41] Ibid, article 23

instance, research on algorithms, on apps and on technical devices are often conducted without any participants. Nevertheless, the research projects can have enormous risks and/or benefits for the whole society, or for some groups or individuals, and persons can be involved in a research study somehow, also if they are not research participants.

To summarize at this point: The Declaration of Helsinki is useful as basis for guiding RECs in the health sector as well as in several non-health sectors. However, further guidance is needed to review research projects in the field of emerging technologies to take their particularities into account.

4.3 The CIOMS International Ethical Guidelines for Health-related Research Involving Humans

In 1949, the Council for International Organizations of Medical Sciences (CIOMS) was established as an international, non-governmental, non-profit organization by the WHO and UNESCO in order to advance public health through guidance on health research and policy, including ethics, medical product development and safety. In 1982, CIOMS, together with the WHO, published the first version of the "International Ethical Guidelines for Biomedical Research Involving Human Subjects". The main objective of the guidelines is to provide RECs, researchers and sponsors with guidance on how to conduct research in a safe and ethical way, with particular attention to conducting research in low- and middle-income countries. In 1993, 2002, 2009 and 2016, updated versions of the guidelines were published. In the latest version, the working group that worked on the revision of the guideline decided to broaden the scope of the 2002 Guidelines from "biomedical research" to "health-related research". The working group considered biomedical research too narrow since that term would not cover research with health-related data, for example. The revised guideline from 2016 is called "International Ethical Guidelines for Health-related research Involving Humans"[42].

The version published in 2016 refers to 25 ethics guidelines for health-related research involving humans, namely:

1. Scientific and social value and respect for rights
2. Research conducted in low-resource settings
3. Equitable distribution of benefits and burdens in the selection of individuals and groups of participants in research
4. Potential individual benefits and risks of research
5. Choice of control in clinical trials
6. Caring for participants' health needs
7. Community engagement
8. Collaborative partnership and capacity-building for research and research review
9. Individuals capable of giving informed consent
10. Modifications and waivers for informed consent
11. Collection, storage and use of biological materials and related data
12. Collection, storage and use of data in health-related research

[42] Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO), "International Ethical Guidelines for Health-related Research Involving Humans", 2016. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

13. Reimbursement and compensation for research participants
14. Treatment and compensation for research-related harms
15. Research involving vulnerable persons and groups
16. Research involving adults incapable of giving informed consent
17. Research involving children and adolescents
18. Women as research participants
19. Pregnant and breastfeeding women as research participants
20. Research in disasters and disease outbreaks
21. Cluster randomized trials
22. Use of data obtained from the online environment and digital tools in health-related research
23. Requirements for establishing research ethics committees and for their review protocols
24. Public accountability for health-related research
25. Conflict of interest

In general, these guidelines can give RECs reviewing health-related research projects a lot of useful guidance. For instance, guideline 1 states that scientific and social value are the fundamental justification for undertaking research. However, scientific and social value cannot legitimize mistreating study participants. Furthermore, guideline 4 outlining guidance on assessing risks and benefits is relevant.

> "Before inviting potential participants to join a study, the researcher, sponsor and the research ethics committee must ensure that risks to participants are minimized and appropriately balanced in relation to the prospect of potential individual benefit and the social and scientific value of the research."[43]

Very helpful for REC members are also the guidelines concerned with informed consent (guideline 9 and 10) and inclusion and exclusion of research participants (guidelines 15 through 19). Moreover, guideline 23 is particularly important for the composition and procedures of RECs. According to the guideline, RECs must include multidisciplinary membership in order to competently review the proposed research. Committee members must be duly qualified and regularly update their knowledge of ethical aspects of health-related research. RECs must have mechanisms to ensure independence of their operations. More concretely, guideline 23 states that REC members should be: physicians, scientists and other professionals such as research coordinators, nurses, lawyers, and ethicists, as well as community members or representatives of patients' groups who can represent the cultural and moral values of study participants. Besides, one or more members should have experience as study participants, and a REC must include both men and women. When a proposed study involves vulnerable individuals or groups, as may be the case in research involving prisoners or illiterate persons, representatives of relevant advocacy groups should be invited to meetings. If committees do not have the relevant expertise to adequately review a protocol, they must consult with external persons with the proper skills or certification.

[43] Ibid, p. 9.

Within the scope of this report, it is important to highlight which of these guidelines could also be helpful to review research projects outside the health-related fields or, more specifically, research projects in the field of emerging technologies. First of all, it is important to mention that all guidance that is given in the CIOMS guideline on how to treat research participants and data of research participants in an ethical way could be helpful to guide research involving participants in general. This means guidance on informed consent, fair selection of participants, on research with vulnerable groups, on collection, storage and use of biological material and related data etc. could be helpful also for non-health related research projects in which research participants are included – for instance in the social and behavioural sciences or also in the field of emerging technologies. In other words: Obtaining informed consent, sensitivity for research with vulnerable groups, fair selection of participants etc. should be important for all research projects that involve humans, and CIOMS offers proper guidance.

However, as already outlined within the analysis of the Declaration of Helsinki above, many research projects in the field of emerging technologies and also in the social sciences and humanities do not involve research participants directly – for instance research on autonomous driving cars is research without participants, even though people on the street are involved in the research project if an autonomously driving vehicle would be tested in real life situations. Therefore, it needs to be analysed if there is also a use of the CIOMS guidelines for non-health research without directly involved study participants. The following guidelines of CIOMS could be particularly relevant:

Guideline 1 on scientific and social value and respect for rights: Especially for research projects in the field of emerging technologies, there is a lot of discussion about social value. The CIOMS guideline 1 outlines that in order to be ethically permissible, health-related research with humans must have social value. “Researchers, sponsors, research ethics committees and relevant health authorities, such as regulators and policy-makers, must ensure that a study has sufficient social value to justify its associated risks, costs and burdens.”[44] This guideline is applicable for ethical review of research projects in all kind of research projects including research participants. It remains unclear if this also applies to research without human participants that however has impact on humans (like research on a care robot or an autonomously driving car). The challenge for health and non-health research is how to define the social value of a specific research project. Social value of research can be difficult to quantify, and this might be especially challenging for research projects in the fields of emerging technologies where many different stakeholders and groups might be affected. The dissemination of research results is also important in this context. Otherwise, social value cannot be achieved.

Guideline 4 on potential individual benefits and risks of research: In this guideline, potential risks and benefits for research participants are in focus. The aim of the guideline is to protect the rights and welfare of study participants. “The ethical justification for exposing participants to risks is the social and scientific value of research (…) However, some risks cannot be justified, even when the research has great social and scientific value.”[45] For many research projects in the field of emerging technologies the situation is different when no research participants are involved. In these research projects, it is

[44] Ibid, p. 2.
[45] Ibid, p. 10.

not benefits and risks for participants, but for individuals, groups or even the whole society that need to be taken into account. Guideline 4 is concentrated on risks and benefits for research participants mainly, though risks to groups are also taken into account. Guideline 4 outlines that research results in certain fields may present risks to the interests of communities, societies, families, or racially or ethnically defined groups.

> "For example, results could indicate – rightly or wrongly – that a group has a higher than average prevalence of alcoholism, mental illness or sexually transmitted disease, or that it is particularly susceptible to certain genetic disorders. Research results could therefore stigmatize a group or expose its members to discrimination."[46]

Risks to groups need to be minimized by maintaining confidentiality during and after the study and publishing the resulting data in a manner that is respectful of the interests of all concerned. Furthermore, it is outlined that RECs must ensure, as part of evaluating the risks and potential individual benefits of research studies, that the interests of all who may be affected are given due consideration. In general, it must be noted that guideline 4 outlines how important it is for RECs to consider risks and benefits not only for research participants but also for groups that might be affected by the research. However, the guideline can neither give concrete help in identifying the relevant risks and benefits nor in measuring them.

Guideline 7 on community engagement: This guideline is highly relevant when it comes to ethical assessment of research projects in the field of emerging technologies. The guideline states:

> "Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results."[47]

The comment on guideline 7 expounds in more detail what a community can be. It describes that a community not only consists of people living in the geographic area where the research is to be carried out. Different stakeholders, groups, organizations, government bodies, or any others who can influence or are affected by the conduct or outcome of the research project need to be engaged. Furthermore, it is important to ensure diversity of views within engagement of a community. "For instance, when community leaders are men only, researchers should actively include the views of women, as well."[48] A plan on how to reach community engagement should be send to the REC and the REC needs to review these plans. For research projects in the field of emerging technologies it is often challenging to define the relevant community or even to say who exactly has a stake in the proposed research. It is questionable if further general guidance on community engagement can be given or if this needs to be defined on a case by case basis.

[46] Ibid, p. 13.
[47] Ibid, p. 25.
[48] Ibid, p. 25.

Guidelines 11 and 12 on storage and use of data and biological material are particularly important for health-related research, yet can perhaps be relevant also for other types of research since they are important for the controversy between research ethics guidelines and data protection law (like the GDPR). These regulations are important for all types of research based on the use of data.

4.4 The guideline for good clinical practice E6(R2)

Another document that is used by medical RECs in their daily practice is the Guideline for good clinical practice E6(R2). In the following we will summarize this document. In annex 3 a more detailed overview of the guide and a statement on its usability as a model for RECs outside biomedical research can be found – this annex was written by Maria Ribeiro (Board member of EUREC and Vice-President of National Ethics Committee for Clinical Research in Portugal).

The guide was published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[49] This council was established in 1995 with the aim to harmonize drug development processes in the European Union, Japan, the United States, Australia, Canada and the Nordic countries. Good Clinical Practice (GCP) is described as an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.[50] The ICH developed and published various GCP guidelines, which are all available online.[51] The GCP E6(R2) guideline was finalized in 1996 and has been amended in 2016 with an integrated addendum in order to implement improved and more efficient approaches to clinical trial research.

The thirteen principles of the GCP guideline E6(R2) are:

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

[49] European Medicines Agency (EMA), "Guideline for good clinical practice E6(R2)", 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

[50] Ibid, p. 1.

[51] International Council for Harmonisation (ICH), "History", undated. https://www.ich.org/page/history

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.[52]

Beside these thirteen principles, the GCP guideline E6(R2) gives detailed information for RECs, which are in this document named as "Institutional Review Boards / Independent Ethics Committees". "A REC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects."[53] RECs need to be an independent committee, particularly separated from the sponsor or the investigator, in order to reduce or minimize potential conflict of interests. This is the only way to assure participant´s protection while reviewing research protocols and improving research conditions. The members of a REC should collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended in the guideline that a REC is constituted by:

- At least five members.
- At least one member whose primary area of interest is in a non-scientific area.
- At least one member who is independent of the institution/trial site.[54]

Furthermore, the REC may invite "nonmembers with expertise in special areas for assistance"[55] if needed.

The guideline also describes how the relationship between RECs and investigators should ideally look like. Investigators are described as a "person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator."[56] RECs need to evaluate the investigator´s qualifications. Especially they need to check if he or she is qualified by education,

[52] European Medicines Agency (EMA), "Guideline for good clinical practice E6(R2)", 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf
[53] Ibid, p. 16.
[54] Ibid, p. 18.
[55] Ibid, p. 18.
[56] Ibid, p. 11.

training, and experience to assume responsibility for the proper conduct of the trial.[57] The investigators must have expertise in the disease and in the group of patients to be recruited, previous experience in clinical research and/or GCP knowledge and training.

Besides the responsibilities of RECs and investigators, the responsibilities of the sponsors are also in focus. Sponsor is defined as an individual, a company, institution or organization who is financing the clinical trial and taking care of the management. Sponsors' main responsibilities are related to the implementation of a robust system for managing the quality of the clinical trial. They are responsible for the trial design and the scientific robustness of the study and the selection of the investigators and sites and the financial agreements. They are also responsible for all details and information of the investigational product, regarding the manufacturing and labelling as well as regarding the supply and handling of the product. Sponsors are also responsible for the Investigator's Brochure (IC), which contains the information regarding the investigational product development. Other major responsibilities are monitoring and audit procedures and the management of adverse reactions. Overall, sponsor responsibilities consist of global trial management, data handling and record keeping.

The principles and the operational standards of the GCP are designed in order to protect the rights, safety and welfare of patients and to ensure the quality and scientific integrity of the data collected. These general principles and aims apply to almost any type of research with humans. Nevertheless, the GCP general principles and procedures cannot be adopted easily as a model for the work of RECs beyond medical research. Since the guideline was developed for drugs, biologics and medicines, using it for other types of research, they can only serve as staring point. More concrete guidance is needed.

4.5 The Guide for Research Ethics Committee Members from the Steering Committee on Bioethics

Another important document which needs to be in focus of this report is the "Guide for Research Ethics Committee Members" published by the Council of Europe in 2010.[58] This document is intended to be used as a tool for REC members and strives to give guidance on how to review research proposals involving human beings. In annex 2 a more detailed overview of the guide and a statement on its usability as a model for RECs outside biomedical research can be found – this annex was written by Elmar Doppelfeld (Chair of EUREC). The text has been elaborated by the Group of Specialists on Biomedical Research (CDBI-CO-GT2) working under the authority of the Steering Committee on Bioethics (CDBI) of the Council of Europe. The introduction outlines that the guide does not provide new principles but highlights the ethical basis for the principles laid down in the European instruments covering biomedical research and indicates operational procedures to facilitate their implementation.

The introduction is followed by a chapter on ethical principles. All research involving human beings should be conducted according to four universally recognized ethical principles: Autonomy, beneficence, non-maleficence and justice.[59] In the following, these principles and how to apply them are described in more detail. The principle of autonomy is applied in biomedical research in particular

[57] Ibid, p. 20.
[58] Steering Committee on Bioethics (CDBI), "Guide for Research Ethics Committee Members", 2012. https://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/Guide/Guide_EN.pdf
[59] Ibid, p. 9.

through the process of free and informed consent, and the guide gives some further information on how to enable a person to make an informed decision, giving special attention to vulnerable groups. Following the principles of beneficence and non-maleficence, researchers have the moral obligation to maximize potential benefits and minimize potential harms.

> "The balance between harms and benefits is therefore critical to the ethics of biomedical research. A research project should proceed only if its foreseeable risks and burdens are not disproportionate to its potential benefits. In practice, this means that all research projects must undergo a thorough comparative risk/benefit assessment."[60]

The principle of justice requires fairness and equity. The key question described here is who ought to receive the benefits of the specific research and who ought to bear its risks and burdens.

In the next section, the guide highlights some legal aspects: RECs need to assess research projects based on applicable legal standards which may vary dependent on the country where the research will be carried out. The guide describes some standard-setting instruments, classified according to their legally non-binding or binding character. As most important non-legally binding instruments the Declaration of Helsinki, the CIOMS guideline and the ICH guideline are mentioned.

In the following section, roles and activities of RECs during the research process are described. RECs should evaluate the ethical acceptability of a research proposal from two main standpoints:

- „from the standpoint of the ethical implications of the research conduct, foreseeable research outcomes, and potential consequences of research results for society. 'Society' can encompass both local and wider contexts and may include the potential interests of future generations.
- from the standpoint of the prospective research participants to safeguard their rights, dignity, safety, and well-being."[61]

For the ethical evaluation RECs should rely on the ethical principles accepted both by the given society and the international community. Furthermore, it is outlined that RECs need to be "independent and demonstrably able to make decisions without undue political, professional, institutional or market influence".[62] It is also mentioned that scientific journals should ideally require that research had been approved by a REC before publishing.[63] Regarding the composition of RECs the guide outlines:

- RECs should possess collective expertise in the fields or disciplines deemed necessary for their work.
- Potential REC members should provide an appropriate balance of scientific expertise, philosophical, legal or ethical backgrounds, and lay views.
- All REC members should have an equal standing.
- REC members should be able to strike an appropriate balance between achieving the greater common good that can be brought about by biomedical research and recognising and

[60] Ibid, p. 10.
[61] Ibid, p. 16.
[62] Ibid, p. 17.
[63] Ibid, p. 17.

protecting the human dignity, rights, health and wellbeing, and interests of research participants.
- RECs should take into account gender balance.
- REC members should receive appropriate independent initial and continuing training relevant to their role in the REC.
- All RECs members and staff should treat any information provided to RECs as confidential.

In the scope of this report, it is again important to answer the question if the guide is helpful for RECs to review research projects outside the health-related field. The guide is developed for RECs to review research projects in the biomedical fields. However, the different sections on principles and on the constitution and power of a REC could also be relevant for other research fields.

4.6 Observations from the breakout session at the online workshop

As outlined above an online workshop was held with REC members in October 2020 to discuss task 5.1 of the SIENNA project. On workshop day 2 the participants were divided into three working groups. In the working groups they examined the question if they are able to assess a research proposal based on the common guidelines from the health-related field. One working group discussed a case from AI&R, one a research proposal from HET and a third group discussed a case from the field HG. All three cases were fictional and developed for the workshop by SIENNA partners. The workshop participants studied the fictional research proposals before the workshop, and they were familiar with the four guidance documents for RECs. In the following the discussions from the three working groups are summarized.

4.6.1 Discussion of a fictional research case from the field AI&R

The working group discussed a fictional research project with the title: SECURE. This project leverages the power of Artificial Intelligence (AI) to combat organised crime and terrorism. Over the last few years, criminals and terrorist groups have increasingly moved their activities to various digital platforms, including the internet, social media (such as Twitter, WeChat, and YouTube) and the darknet. These groups use these platforms to recruit members, spread propaganda, raise funding, do money laundering, and plan illegal and violent acts. To fight criminality and terrorism, law enforcement agencies (LEAs) need to monitor, access and analyse data on these digital platforms. However, the massive amount of data makes such tasks very challenging (resource-wise). Hence, the need for automatic tools is pressing. Recent advances in AI, especially machine learning, offer powerful automatized tools that can help LEAs identify, analyse, and track criminal and terrorist activities on the internet and other digital platforms.

The SECURE platform will offer LEAs a series of automatic tools to crawl and analyse massive amount of heterogenous data in their fight against criminality and terrorism. These tools will make it possible to *investigate* threats of this nature and *prevent* them before their happening. Anticipation is key in policing: the earlier the identification of a threat, the higher chance it will be prevented. This has the power to significantly enhance the efficiency and effectiveness of policing by improving law-enforcement agencies' capacity at identifying trends and conducting risk assessments in real-time. Great benefits to society are expected from this platform.

Key points of the discussion

There was general agreement that the main guidelines developed for the medical/health sector would be useful, but definitely not sufficient on their own, to review a research project such as the SECURE project. These guidelines would need to be complemented by additional guidelines engaging with the specific ethical challenges associated with AI, including challenges specific to AI applications used by law-enforcement agencies to respond to crime and terrorism. Participants noted that a number of general ethics guidelines already exist. These have been developed at the EU and the national levels, and are of particular value to RECs reviewing such research proposals. At the national level, participants noted that guidelines for AI research projects exist, including in France and in Norway, which are used by research ethics committees when reviewing AI projects. At the European level, the High-Level Expert Group on Artificial Intelligence has developed a set of requirements for trustworthy AI, as well as an Assessment List for Trustworthy AI (ALTAI).[64] Participants indicated that these guidelines, especially the more practically oriented Assessment List are particularly useful to complement existing research ethics guidelines because they are specific to ethics issues raised by AI. Therefore, the general agreement was that no additional new guidance is necessary. However, existing general ethics guidelines need to be translated into research ethics guidelines or rather into guidance documents for RECs. The SIENNA project did this in D5.4, annex 4 on "Research ethics guidelines for AI&R.

Participants also highlighted a key limit of existing guidelines that are developed for the medical/health sector: the fact that these guidelines focus primarily on the ethical concerns raised *during* the research project. For instance, in Norway it is difficult for the medical research ethics committees to include a societal impacts assessment. Norwegian REC's reviews are legally binding and have the power to stop a research project for ethical reasons. This format of REC makes it difficult to include a broader assessment of societal impacts. However, non-medical RECs in Norway function differently: they only give advice and have a broader scope. For AI projects, it is very important that these broader societal impacts are taken into account by research ethics committees.

In the context of the hypothetical SECURE proposal, the use of the tools raises a number of issues that were discussed during the break-out session. These include misuse of the tools, potentially undermining human dignity, self-determination and privacy. In addition, participants noted that the concept of terrorism is a highly contested one with deep political implications. Here as well, the challenge of misuse was raised, such as misusing the tools to unfairly target a community. A participant mentioned that REC focused on science and technology have experience dealing with broader impacts and noted that such experience would be useful to help broaden the scope of assessment toward larger societal concerns.

Another point made during the discussion was that *compliance* with research ethics requirements is not enough to ensure proper conduct of research project on AI. In order to conduct the research

[64] High-Level Expert Group on Artificial Intelligence, "Ethics guidelines for trustworthy AI", 2019. https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai; European AI Alliance, "Assessment List for Trustworthy AI (ALTAI)", undated. https://futurium.ec.europa.eu/en/european-ai-alliance/pages/altai-assessment-list-trustworthy-artificial-intelligence

project ethically, it is essential to also ensure ethics-by-design and an iterative ethics process throughout the project. A one-time legal check is not sufficient. The presence of an ethics board in the research project was also deemed to be of value for research ethics concerns. However, although the need to go beyond mere compliance was acknowledged, the necessity to put hard lines was also recognized, especially in light of the risk of ethics washing in the field of AI.

Another key point was made regarding research in the private versus in the public sector. While medical research primarily takes place in the public sector, it is mainly private companies that carry out most of AI research and innovation. As such, most of AI research is kept hidden and do not go through due research ethics processes. As indicated by a participant, the main question here is: how to create incentives for the private sector to ensure their research go through proper research ethics? It was noted that this might be difficult to do through regulatory requirements. In addition, most of the big technology companies are not in the EU, but rather in the US and China, hence European legislation would not have any effectivity. However, what private companies might be sensitive to is their reputation. Good reputation was identified as a potential leverage to the promotion of research ethics process in private companies developing AI. The recent creation of the Global Partnership on Artificial Intelligence[65] was mentioned as a promising initiative to encourage the private sector to promote ethical AI.

Participants also made a number of other points that are important to consider for research ethics committees reviewing AI projects:

- It was noted that RECs always have the possibility to reach out to external experts on specific questions requiring technical expertise. However, if many proposals are submitted with similar issues, then a permanent member needs to be appointed.
- Participants highlighted the fact that AI research projects raise significant concerns regarding protection of personal data, concerns that are specific to this field of research. Whether responsibility to ensure protection of personal data in these cases fall into the hands of lawyers or research ethicists still needs to be clarified. More guidance on this is necessary to clarify remaining uncertainties.
- Another challenge that was raised is the conflict between, on the one hand, the need for transparency of the tools that could be realised by making the algorithm open source, and on the other hand, the fact that the disclosure of the code might make the tool easily manipulated by criminals and therefore ineffective. In addition, the risk of black boxes in the system, and therefore the impossibility of transparency and oversight, was raised.

4.6.2 Discussion of a fictional research case from the field HET

The example technology considered by the working group for HET concerned the 'SuperSPEED' project's development of an exoskeleton to, on the one hand, improve the mobility of people who experience walking problems, and on the other to improve individual speed by up to 20%, together with easing the running activity itself so as to extend the duration of use. The project aims to develop

[65] Plonk, Audrey, "The Global Partnership on AI takes off – at the OECD", *OECD.AI*, 9 July 2020. https://oecd.ai/wonk/oecd-and-g7-artificial-intelligence-initiatives-side-by-side-for-responsible-ai

a wearable device that can be worn discreetly under clothing, consisting of a frame that has an ankle exoskeleton attached to the shoe using a rope loop under the heel, together with a carbon fiber bar inserted into the sole. The exoskeleton is moved by a motor placed on a waistband, connected to the frame with a cable. The tool aims to facilitate both walking and running activities, pulling up the foot during toe-off and extending the ankle at the end of the step. It is aimed to help people with reduced mobility, as well as athletes and people who run for a hobby.

Key points of the discussion

The first thing to note is that the reviewers considered the information regarding the technology, as well as the consortium of developers, insufficient to properly assess the technology. There were many points that were considered problematic regarding SuperSPEED, though a lack of information was key to many. This made it tricky to assess whether (and how) the kinds of guidelines already available would be useful for technologies with HET potential.

With a technology like SuperSPEED, one difficulty in assessment comes from the fact that it is not clearly specified who the technology is built for. Both people with disabilities and athletes – professional and non – are mentioned as potential users, however this lack of specification makes it difficult to know how to evaluate the device. That said, the declaration of Helsinki may be applicable for use with patients. As the project is described as health-related research, CIOMS guidelines should apply as well, yet it was noted that they would only apply partially, especially as it is not clear how to assess in terms of applicability to athletes. Dual use guidelines may be applicable as well, but there too it is unclear which ones could be applicable – if any – in such cases, and how to apply them.

Another issue that generates uncertainty is the lack of specification in a project like this regarding how user data would be treated. Many privacy risks can emerge in cases where data privacy is not specifically addressed and assessed. Discussion noted that current data protection legislation makes it unfeasible to answer whether there are noteworthy gaps. This is again caused by the fact that information regarding specific details of the project was not available, and this may be a more general issue than one specific to HET, namely, the quality of project proposals.

As far as the HET aspect of the project is concerned, the group did not consider this to be a notable worry. The idea of a “person” is not particularly challenged by the device, as it only allows users to run faster. What may represent a worry is the fact that it might cause unrealistic expectations. Especially in the case of athletes, where there were considered to be no specific guidelines that could apply to this specific case. It was commented that it would be ideal to develop just a few criteria to assess the technology, rather than a fully-fledged set of guidelines, but the differences between these two positions were not sufficiently developed in the time available.

One last aspect that participants highlighted concerns issues of justice and social value, especially for projects like this which could further exacerbate inequalities and disparities. Questions discussed here concerned how developers and potential companies could profit from a project of this kind (including economic costs), and whether it would be accessible to all who need it. These issues represent a notable gap, in the sense that it is not clear which criteria of evaluation should be applied to evaluate the social value of the technology, though it was considered important to do so.

To conclude, the SuperSPEED example brought to the fore how difficult it can be to evaluate technologies with HE potential but where the technology does not incorporate more general ethical issues as might be already assessed by RECs. For instance, if is it not clearly a medical device that is targeted to vulnerable patients (unable to give informed consent) or is not a technology that would be implanted and/or in some way irreversible, then it is not least which guidelines or documents could assist with the ethical evaluation in terms of HET. Especially if the technology or process doesn't actually impact on the person as such. This includes projects with elements of human enhancement, but which have low overall risks, e.g., because the technologies are wearable and removable, rather than permanent or irreversible. In these cases, it seemed clear that existing guidelines offer few obvious grounds on which to object to a project being carried out, even if there were other concerns about the HET, e.g., in terms of justice and social value. There may be scope for assessment in terms of potential dual use problems, though here again there was some uncertainty, not least because it requires a level of prediction about what the technologies might offer, whether now or in the near-, medium-, or long-term future. For these reasons it was suggested that a comprehensive review of the HET elements of a technology like this would not currently be possible given that available guidelines do not directly address human enhancement aspect.

4.6.3 Discussion of a fictional research case from the field HG

The working group discussed a fictional research proposal for which a new genomic technology should be developed: a combination of two currently existing and in use genomic tools: genome editing and gene therapy. This technology should be tested on prisoners convicted of severe violent crimes and are receiving life sentences (25 years or more). The tool would identify certain genes that were demonstrated to be responsible for extreme violent behaviours and replace them with empathy genes. There is supporting evidence to the effectiveness of the therapy originating from published research as well as citizen DIY science. The research would be conducted on inmates in a high security prison in a developing country, where conviction rate of very violent crime is quite high. Other co-variables such as extreme poverty and widespread abuse of drugs exist in that country. Orientation sessions are scheduled with inmates to explain the research in details and to answer their questions. A RCT would run for a couple of months during which the therapy is given to inmates who test positive for the genes, followed by a period of psychological support and assessment. Upon success of the therapy, inmates can gradually integrate back into the society under supervision.

Key points of the discussion

Initially, the discussion revolved around weighing of risks and benefits particularly in regards to gene editing particularly and gene technology in general. Participants requested more information and evidence regarding the technology as they believed it was described inadequately in the proposed case. Furthermore, participants questioned the biological/genetic basis of criminal behavior in the presence of other social variables such as extreme poverty.

Assessing social value of the study and conducting research on prisoners were two other concerns raised during the session. Regarding the latter current national laws in a number of European countries restrict clinical trials on prisoners, since they invoke questions regarding voluntary participation and fair distribution of research subjects. Furthermore, participants agreed there was no social value for

the research though they alluded at the difficulty of such assessment in the proposed case. Interestingly, none of the participants raised a concern on gender representation and the assumption (or the lack of) that the prisoners were all male. The use of social media as a form of extracting evidence or engagement in clinical trials was frowned upon by participants and a few indicated that it was prohibited in their countries. Participants also discussed a more existential issue regarding the ethics of changing personality and characters of someone by altering their genes. There were concerns over the irreversibility of the treatment as well as directing the technology for what seems like psychological behavior rather than "a disease". Some viewed the trial as a form of human enhancement procedure and therefore a more important topic to deliberate ethically before addressing ethics of research conducted on prisoners.

The main conclusions regarding the usability of the existing guidelines were:

- There are no guidelines to address germline gene editing that would affect future generations.
- More guidance is needed to be able to face the following main issues:
  - Assessing the social value of conducting a research in a country rampant with very violent crime — covered by social value.
  - Scientific evidence is not sufficient and based on sources besides research: biohackers; assessing scientific validity.
  - It is a research outsourced to a LMIC and it involves a vulnerable population: prisoners; addressed by the principle of fair distribution of subjects. (There was no mention of gender representation as a concern.)
  - Evaluating risks/benefits: direct risks/benefits and societal risks/benefits have not been well described and would need further information; covered by favorable benefits/risks ratio assessment.
  - Judging success of treatment or its end points is problematic; assessed under scientific validity clause.
  - Informed consent: voluntariness of participation; assessed by informed consent requirements.
  - Irreversibility of the procedure that would be transmitted to future generations through germ cells affection; assessment societal impact in the future.

4.7 Specific guidance to develop RECs in the field AI

In our search for guidance documents for RECs (see annex 4) we did not find any guidance documents or guidelines for RECs specifically developed for the field emerging technologies. However, we did find an interesting document on how to set up ethics committees for the AI field.[66] This document is developed in collaboration of the Ethics Institute at North Eastern University and Accenture, a leading global professional services company and published under the title "Building data and AI ethics committees"[67]. The authors write:

> "This report does not recommend a specific form of data and AI ethics committee. Rather, the goal of the report is to draw from knowledge gained in the development and functioning of ethics committees in other domains, in order to highlight questions that must be asked and decisions made in the process of developing effective ethics committees in the data and AI domain."[68]

That is, the authors have a similar goal to ours in writing this report. They and we wanted to find out what we can learn from RECs in the health-related field for the field of emerging technologies. In a clear language and a well-structured document, it presents the most important issues in building a REC for the AI field. The work a REC can do is described in this document as "committee-based oversight"[69] and it is outlined "that there are not yet data and AI ethics committees with established records of being effective and well-functioning, so there are no success models to serve as case-studies or best practices for how to design and implement them"[70].

The following road map gives a good overview of the most important questions that arise when setting up an ethics committee in the AI field:

[66] Sandler, Ronald, and John Basl, "Building Data and AI Ethics Committees", 2019. https://www.accenture.com/_acnmedia/PDF-107/Accenture-AI-And-Data-Ethics-Committee-Report-11.pdf#zoom=50. Interesting as well, but not with same relevance for our report is: Jordan, Sara R., "Designing an Artificial Intelligence Research Review Committee", October 2019. https://fpf.org/wp-content/uploads/2019/10/DesigningAIResearchReviewCommittee.pdf

[67] Sandler, Ronald, and John Basl, "Building Data and AI Ethics Committees", 2019. https://www.accenture.com/_acnmedia/PDF-107/Accenture-AI-And-Data-Ethics-Committee-Report-11.pdf#zoom=50

[68] Ibid, p. 7.

[69] Ibid, p. 7.

[70] Ibid, p. 8.

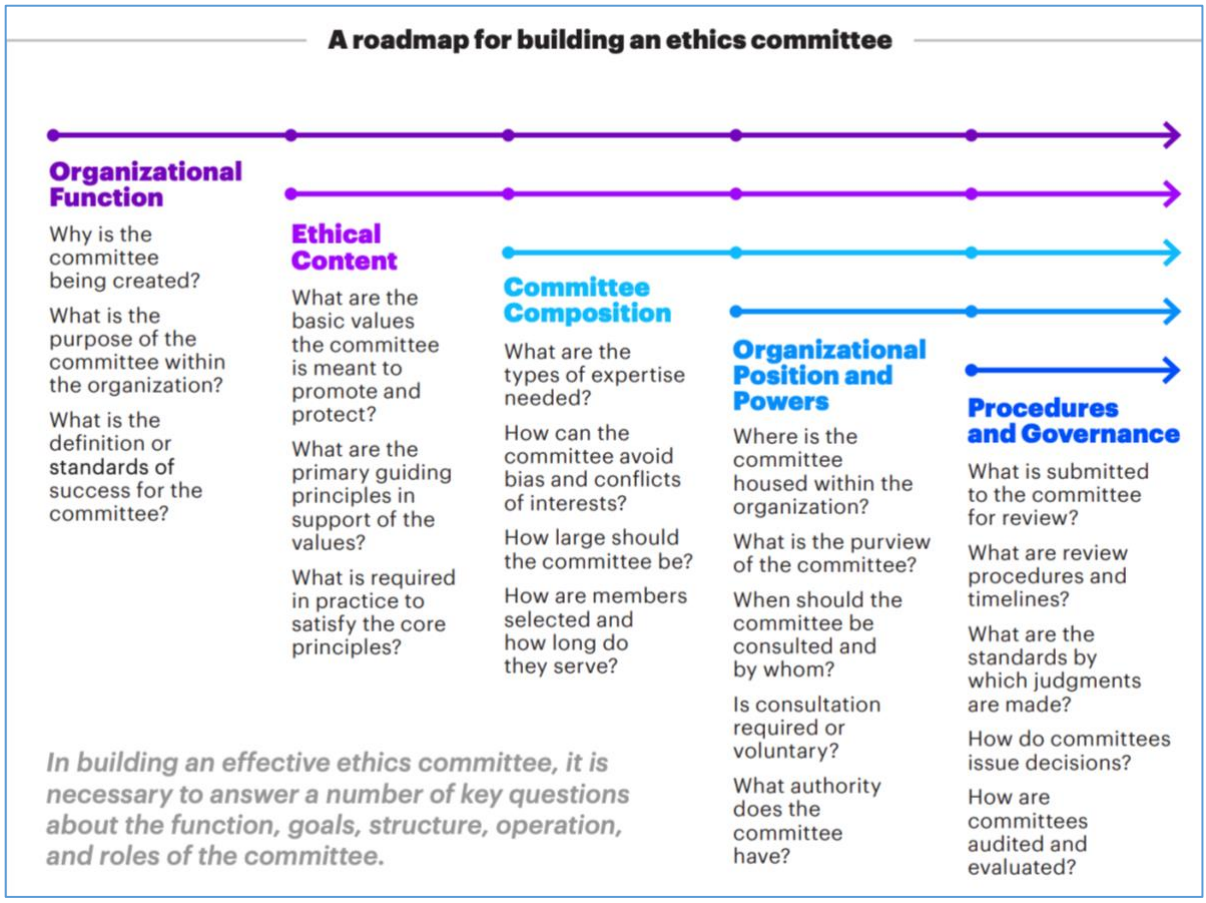

Figure 1: A roadmap for building an ethics committee[71]

The authors differentiate between basic values and core principles. While basic values indicate what the committee is meant to care about or protect and promote, the core principles are the norms or rules that describe in general how to do this.[72] The core principles provide general norms – examples are fairness, informed consent, explainability, anonymity. It is the responsibility of the ethics committee to assess whether the norms are satisfied in a particular research project. The authors of the document outline that it is a challenging task for ethics committees to decide in practice how a specific core principle could be operationalized.

> "No ethics committee can itself develop all these. But each can contribute (along with the research community, practitioners, policy makers, and others) to building the field by drawing on existing expertise, resources, and analogs to best operationalize their core principles, developing new standards and solutions when needed for the types of questions and problems they face, and sharing knowledge gained through experience."[73]

[71] Ibid, p. 8.
[72] Ibid, p. 10.
[73] Ibid, p. 12.

Moreover, information on the question who should be on a data and AI ethics committee is given.[74] The following types of members should be ideally represented:

- Technical experts
- Ethical experts
- Legal Experts
- Subject matter experts
- Citizen Participants

It is clearly stated that the aim of the report has been to help identify the types of questions that need to be answered in the building of an effective ethics committee.[75] Therefore, the document gives no direct answers to the questions outlined in the roadmap above, but some more orientation is given on basic values, guiding principles, on the committee composition and on its power.

5. Conclusion

Within the scope of this report four guidance documents relevant for RECs to review health-related research were in focus. While the Declaration of Helsinki mainly refers to principles and obligations physicians need to follow during clinical trials, the CIOMS guidelines, the guideline on good clinical practice by ICH and the guide for RECs contain detailed information on how a REC should be constituted, how a REC should assess research projects and how a REC should be organized in general. Another document in focus was the document on "Building data and AI ethics committees" published by the Ethics Institute at North Eastern University and Accenture. In this document some challenges and important questions when setting up an AI ethics committee are outlined.

A closer look at the discussed documents shows that they are not sufficient as guidance documents for RECs to review research projects outside health-related research. The main challenges are documented in table 3 and table 4 below. Table 3 gives an overview of guidance on the composition of RECs to review health-related research with humans and the usability of this guidance for the establishment of RECs to review research projects in the field of new emerging technologies. Table 4 shows which guidance RECs can find in the discussed documents on criteria for ethical assessment of health-related research with humans and how useful these are to review research projects in the field of emerging technologies.

Guidance on the composition of RECs	**Usefulness of this guidance for the establishment of RECs to review research projects in the field of emerging technologies**
The members of RECs need to come from **different disciplines**. What disciplines need to be represented exactly depends on the research project at stake. The members of a	A **multi-disciplinary REC** is necessary not only for ethical review of clinical trials, but also for ethical assessment of research projects in all other fields. The challenge will be how to define which disciplines need to be represented for specific research fields.

[74] Ibid, p. 14-16.
[75] Ibid, p. 24.

Guidance on the <u>composition of RECs</u>	**Usefulness of this guidance for the establishment of RECs to review research projects in the field of emerging technologies**
REC should **collectively have the qualifications and experience** to review and evaluate the research proposal. REC members should display an **appropriate balance of scientific expertise, philosophical, legal or ethical backgrounds**. RECs may invite **non-members with expertise** in special areas for assistance if needed.	
Community members or representatives and/or **laypersons** need to be members of a REC with equal standing.	**Community engagement** and the involvement of **laypersons** in RECs is crucial for all research fields. The challenge that arises is **how to define the relevant community** for a specific research project.
When a proposed study involves **vulnerable individuals** or groups representatives need to be members.	These criteria for the composition of a REC apply also for a REC in the field of emerging technologies.
Woman and men should be represented equal (gender balance).	
A REC should have 5 members minimum.	
REC members should be **trained** regularly relevant to their role in the REC.	

Table 3: Composition of RECs

Points to consider for ethical assessment of health-related research with humans	**How useful are these criteria to review research projects in the field of emerging technologies?**
Principles (autonomy, beneficence, non-maleficence, justice)	Principles are a good starting point. The principles mentioned in the Declaration of Helsinki and also in the CIOMS guideline and the guide for REC members provide a good basis for ethical review of research projects in the field of emerging technologies. The challenge however is that concrete guidance on h**ow to apply the principles** in specific research assessments is needed and, furthermore, for some research fields principles need to be added – more on this follows below. “In addition to these general ethical principles, the ethics committee should include ethical principles that apply to special conditions that

Points to consider for ethical assessment of health-related research with humans	How useful are these criteria to review research projects in the field of emerging technologies?
	may come up in research and innovation that raise ethical issues. […] In different scientific fields, different special conditions may arise, and with differing frequency. In addition, fields may include field-specific methods, approaches, practices and conventions that also necessitate field-specific principles and protocols."[76]
Informed consent **Vulnerable** groups **Fair selection** of participants	Guidance on informed consent, the inclusion of vulnerable groups and the fair selection of participants is developed especially for health-related research studies with humans (especially clinical trials). The analysis showed that the discussed guidelines and guidance could also be applied for research projects in the field of emerging technologies (and also in the behavioural and social sciences) that involve research participants. For other research projects (research without research participants) this information is not relevant.
Guidance on **how to assess risks and benefits**	The discussed documents concentrate mainly on risks and benefits for research participants and the community. This guidance can be helpful to review risks and benefits for participants of research projects in the field of emerging technologies. This is different for **emerging technology research without research participants**. In these research projects **proper risk assessment** is highly important. It is unclear which role a REC can have during risk assessment and how RECs need to work closely with other ethics bodies and other bodies.
Scientific and social value	It is important for ethics assessments of all research types to evaluate the scientific and social value. The CIOMS guideline gives guidance on how to define the social value for health-related research projects. These information are not sufficient alone to evaluate the social value of research projects in the field of emerging technologies. This can be very challenging.
Data collection and storage	The guidance given on data collection and storage is relevant, but not sufficient for ethical reviews in the field of emerging technologies. The **GDPR** offers more guidance, not least by defining legally binding data subject rights that need to be respected by data controllers, including researchers. While data processing for research purposes is facilitated by research exemptions, the GDPR specifies **clear obligations data controllers have to adhere** to. Aside from data subject rights, especially principle of data minimisation is relevant (collecting only data that is necessary, deleting the data once they are not needed anymore). Unlike REC guidelines and

[76] Ibid, p. 19.

Points to consider for ethical assessment of health-related research with humans	How useful are these criteria to review research projects in the field of emerging technologies?
	guidance documents, the **GDPR is legally binding**. Thus, it does not define **ethical 'shoulds', but legal 'musts'**, narrowing the scope for moral judgment. The role of RECs with regard to enforcing compliance with data protection law varies from country to country, and so far no widely accepted best practice has emerged.

Table 4: Criteria for ethics assessment by RECs

In general, the following conclusions can be drawn: The guidelines developed for the health-related field are useful but not sufficient on their own to review research projects in the field of emerging technologies. This is because research projects in the field of emerging technologies are often different from health-related research projects on humans, especially clinical trials. As outlined in this report, emerging technologies research projects do not always involve human participants as research subjects directly. Nevertheless, humans are involved as users of technology or otherwise affected by the development or deployment of a technology, and this means that their autonomy, privacy and safety and other ethical values may be violated. Therefore, the existing guidelines need to be complemented by additional information that addresses the specific ethical challenges associated with new technologies. The question of what these additional information or elements are cannot be answered easily and requires further research.

One way could be to extend the core principles used by RECs. The work of RECs is guided by values, norms and standards and ideally, by core principles. The core principles used for ethical reviews of health-related research projects with humans are: respect for persons namely autonomy, beneficence, non-maleficence and justice. These core principles can guide the work of RECs to review health-related research. A good example in clinical research is informed consent. To protect the autonomy of research participants they need to be informed about all potential risks and benefits of the study in a way that they adequately understand the given information. The REC has to prove carefully if all information has been given in a way that the research participants can give informed consent so that that their autonomy can be protected. Applying the core principle of autonomy in research with emerging technologies is different. It is not clear whose autonomy needs to be protected. The autonomy of users of the technology? The autonomy of humans that might be discriminated by the development or deployment of the new technology? The autonomy of specific stakeholder groups or a specific community? These questions are difficult to answer in general and RECs need to examine them together with ethics bodies and advisory boards, researchers, policy makers and lay persons. Furthermore, the core principles for RECs need to be extended with a principle that protects humans and the society as a whole (not only humans as research participants). We suggest that RECs include **social and environmental well-being** as fifth core principle, beside autonomy, beneficence, non-maleficence and justice in their guidance.

Moreover, additional guidance is needed regarding the composition of RECs. The members of a REC collectively need to have the qualifications and experience to review and evaluate the research

proposal. This can be fulfilled in the following way. A REC needs to have a core committee. Members of the core committee need to be philosophers trained in ethics or ethicists from other disciplines, lawyers and researchers or developers with scientific expertise with emerging technology research in general. The core REC group needs to invite members with expertise in special areas, for assistance, based on the relevant project. Furthermore, the core group needs to invite relevant community representatives, based on the specific field. In addition, the core group must regularly participate in trainings.

Further research on guidance for RECs is needed to review research projects in the field of emerging technologies and some questions remain open at this point, especially: What kind of guidance documents for RECs are useful in general for the field of emerging technologies? Do RECs need operational guidelines or rather living documents and tools (e.g. a decision tree) to be able to give opinions on research projects in the field emerging technologies? In task 6.3 of the SIENNA project this question will be analysed in more detail and the answers will be documented in D6.3 on "Methods for translating ethical analysis into instruments for the ethical development and deployment of emerging technologies".

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Annex 1: Legal status of RECs

Written by HFHR (SIENNA partner)

I. EU LEGISLATION

The following part aims at presenting the most relevant European Union law with regard to ethics review performed by research ethics committees (RECs).

Clinical Trials Regulation (2014/536)

The main piece of applicable secondary EU legislation concerning research ethics committees (RECs) is the Clinical Trials Regulation of 2014.[1] The Regulation provides for a definition of an ethics committee, which is "an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations". The Regulation requires that a clinical trial be subject to ethical review, performed by an ethics committee in accordance with the Member States' domestic laws, as well as that timelines and procedures for ethical review be compatible with those set out in it.

The Regulation leaves it to each Member State to determine the appropriate body or bodies to be involved in the assessment of the application to conduct a clinical trial, as well as to organise the involvement of ethics committees (within the timelines for the authorisation of a clinical trial set out in the Regulation). It is emphasised, however, that when determining the appropriate body or bodies, Member States should ensure the involvement of laypersons (in particular patients or patients' organisations) and ensure that the necessary expertise is available. The assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. Moreover, the independence and impartiality of persons assessing the application should be safeguarded, taking into account factors such as independence of the research sponsor and from any other undue influence.

According to the Clinical Trials Regulation, a Member State should refuse to authorise a clinical trial in the event that a research ethics committee has issued a negative opinion which, in accordance with the law of the state concerned, is valid for that entire state. That Member State shall provide, however, for an appeal procedure in respect of such refusal.[2]

Good Clinical Practice Directive (2005/28/EC)

The Clinical Trials Regulation should be taken in conjunction with the Good Clinical Practice Directive of 2005,[3] which was issued to substantiate the earlier 2002 Clinical Trials Directive.[4] The Directive emphasises the necessity for each Member State to establish provisions for the functioning of the ethics committees on the basis of common detailed guidelines, "in order to ensure the protection of the trial subject while at the same time allowing a harmonised application in the different Member

[1] European Parliament and the Council, Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC of 16.04.2014, OJ L 158, 27.5.2014.
[2] Ibid., Article 8(4).
[3] European Commission, Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products of 8.04.2005, OJ L 91, 9.4.2005.
[4] European Parliament and the Council, Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use of 4.04.2001, OJ L 121, 1.5.2001.

States of the procedures to be used by Ethics Committees". It indicates also that clinical trials should be guided by ethical principles in all their aspects.

The role of ethics committees is described under Section 2 of the Directive. In particular, the Directive obliges ethics committees to adopt the relevant rules of procedure necessary to implement the requirements set out in the Clinical Trials Directive of 2002 (repealed by the Regulation 536/2014). One of such requirements was the prohibition of starting a clinical trial until the ethics committee has issued a favourable opinion,[5] which proves the opinion's legally-binding character.

Horizon 2020 regulations

Ethics have also been an object of regulatory attention at the European Union level in relation to research activities funded by the EU within the framework of Horizon 2020 programme for research and innovation.

Pursuant to EU regulations adopted in this regard, all the research and innovation activities carried out under Horizon 2020 shall comply with ethical principles and relevant national, Union and international legislation, including the Charter of Fundamental Rights of the European Union and the European Convention on Human Rights. Values that particular attention should be paid to, according to the regulation, are the following: the principle of proportionality, the right to privacy, the right to the protection of personal data, the right to the physical and mental integrity of a person, the right to non-discrimination and the need to ensure high levels of human health protection.[6]

Another regulation, laying down the rules for participation in Horizon 2020, specifies that participants shall comply with national legislation, regulations and ethical rules in the countries where the action will be carried out. Where appropriate, participants shall seek the approval of the relevant national or local ethics committees prior to the start of the research activities.[7]

II. NATIONAL LEGISLATION

This part will focus on the comparative analysis of national legislation requiring approval or opinion from research ethics committees (RECs) in order to initiate research activities. The following countries have been included (in alphabetical order): Austria, France, Germany, the Netherlands, Poland, Spain and the United Kingdom. Due to methodological reasons, unless explicitly stated otherwise, information covered in this part refer to legal situation as of 2015.

Austria

[5] Ibid., Article 9(1).

[6] European Parliament and the Council, Regulation (EU) No 1291/2013 establishing "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Decision No 1982/2006/EC of 11.12.2013 (consolidated), OJ L 347, 20.12.2013, Article 19(1).

[7] European Parliament and the Council, Regulation (EU) No 1290/2013 laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006 of 11.12.2013, OJ L 347, 20.12.2013, Article 23(9).

In Austria, the two fields of research in which a permission or opinion of a REC is required by law are human subject research and animal research.[8] National legislation adopted in this regard transposes respective EU law: Regulation on clinical trials on medicinal products for human use (2014/536/EU), Council Directive concerning medical devices (93/42/EEC), and Directive on the protection of animals used for scientific purposes (2010/63/EU).

With regard to human subject research, the law requires the following types of research to be assessed by a REC: clinical tests of drugs and medical products, the application of new medical methods and applied medical research involving human subjects.[9] Moreover, an Ethics Committee should review clinical trials of drugs and medical products and the use of new medical methods in the hospital.[10] A role for RECs is also provided for by provisions of the 1983 Medicinal Products Acts,[11] as well as the Medical Devices Act of 1996.[12]

Animal research projects, on the other hand, are reviewed by national bodies supported by ethics committees. Depending on the research institution, these are Ministry of Science and Research (for universities) or *Landeshauptmann* (for projects conducted at the regional level).

As of 2015, there were no other types of research requiring legally-binding approval of RECs in Austria.

France

In France, national legislation requires ethics review in human subject research in biomedical research, as well as where the use of animals in research is concerned.[13]

According to the Public Health Code (articles L. 1121-1 et seq.), obtaining approval from a research ethics committee is mandatory when it comes to "interventional research". Moreover, such ethics review is required with respect to collection of human biological samples for scientific purposes, including clinical trials of medicinal products and medical devices, application of new medical methods, applied medical research and research in everyday care.

[8] Wolfslehner, D., and E. Griessler, "Ethics Assessment in Different Countries: Austria", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, p. 9-10. https://satoriproject.eu/media/4.a-Country-report-Austria.pdf

[9] Austria, Bundesgesetz über die Organisation der Universitäten und ihre Studien (Federal Act on the Organisation of Universities and their Studies), 2002, § 30(1). https://www.ris.bka.gv.at/Dokumente/Erv/ERV_2002_1_120/ERV_2002_1_120.html

[10] Austria, Kranken- und Kuranstaltengesetz (Hospital Act), 1957, § 8c.(1).

[11] Austria, Bundesgesetz über die Herstellung und das Inverkehrbringen von Arzneimitteln (Medicinal Products Act), 2 March 1983, §2a (6) and (7), §32, § 37a, § 40; §41, § 43, § 47.

[12] Austria, Bundesgesetz betreffend Medizinprodukte (Medical Devices Act), 29 November 1996, § 3 (9) and (14), § 40, § 44, § 51 (9), § 52a (5), § 56, § 57, § 58.

[13], Stoffel, Delphine, Ingrid Callies, Katrine Rojkova, and Sudeep Rangi, "Ethics Assessment in Different Countries: France", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, p. 10-11. https://satoriproject.eu/media/4.d-Country-report-France.pdf

As far as the use of animals in research is concerned, French law stipulates that a favourable opinion by the Ethical Committees for Animal Experimentation (*Comités d'éthique en expérimentation animale – C.E.E.A.*) is issued, prior to the beginning of such experimentation.[14]

Germany

In Germany, legislation addressing research ethics review is split between the federal and regional (states') level.[15]

Federal law regulates research conducted with participation of human subjects and animals. With regard to human subjects, applicable provisions can be found in the Medicinal Products Act[16] and the Medical Devices Act.[17] According to these laws, research projects involving clinical trials of medicinal products or medical devices are subject to a review of a competent ethics committee. A favourable opinion of the ethics committee on regional level is a prerequisite of conducting such research. When it comes to the use of animals in research, the Animal Protection Act[18] stipulates that research projects involving animals should be consulted by a committee on animal experimentation.

Moreover, there are substantial pieces of legislation adopted in Germany at the regional level with respect to research and innovation, applicable only to its respective regions (*Länder*). Both the Medicinal Products Act and the Medical Device Act stipulate that the ethics committees which review research involving human clinical drug trials are to be responsible under regional laws. Consequently, regional laws specify, among others, the scope of such trials in which an opinion of the ethics committee is required.

It should be noted that only in the case of medical products and medicinal devices the opinion issued by a REC is of legally-binding character.

The Netherlands

[14] France, Code rural et de la pêche maritime (Rural and Maritime Fishing Code), 1 December 1979, Articles R214-117 – R214-126. https://www.legifrance.gouv.fr/codes/id/LEGIARTI000027040773/2013-02-08/; Arrêté relatif à l'évaluation éthique et à l'autorisation des projets impliquant l'utilisation d'animaux dans des procédures expérimentales, 1 February 2013. https://www.legifrance.gouv.fr/loda/id/JORFTEXT000027038013/2021-01-19/

[15] Nagel, Saskia K., Michael Nagenborg, Wessel Reijers, Rok Benčin, Gregor Strle and Boštjan Nedoh, "Ethics Assessment in Different Countries: Germany", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, pp. 10-12. https://satoriproject.eu/media/4.e-Country-report-Germany.pdf

[16] Germany, Gesetz über den Verkehr mit Arzneimitteln (Medicinal Products Act), 24 August 1976. http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf; English translation: http://www.gesetze-im-internet.de/englisch_amg/index.html

[17] Germany, Gesetz über Medizinprodukte (Medical Devices Act), 2 August 1994. For unofficial English translation see : http://www.bmg.bund.de/fileadmin/dateien/Downloads/Gesetze_und_Verordnungen/GuV/M/MPG_englisch.pdf

[18] Germany, Tierschutzgesetz (Animal Protection Act), 24 July 1972. http://www.gesetze-iminternet.de/bundesrecht/tierschg/gesamt.pdf

In the Netherlands, although domestic law does not put many explicit restrictions on research, there are two notable areas of particular ethical significance that have been regulated: research involving human subjects and research involving animals.[19]

Under Dutch law, all medical-scientific research involving human subjects (that undergo procedures or follow rules of behaviour), animal experimentation, or population screening, requires a permit by, respectively, an accredited Dutch medical research ethics committee or the Dutch Central Committee on Research Involving Human Subjects (CCMO), the Central Committee on Animal Experimentation (CCD), or the Committee on Population Screening (SPC) of the Health Council of the Netherlands.

The Central Committee on Research Involving Human Subjects (*Centrale Commissie Mensgebonden Onderzoek; CCMO*) is an independent, government-funded body that is responsible for implementing the Medical Research Involving Human Subjects Act.[20] The Committee performs the function of a reviewing body within the scope limited by applicable laws, namely the Medical Research Involving Human Subjects Act (WMO), the Embryo's Act and the Central Review Decree (*Besluit Centrale Beoordeling*, BCB).[21]

The Central Committee on Animal Experimentation (*Centrale Commissie Dierproeven; CCD*) is also an independent, government-funded body. Its tasks include, among others, reviewing research involving animal experimentation and providing permits for such research.[22]

Poland

Although Polish Constitution guarantees in Article 73 the freedom of scientific research, in some research fields it is legally required to obtain certain permissions or clearances. These areas of research include medical experiments (with specific rules relating to clinical trials), research performed on animals or on protected species, and the use of GMO.[23]

Poland lacks one uniform piece of legislation on research, which is why relevant provisions are scattered between various legal acts. The following are applicable to certain research areas:

[19] Jansen, Philip and Wessel Reijers, "Ethics Assessment in Different Countries: The Netherlands", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, p. 10. https://satoriproject.eu/media/4.f-Country-report-the-Netherlands.pdf

[20] The Netherlands, Wet medisch-wetenschappelijk onderzoek met mensen (Medical Research Involving Human Subjects Act), 26 February 1998. https://wetten.overheid.nl/BWBR0009408/2020-01-01

[21] Central Committee on Research Involving Human Subjects, "Tasks" (undated). https://english.ccmo.nl/about-the-ccmo/tasks

[22] Jansen, Philip and Wessel Reijers, op. cit., 2015, pp. 8-9.

[23] Warso, Zuzanna and Agata Gurzawska, "Ethics Assessment in Different Countries: Poland", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, p. 8. https://satoriproject.eu/media/4.g-Country-report-Poland.pdf

- with respect to human beings: Pharmaceutical Law of 2001,[24] the Act on Medical Devices of 2010[25] and the Act on Medical Profession of 1996,[26] taken together with certain regulations of the Minister of Health;
- with respect to animals: the Animal Research Act of 2015,[27] accompanied by executive acts.

When it comes to research involving humans, the Pharmaceutical Law (in its current wording) stipulates in Article 37l that a clinical trial can only be commenced provided that a positive opinion has been issued by a bioethics committee. A similar provision – Article 44(3)(11) can be found in the Act on Medical Devices (also in its current wording).

The role of bioethics committees has also been regulated in the Act on Medical Profession. The relevant provision (Article 29) requires that a medical experiment can only be performed after obtaining a positive opinion from an "independent bioethics committee", which should take into account ethics criteria relating to experiments involving humans, as well as the desirability and feasibility of the particular experiment.

An exhaustive regulation of the role of ethics assessment in research involving animals has been adopted in 2015 Animal Research Act (Chapter 5 – Ethics committees for animal research; Chapter 6 – Rules of conducting experiments). The act establishes the National Animal Research Ethics Committee and its local counterparts. According to the act, it is the task of local animal research ethics committees to issue approvals for performing experiments involving animals.[28] Before issuing a positive opinion, a local committee should take into account, among others, whether the planned outcome of the research justifies the use of animals, as well as if the level of suffering it may cause can be accepted given the ethics issues.[29]

Spain

Spanish law, similar to the previously discussed states, regulates the matter of research ethics review with relation to two main spheres: human subject research and animal research.[30]

Human subject research is governed mainly by the Law on Biomedical Research of 2007.[31] The law refers to human rights indicated in the Spanish Constitution, putting emphasis on the protection of the dignity of human beings, as well as indicates that health, interest and well-being of humans

[24] Poland, Prawo farmaceutyczne (Pharmaceutical Law), 6 September 2001. http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20011261381/U/D20011381Lj.pdf

[25] Poland, Ustawa o wyrobach medycznych (Act on Medical Devices), 20 May 2010. http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20101070679/U/D20100679Lj.pdf

[26] Poland, Ustawa o zawodach lekarza i lekarza dentysty (Act on Medical Profession), 5 December 1996. http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU19970280152/U/D19970152Lj.pdf

[27] Poland, Ustawa o ochronie zwierząt wykorzystywanych do celów naukowych lub edukacyjnych (Animal Research Act), 15 January 2015. http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20150000266/U/D20150266Lj.pdf

[28] Ibid., Article 36(1)(a).

[29] Ibid., Article 47(1).

[30] Arias Díaz, Javier, Leyre de Sola Perea and Maria Concepción Martín-Arribas, "Ethics Assessment in Different Countries: Spain", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, pp. 10-12. https://satoriproject.eu/media/4.i-Country-report-Spain.pdf

[31] Spain, Ley de Investigación Biomédica (Law on Biomedical Research), 3 July 2007, Articles 77-81.

participating in biomedical research shall prevail over the interest of society or science. In order to safeguard methodological and ethical adequacy and regulatory compliance regarding research on human subjects, the law provides for the role of research ethics committees in research centres that undertake biomedical research.[32] An opinion from REC is also required in the case of clinical drug trials. Moreover, according to the provisions of Law on Biomedical Research and Royal Decree 2132/2004,[33] any research project involving the use of human embryonic stem cells or cell lines derived from them, as well as research projects involving the use of tissues and cells of human origin in the field of regenerative medicine needs the approval of the Commission of Guarantees for the Donation and Use of Human Cells and Tissues40 and the research ethics committee.

As regards animal research, the Royal Decree 53/2013,[34] establishing the basic rules applicable to the protection of animals used in experiments and other scientific purposes, including teaching, stipulates that such research should be subject to evaluation by a research ethics committee.

United Kingdom

Although the emergence of research ethics committees in the United Kingdom dates back to 1991, there is no single piece of national legislation (hard law) regulating the issue of ethics review performed by RECs.[35]

According to the information of the National Health Service (NHS),[36] a network of more than 80 RECs functions in the UK in order to safeguard the rights, safety, dignity and well-being of research participants. Their task is to review research proposals and give an opinion about whether the research is ethical. These RECs perform ethical review in a wide variety of areas. An exhaustive list of situations in which an ethical review of research is legally required has been included in the recently-adopted Governance arrangements for research ethics committees.[37] The list includes, among others:

- clinical trials of investigational medicinal products;
- research involving medical devices;

[32] Ibid, Article 12.
[33] Spain, Real Decreto 2132/2004 por el que se establecen los requisitos y procedimientos para solicitar el desarrollo de proyectos de investigación con células troncales obtenidas de preembriones sobrantes (Royal Decree 2132/2004 that regulates the requirements and procedures for requesting the development of research projects involving stem cells obtained from surplus pre-embryos), 29 October 2004.
[34] Spain, Real Decreto 53/2013 por el que se establecen las normas básicas aplicables para la protección de los animales utilizados en experimentación y otros fines científicos, incluyendo la docencia (Royal Decree 53/2013 establishing the basic rules applicable to the protection of animals used in experiments and other scientific purposes, including teaching), 1 February 2013.
[35] Rodrigues, Rowena and Clare Shelley-Egan, "Ethics Assessment in Different Countries: United Kingdom", in TRI, *SATORI Deliverable 1.1: Ethical Assessment of R&I: a Comparative Analysis*, June 2015, p. 13. https://satoriproject.eu/media/4.j-Country-report-UK.pdf
[36] National Health Service Health Research Authority, "Research Ethics Service and Research Ethics Committees" (undated). https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/#sthash.SX2Euoef.dpuf
[37] National Health Service Health Research Authority, "Governance arrangements for research ethics committees: 2020 edition", 26 March 2020. https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/GAfREC_Final_v2.0_26.03.2020.pdf

- clinical trials of medicines for human use;
- research involving prisoners;
- research involving adults lacking capacity;
- establishment of research tissue banks;
- human fertilisation and embryology;
- ionising radiation;
- research involving psychoactive substances.

Apart from the research conducted in the abovementioned health-related areas, another example of a REC can be provided from the field of defence. The Ministry of Defence Research Ethics Committee (MODREC) ensures that all research involving human participants either undertaken, funded or sponsored by MOD meets nationally and internationally accepted ethical standards.[38] MODREC Terms of Reference specify that it should "should scrutinise the ethical implications of all submitted protocols for all research involving human participants, undertaken, funded or sponsored by the MOD".[39]

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European Parliament and the Council, Directive 2010/63/EU on the protection of animals used for scientific purposes of 22.09.2010, OJ L 276, 20.10.2010

European Parliament and the Council, Regulation (EU) No 1291/2013 establishing "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Decision No 1982/2006/EC of 11.12.2013 (consolidated), OJ L 347, 20.12.2013

European Parliament and the Council, Regulation (EU) No 1290/2013 laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and

[38] Ministry of Defence, "Ministry of Defence Research Ethics Committee" (undated). https://www.gov.uk/government/groups/ministry-of-defence-research-ethics-committees
[39] Ministry of Defence, "MOD Research Ethics Committees – Terms of Reference", 24 March 2006. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/325461/modrec_tors.pdf

Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006 of 11.12.2013, OJ L 347, 20.12.2013

National legislation

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Austria, Kranken- und Kuranstaltengesetz (Hospital Act), 1957

Austria, Bundesgesetz über die Herstellung und das Inverkehrbringen von Arzneimitteln (Medicinal Products Act), 2 March 1983

Austria, Bundesgesetz betreffend Medizinprodukte (Medical Devices Act), 29 November 1996

France, Code rural et de la pêche maritime (Rural and Maritime Fishing Code), 1 December 1979

France, Arrêté relatif à l'évaluation éthique et à l'autorisation des projets impliquant l'utilisation d'animaux dans des procédures expérimentales, 1 February 2013

Germany, Gesetz über den Verkehr mit Arzneimitteln (Medicinal Products Act), 24 August 1976

Germany, Gesetz über Medizinprodukte (Medical Devices Act), 2 August 1994

Germany, Tierschutzgesetz (Animal Protection Act), 24 July 1972

The Netherlands, Wet medisch-wetenschappelijk onderzoek met mensen (Medical Research Involving Human Subjects Act), 26 February 1998

Poland, Prawo farmaceutyczne (Pharmaceutical Law), 6 September 2001

Poland, Ustawa o wyrobach medycznych (Act on Medical Devices), 20 May 2010

Poland, Ustawa o zawodach lekarza i lekarza dentysty (Act on Medical Profession), 5 December 1996

Poland, Ustawa o ochronie zwierząt wykorzystywanych do celów naukowych lub edukacyjnych (Animal Research Act), 15 January 2015

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Annex 2: Statement on the guide for Research Ethics Committee Members from the Steering Committee on Bioethics/Council of Europe1

Written by Elmar Doppelfeld (Chair of EUREC)

The Council of Europe, established in 1949, composed actually by 47 Member States representing 820million of citizens, has the mission, among others, to protect human rights and fundamental freedoms. Principal legal instruments in the sense of treaties are conventions and additional protocols to conventions. These instruments enter into force in a State after signature and ratification.

Prompted by the first successful in-vitro-fertilization (1979) the Council established the CAHBI ("Comité ad hoc des experts sur la Bioéthique") to address problems linked to this new method of procreation. Later on, the view was widened to the whole development in biology and medicine with inherent ethical aspects. A committee to deal with the field of bioethics a such was established, the "Steering Committee on Bioethics (CDBI)". As first result the CDBI presented the "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine" (1997)[1] , known as Oviedo Convention. In the frame of this convention the "Additional Protocol to the Convention concerning biomedical Research"[2] was elaborated (2005). Both documents are legal instruments in the sense of treaties.

The CDBI decided to elaborate a proposal for the practical implementation of these instruments. The neutral term "Guide" was chosen to prevent any discussion on its binding, semi-binding or other character. The Guide is formally addressed to REC members. It contains all practical points for RECs, predominantly addressed to biomedical research. The Guide is intended to be used as a tool for research ethics committee (REC) members. The text has been elaborated by the Group of Specialists on Biomedical Research (CDBI-CO- GT2) working under the authority of the Steering Committee on Bioethics (CDBI). The Guide does not provide new principles, but highlights the ethical basis for the principles laid down in the European instruments covering biomedical research and indicates operational procedures to facilitate their implementation. It was adopted by the Steering Committee on Bioethics on 3 December 2010.

The Guide proposes practical points of view for the implementation of these ethical principles into research. Additionally, the Guide outlines operational procedures as a basis on which RECs can develop their own organizational methods. The Guide is intended to be useful in practice, succinct and readable.

Research ethics committees are charged to ensure the respect for the accepted principles autonomy, beneficence, non-maleficence and justice.[3] In addition RECs contribute by the assessment of a project to safeguard the scientific quality of research.
After highlighting the importance of the underlying ethical principles, the Guide addresses in several chapters the relevant more practical aspects of RECs work like mandate and legal basis, establishment, composition and procedure of assessment of research proposal. General and specific fields of biomedical research are covered. This presentation follows the order of the Guide partially using its wording.

[1] The author of this contribution to the report, president (2005 – 2007) of the CDBI, was chairman of the Group of Specialists on Biomedical Research (CDBI-CO- GT2) drafting the Guide.

Legal aspects

From a legal perspective, research projects must comply with relevant national laws. The national law must fulfil the requirements of any international laws/treaties to which the country as place of a research has subscribed. RECs must be satisfied that submitted projects conform with applicable legal standards. Legal standards are the frame for the application of provisions which are by their origin not legally binding. Examples are e.g. the Declaration of Helsinki of the World Medical Association, the Universal Declaration on bioethics and human rights, drawn up within the UNESCO or the International Ethical Guidelines for Biomedical Research Involving Human Subjects of CIOMS. Examples for legally binding instruments are EU-Regulations on clinical trials with drugs or with medical devices. Whereas these EU-Regulations cover specific fields of research the“ Convention on Human Rights and Biomedicine” (Oviedo Convention) and its Additional Protocol concerning Biomedical Research of the Council of Europe address the whole field of biomedical research involving persons including the use of identifiable data or stored biological material. The instruments of the Council of Europe enter into legal force by ratification by States. The latter are the only international legally binding instruments covering the complete biomedical research involving human beings.

Domestic law often contains provisions on biomedical research, whether in texts dedicated to this question or in more general texts.

Research Ethics Committees

The Guide entails this definition of RECs: “Research Ethics Committees (RECs) are multidisciplinary, independent groups of individuals appointed to review biomedical research protocols involving human beings to help ensure in particular that the dignity, fundamental rights, safety, and well-being of research participants are duly respected and protected.

RECs may be established at local, regional or national level. They may be appointed by institutions or by regional or national authorities and are increasingly provided for by law. Their scope as a local, regional or national REC is defined by the appointing authorities.”

RECs have a responsibility before, during and after authorization and performance of a project including the evaluation and reporting of the results. During the planning phase the REC may provide information to the researcher if needed. After ethical review ending with a favorable opinion the REC will follow up the project in particular with the attention to results which may require a re-review. This review may require a change of the project, eventually with the need of an adopted free informed consent of participants. The review can also end with the result to stop the research. After the end of the research the REC will consider the reports of the researcher including the steps to publish the results.

RECs should possess collective expertise in the fields touched by their work. Potential REC members may provide a balance of scientific expertise, philosophical, legal or ethical backgrounds and lay views. All members should have an equal standing. RECs should have a Chair, a Vice-Chair and an administrator with specific precisely defined responsibilities. The procedure, in conformity with national provisions, for the appointment of REC members, the period of appointment and the renewal of membership must be transparent and may not touch the independence of the committee. Foreseen members of a REC shall declare conflict of any interests before appointment is required. Adapted to the professional expertise and to the need of members initial and. later continuing training covering all aspects of the obligations of RECs is necessary. RECs should fulfil their practical work according to procedural standards, laid down in statutes and rules of procedure. There will be plenary meetings, ad hoc rapporteurs may we appointed. RECs should seek an exchange with other relevant bodies charged with responsibilities on a similar field. Self-evaluation and independent audit of REC functioning contribute to keep standards.

Independent REC examination of a research project

For each application, the REC must prove its legal competence to deal with the applicant and the research proposal on the basis of national law. The applicant or his authorized representative must ascertain that they are entitled to submit the project. The REC should have established procedures for safeguarding the confidentiality. If all requirements for the application are met, the REC should inform the applicant on the beginning of the assessment, adding a timetable and mention that additional documents or information may be asked. The applicant should be informed that he or she may be invited to a discussion with the REC, but will not take a part of the assessment process and of the final decision. Prior to commencement, members of the RECs are asked to declare any conflict of interest pertaining to the submitted research proposal. These members are excluded from any participation in the examination of the project, including the final outcome. The REC should invite external experts or ask for external expertise in case no member has scientific experience with the field of the submitted proposal or if a member with sufficient experience is excluded due to a conflict of interests.

The Guide contains in detailed figures the information to be presented to the REC. Only the leading topics are mentioned: name, qualification and experience of the researcher including clinical care of participants; funding arrangements, methods to be applied, justification for involving human beings, inclusion/exclusion criteria; risk/benefit calculation, justification for control groups or for the use of placebo; recruitment arrangements, information for potential participants, avoiding undue influence on persons to participate, free informed consent or authorization in case persons not able to consent are involved and how to seek, new information, which could change the risk/benefit calculation, confidentiality and right to information, right to know or not to know results pertaining to the health of the participant, duty of care prior to research, availability of results for the participant on request and for publication, arrangement for compensation of damage, payments and rewards for the researcher, foreseen potential further uses, including commercial uses, of the research results, data, or biological materials

The Guide specifically addresses research involving healthy volunteers and research involving persons not able to consent, such as minors or persons who are not able to consent due to an illness.
Specific attention is drawn to research in specific situations like clinical emergencies, research including persons deprived of liberty, research during pregnancy and breastfeeding, cluster randomized trials. Another field of competence of the REC is research using biological materials of human origin. The plenitude of responsibilities of RECs can in context of this presentation only be listed. For details the reader may turn to the Guide itself.

The Guide - a model for RECs outside biomedical research

The Guide has been elaborated on the basis and in the frame of the Oviedo Convention and its Additional Protocol concerning biomedical research. Therefore, its practical application covers this research. However, apart from this objective and frame the Guide contains basic ethical principles and fundamental structural elements for RECs regardless of the research to be assessed. Common elements are the ethical principles, the establishment of a REC by a competent institution including the mandate. Furthermore, the composition of and the conditions for membership in a REC are described, statutes and rules of procedure are similar to all reviews. Concerning a research project to be reviewed, philosophers, lawyers, laypersons can be the same members of the REC in charge. However, it is clear that members with the appropriate scientific expertise in relation to the submitted research project must be added to this basic group.

[1] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention

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[2] Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research, Strasbourg, 25.I.2005, Council of Europe Treaty Series – No. 195, Council of Europe, Strasbourg, www.Council of Europe, /Treaty Office

[3] Beauchamp, Tom L., Childress, James F. (2013): Principles of Biomedical Ethics. 7. ed. Oxford: Oxford University Press.

Annex 3: Statement on the guideline for good clinical practice E6(R2)

Written by Maria Alexandra Ribeiro (Member of the EUREC Board)

The origins of ICH –GCP Guideline

The very beginning of Good Clinical Practices (GCP) started with the first American Regulation on medicines in 1938, after the incident of the Elixir Sulfanilamide containing a poisonous compound that killed a large number of people and almost one hundred children. Later, the Thalidomide tragedy in the sixties changed the USA regulations establishing that drugs had to demonstrate efficacy and safety before having authorization for commercialization. Almost at the same time, Europe had its first Regulation on medicinal products for market authorization (Directive 65/65/CEE). Between the end of the eighties and 1995, when WHO published the Guidelines for GCP for trials on pharmaceutical products, several guidelines for drug development research and principles for clinical evaluation and testing for drugs exist across Europe and Nordic countries. At the same time conversation between Europe, Japan and the USA started.

Considering the large number of guidelines and different requirements regarding drug development, representatives from Industry and Regulatory Authorities in Europe, Japan, EUA, Canada, Australia, and the WHO organization, recognized the need to harmonize and provide a unified standard. This would facilitate the mutual acceptance of clinical data by all the Regulatory Authorities, remove redundancies and/or duplications in drugs development and review process. The expensive and time-consuming drug´s development, the global drug market and the existence of national laws and regulations and several GCP guidelines, were the ground for an International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. It took place in 1995, and the ICH-GCP Guideline is the unified standard that was agreed at the Conference, incorporating GCP provisions and requirements from all the interveners. This first guideline on harmonized Good Clinical Practices for drugs, biologics, and medical devices, approved by the ICH members, and by National Medicine´s Regulatory Authorities for the registration of pharmaceuticals for human use was finalised in 1996 and published as ICH E6 Good Clinical Practice (GCP). This Guideline has been amended in 2016 with an integrated Addendum in order to implement improved and more efficient approaches to clinical trial research. The E6(R2) Guideline is being revised keeping the original scope regarding drugs, medicines and biologics, now extended to vaccines, addressing the application of GCP principles to diverse trial types and data sources being employed to support regulatory and healthcare-related decision-making on drugs, and provide some flexibility to facilitate the use of technological innovations in clinical trials.

ICH –GCP Guideline

The ICH-GCP guideline establishes thirteen principles for good clinical practices for clinical trials, considering as the very first principle that any clinical trial must be conducted in accordance with the ethical principles of Helsinki´s Declaration and the good clinical practices and the regulatory requirements. Among other considerations, the principles of this guideline reinforce that the rights, safety, and well-being of the subjects prevail over the interests of science and society, and that before any clinical trial is initiated, foreseeable risks and inconveniences have to be

weighed against the anticipated benefit for individual subject and society, according to a scientifically sound, clear and detailed protocol.
Besides the principles, this Guideline is more practical than other guidelines or recommendations regarding ethical research, since this document establish rules and procedures to comply and follow. Furthermore, the Guideline itself defines what is meant by good clinical practices, describing those as:

> "A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that assures the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected" (ICH-GCP(R2) 1.24).

From the definition of good clinical practices, it is clear that those practices apply to all phases of the development of a clinical trial, from its design to its conduction, ending with the report. Additionally, from the definition, we understand that this Guideline is not just about the integrity of the clinical trial data, in order to get market approval for the drug by the Regulatory Authorities, but it also aimed at an ethical research and participant´s protection.
Having this in mind, can we assume that all parties involved in the research outside the clinical trials could adopt the rules established in this Guideline, becoming a role model for the work of research ethics committees beyond medicine?

To answer these important questions, we need to know the contents of this Guideline. By describing some of the key issues, I intend to establish possible links between this specific Guideline for research in the medical area with other types of research in humans.
The GCP standards related to design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials, describe procedures for all of the parties involved in the research. Considering the immense number of procedures and ruling, it is essential to define who is responsible for what. In fact, the Guideline is written considering the responsibilities of the different parties such as the Institutional Review Board/Independent Ethics Committee (IRB/IEC), the Investigators, the Sponsor and Contract Research Organizations (CROs), and establish considerations regarding the Protocol, the Investigator´s Brochure and the Essential Documents for conducting the clinical trial.

In what concerns with the conduction and all the activities of a trial, this Guideline establishes the need for IRB/IEC and Regulatory approval and compliance with the protocol. Also, establishes procedures regarding the Informed Consent of the trial subjects, the guarantee for the confidentiality of data, medical management of adverse events, product accountability and qualification and training of the research team. Furthermore, appropriate and prompt report of adverse events and interim reviews is a requirement, with several reports as the progress and final report; regarding the integrity of the data and the research itself, monitoring and audit reports have also to be made. Good practices for analysis and recording is another important issue regarding the integrity of data; standard procedures regarding the trial subject report forms completion, data handling and security maintenance are described in the Guideline. Monitoring and Audit requirements, product accountability, and management of the study files and for the essential documents also have detailed rules and procedures.

Finally, a scientific soundness Protocol, an up-to-date Investigator´s Brochure, the feasibility of the study and adequate resources, together with proper randomization and blinding considerations in the Guideline are provisions for robust and ethical trial conduction and

performance. For achieving all of this, all parties involved in the research have responsibilities that I´ll try to summarize in the next lines.

IRB/IEC Responsibilities

Research ethics committees have the mission of safeguarding the rights, safety, and wellbeing of the participants, with special attention to the inclusion of vulnerable subjects. For that reason, IRB/IEC needs to be an independent committee, particularly separated from the sponsor or the investigator, in order to reduce or minimize potential conflict of interests. This is the only way to assure participant´s protection while reviewing research protocols and improving research conditions. Medical research, and clinical trials in particular, bring new tools for dealing with diseases and innovative medicines for individual patients and society in general. Notwithstanding, considering the general principle that individual patient's interests overcome the scientific knowledge and the social interests, participant´s safety and wellbeing are the priority.

In order to achieve these goals besides several standard operations that IRB/IEC need to have, their responsibilities are the evaluation of investigator´s qualifications, the review of the research proposals within a reasonable time and continuous monitoring of the ongoing trials. Other mandatory issues are related with the recruitment of the trial participants, assuring that no subject should be admitted to a trial before the written favourable opinion is issued and that the investigator should promptly report any deviation from or changes of the protocol and on all the adverse drug´s reactions.

Investigator responsibilities

Regarding the investigator´s responsibilities, it is particularly important to refer that the person responsible for conducting the clinical trial on the site in charge of the research team is called Principal Investigator (ICH-GCP 1.34).

The guidance for Principal Investigator (PI) responsibilities on the quality management of the clinical trial is focused on three key areas: patients (participants), data and documentation, and investigational products. In fact, all the responsibilities regarding the PI such as his qualifications and agreements, adequate resources, participant's welfare, ethical approval, compliance with the protocol and those related with the records, are related with participants, data and records. The investigators have the duty to minimize risks or inconveniences of the research, informing participants about the study and obtaining their informed consent, guaranteeing the confidentiality of their information and, at the end of the study, return the results to the participants.

Regarding qualifications, the investigators must have expertise in the disease and in the group of patients to be recruited, previous experience in clinical research and/or GCP knowledge and training. PI needs to gather qualified staff for performing the clinical trial, in whom he trusts and might assign responsibilities, but also the institution has the responsibility to provide for adequate human and material resources. Appropriate site resources are required not only for the performance of the trial but also for the treatment and management of severe adverse reactions of the trial participants that might occur. Investigator´s responsibilities respecting the medical supervision of the trial participant´s persists after the completion of the trial. The reception, traceability, and storage of the investigational products in the clinical trial site is

another responsibility of the PI unless he delegates his responsibility in the site pharmacist or pharmaceutical services. Finally, the investigator and/or the institution where the clinical trial occurs should maintain the source documents and the trial records adequate and accurate.
Principal investigator, besides the protection of research subjects, should ensure the accuracy, completeness, legibility, and prompt communication of data and reports to the sponsor.

Sponsor´s responsibilities
Sponsor´s main responsibilities are related to the implementation of a robust system for managing the quality of the clinical trial. They are responsible for the trial design and the scientific robustness of the study and the selection of the investigators and sites and the financial agreements. They are also responsible for all details and information of the investigational product, regarding the manufacturing and labelling but also regarding the supply and handling of the product. Sponsor is also responsible for the Investigator's Brochure (IC), which contains the information regarding the investigational product development. Other major responsibilities are the monitoring and audit procedures and the management of adverse reactions. Overall, sponsor responsibilities consist of global trial management, data handling and record keeping.
Considering what has been said on stakeholders´ responsibilities is important to underline that all parties are responsible for the assurance of good clinical practices, and many of their responsibilities are shared responsibilities. As an example, regarding the investigational product, sponsor responsibilities lie on manufacturing, delivering to the sites and afterwards it´s destruction, and in the clinical trial site, the responsibility for the investigational product complete traceability relies on the Principal Investigator or the pharmacist, respecting the sponsors' product maintenance requirements.

Using the ICH-GCP guideline for non-medical studies
The principles and the operational standards of the GCP, besides aiming at the harmonized procedures for submission and approval of the regulatory authorities, are designed in order to protect the rights, safety and welfare of patients and to ensure the quality and scientific integrity of the data collected. These general principles and aims apply almost to any type of research with humans since they are designed to respect the ethical principle of Human Dignity and ensure the integrity of the research. Thus, the GCP general principles and procedures can be adopted by all the stakeholders outside clinical trials and might be used as a model for the work of RECs beyond medical research. Since the Guideline was developed for drugs, biologics and medicines, for using this for other types of research, some adaptations are required.
In this section, I will try to exemplify when and how the E6 (R2) Guideline could be used as inspiring guidance for all the different stakeholders and quality management of the non-medical studies.

From the thirteen principles of this guideline, I would emphasise six, those that I consider that are common through different types of research. The first principle of ICH-GCP could be adopted for all types of research, establishing the need to conduct research according to good practices (not necessarily clinical practices) and regulatory requirements. The third principle: "The Rights and the well-being of the participants must prevail over the interests of science and society", applies to all research, involving human beings, and the same applies to the fourth principle: "The research must be scientifically sound, with a clear and detailed protocol". Having in mind the importance of the review of research with humans by an independent ethics committee,

and the autonomy of the research participants and their voluntariness, the principles number five and nine should also apply for research with humans. They are, “Conducted in compliance with protocol that has received independent ethics committee favourable opinion” and “Freely given informed consent obtained prior to participation”. The requirement for having ethical approval for all types of studies involving humans or data is by far the one that involves great discussion. I´ll be back to this issue later on. Finally, the eleventh principle of this guideline stating that all study´s records must respect the privacy and confidentiality of the participants is an utmost for the trust of the society in the investigators and the scientific research.

Going deep into the procedures established in the Guideline, some of the good (clinical) practices established for the design, recording, reporting and conduction of the study have several common issues with non-medical studies. In addition, adverse effects from social or psychological studies can occur when applying questionnaires or interviews, and these have to be taken into consideration for improving the participant’s well-being. When adverse events happen, investigators need to understand the causal relation with the questionnaire and whenever applicable, this questionnaire or the protocol might need to be changed. Some rules in how to deal with adverse events established in the Guideline could inspire the investigators for other types of studies.

Considering the principle in human research, bad science is bad ethics, having a scientific soundness protocol and adequate human and material resources are a requirement. The Guideline has some consideration on these issues with practical procedures and rules. Those involved in any research with humans or with personal data need to comply with these general rules in order to perform ethical research, respecting the Dignity of the human beings, that had volunteered for the scientific knowledge and the society. Non-medical research usually does not bring any expected benefit for the research participants, but they might be exposed to some kind of risks or discomfort.

Among general investigator´s responsibilities, regardless the type of research, their qualifications and agreements, adequate resources and proper conditions for performing the study, participant´s welfare, ethical approval, compliance with protocol and the accuracy of study´s records, are of utmost importance.

When considering essential documents for conducting any research, the investigator´s responsibilities apply before, during and after the termination of the study. Informed consent documents and information to participants and procedures for obtaining this is another ethical requirement with some principles and practical issues established in the Guideline. Proper recording and observations during the study, adequate analysis of data and report of the study results can also be adopted from the approach in the Guideline.

These are only some examples, regarding the participant’s protection and welfare and research integrity from the investigators´ perspective. Regarding IRB/IRC responsibilities, the rules and procedures established for medical research also apply for non-medical research with humans. IRB/IRC reviewing research with humans, even outside medical research, need to know and be aware of the major guidance on this Guideline.

Concluding, protecting the rights, safety and welfare of participants and ensuring the quality and scientific integrity of the data collected, foreseen in the Guideline “Good Clinical Practices” [E6(R2)] whenever applicable, or adapted for a different type of studies is a good starting point

in the governance of nonmedical research. For this reason, boosting his use by all the stakeholders outside medical research, and as a model for the work of research ethics committees beyond medicine should be considered. [https://www.ich.org/page/efficacy-guidelines]

Annex 4: Results of the search for guidance documents and guidelines for RECs

Prepared by EUREC Office gUG

Nr.	Title	Author	Year	Link	Summary / Target Group
Guidelines and guidance documents for RECs					
1	Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), , 2016.	2016	https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf	Beside thirteen principles, the GCP guideline E6(R2) gives detailed information for RECs.
2	Guide for Research Ethics Committee Members	CDBI	2012	https://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/Guide/Guide_EN.pdf	This Guide is designed to **assist RECs in fulfilling their important role when they review research proposals involving human beings**. The aim is to highlight, from a European perspective, the key ethical issues that RECs are likely to face. The guide does not define new principles. It highlights the ethical basis for the principles laid down in the European instruments **covering biomedical research**, and widely accepted at international level. Additionally, the guide outlines operational procedures as a basis on which RECs can develop their own organisational methods.
3	Guidelines for the Ethical Use of Digital Data in Human Research	Clark, Karin, Matt Duckham, Marilys Guillemin, Assunta Hunter, Jodie McVernon, Christine O'Keefe, Cathy Pitkin, Steven Prawer, Richard Sinnott, Deborah Warr,	2015	http://ethics.iit.edu/codes/Ethical-Use-of-Digital-Data.pdf	The guidelines presented here have been developed to assist researchers who are conducting, and **ethics committee members who are assessing, research involving digital data**. *For RECs see Part C " Practical Approaches for RECs"*

		and Jenny Waycott			
4	Ethical review and qualitative research competence: Guidance for reviewers and applicants	Mooney-Somers, J., and A. Olsen	2016	https://journals.sagepub.com/doi/pdf/10.1177/1747016116677636	This article provides practical guidance to researchers and **review committees** on using formal qualifications and training, explicit claims of competence, and markers of in/competence to assess qualitative research competence.
5	The Ethics of Research related to Healthcare in Developing Countries	Nuffield Council on Bioethics	2002	https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=2ahUKEwj_oOfchZLnAhUCoqQKHf0ICNgQFjABegQIAhAB&url=https%3A%2F%2Fnuffieldbioethics.org%2Fassets%2Fpdfs%2FEthics-of-research-related-to-healthcare-in-developing-countries.pdf&usg=AOvVaw06rkLCgpmDBpmxJGmRd_xO	The role of ethical review of research in developing countries and **how RECs are involved in that** is discussed in *chapter 8 "Ethical review of the research*", see also the follow-up Discussion Paper, especially *chapter 5 "Ethical review"*
6	Research with human subjects. A manual for practitioners	Swiss Academy of Medical Sciences (SAMS)	2015	https://swissethics.ch/doc/swissethics/manual_research_nov2015_e.pdf	The revised manual is addressed primarily to researchers and **to members of research ethics committees** *for RECs see chapter 7 "Independent review by the REC"*
7	Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants	World Health Organization (WHO)	2011	https://www.ncbi.nlm.nih.gov/books/NBK310671/	This document has been developed for individuals and **organizations involved in health-related research with human participants**, including biomedical, behavioural, social science, and epidemiological research. In particular, this document is intended to **provide guidance to the research ethics committees (RECs) on which organizations rely to review and oversee the ethical aspects of research**, as well as to the researchers who design and carry out health research studies. *Especially chapter 3 "Standards and Guidance for Members of the Research Ethics Committee"*
Guidelines for RECs (special focus on composition of the REC)					

8	Building Data and AI Ethics Committees	Accenture	2019	https://www.accenture.com/_acnmedia/PDF-107/Accenture-AI-And-Data-Ethics-Committee-Report-11.pdf#zoom=50	Aspects of building a REC in the field of AI.
9	Expertise, Ethics Expertise, and Clinical Ethics Consultation: Achieving Terminological Clarity	Iltis, Ana S., and Mark Sheehan	2016	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4986006/pdf/jhw014.pdf	The language of ethics expertise has become particularly important in **bioethics** in light of efforts to establish the value of the clinical ethics consultation (CEC), to specify who is qualified to function as a clinical ethics consultant, and to characterize how one should evaluate whether or not a person is so qualified.
10	Designing an Artificial Intelligence Research Review Committee	Jordan, Sara R.	2019	https://fpf.org/wp-content/uploads/2019/10/DesigningAIResearchReviewCommittee.pdf	Calls for a review committee dedicated to ethical oversight of artificial intelligence research have not yet included serious considerations of the design of this committee. Here, **a proposal for design of an artificial intelligence review committee review board** is developed drawing upon the history and structure of existing research review committees. *Especially from page 13.*
11	Standard Operating Procedures for Research Ethics Committees	NHS Health Research Authority	2019	https://www.hra.nhs.uk/documents/1775/RES_Standard_Operating_Procedures_Version_7.4_June_2019_lHKuibH.pdf	This document sets out **standard operating procedures (SOPs) for Research Ethics Committees (RECs) within the UK** Health Departments' Research Ethics Service.
12	Ethikkommission	University of Bremen	2020	https://www.uni-bremen.de/rechtsstelle/ethikkommission.html	exemplary for superordinate RECs at German Universities, code of procedure, for further examples see here.
13	Operational guidelines for ethics committees that review biomedical research	World Health Organization (WHO)	2000	https://apps.who.int/iris/handle/10665/66429	The Guidelines are intended to complement existing laws, regulations, and practices, and to serve as a **basis upon which ethics committees (ECs) can develop their own specific written procedures for their functions in biomedical research**.
General Guidelines					

14	Ethics Guidelines for Human Biomedical Research	Bioethics Advisory Committee Singapore	2015	https://www.bioethics-singapore.org/files/publications/reports/ethics-guidelines-for-human-biomedical-research-report-only.pdf	The Ethical Guidelines for Human Biomedical Research are intended to **serve as an ethical resource for researchers and members of ethics committees or institutional review boards (IRBs**).
15	International Ethical Guidelines for Health-related Research Involving Humans	Council for International Organizations of Medical Sciences (CIOMS)	2017	https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf	The ethical principles set forth in these Guidelines should be upheld in the ethical review of research protocols. **The ethical principles are regarded as universal.**
16	Convention on Human Rights and Biomedicine	Council of Europe	2017	http://conventions.coe.int/treaty/EN/Treaties/Html/164.html	The Convention is the first legally binding international text designed to preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances. *RECs are just mentioned in chapter 3 of the Additional Protocol:* Council of Europe, "Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research", 2005. http://conventions.coe.int/treaty/EN/Treaties/Html/195.html
17	GDPR, EU General Data Protection Regulation	Council of Europe	2018	https://gdpr.eu/	General Data Protection Regulation
18	Nuremberg Code	National Institute of Health	2007	https://web.archive.org/web/20071029120713/http://ohsr.od.nih.gov/guidelines/nuremberg.html	Directives for Human Experimentation
19	Belmont Report	U.S. Department of Health & Human Services	2016	https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html	The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations.
20	Universal Declaration on bioethics and human rights	UNESCO	2006	https://unesdoc.unesco.org/ark:/48223/pf0000146180	This Declaration is **addressed to States**. As appropriate and relevant, it also provides guidance to decisions or practices of individuals, groups, communities, institutions and corporations, public and private.
21	Declaration of Helsinki	World Medical Association	2013	https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/	Consistent with the mandate of the WMA, the Declaration is **addressed primarily to physicians**. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Guidelines for emerging technologies					
22	Ethics Assessment in Different Fields. Engineering Sciences	Brey, Philip, and Philip Jansen	2015	http://satoriproject.eu/media/2.b-Engineering.pdf	This is a report on **ethics assessment of research and innovation in engineering**. The report will cover both the academic traditions of ethics assessment in engineering and the institutionalisation of it in different types of organisations, including national and international standards and legislation. It is part of a larger study of the SATORI project
23	EGE statements	European Group on Ethics in Science and New Technologies (EGE)	2019	https://ec.europa.eu/info/research-and-innovation/strategy/support-policy-making/scientific-support-eu-policies/european-group-ethics-science-and-new-technologies-ege_en	Might develop guidelines, currently working on gene editing, artificial intelligence and the future of work.
24	EU guidelines on ethics in artificial intelligence: Context and implementation	European Parliament	2019	https://www.europarl.europa.eu/RegData/etudes/BRIE/2019/640163/EPRS_BRI(2019)640163_EN.pdf	This paper aims to shed some light on the ethical rules that are now recommended when designing, developing, deploying, implementing or using **AI products** and services in the EU. Moreover, it identifies some implementation challenges and presents possible further EU action ranging from soft law guidance to standardisation to legislation in the field of ethics and AI.
25	Ethics Guidelines for Trustworthy AI	Independent High-Level Expert Group on Artificial Intelligence	2019	https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai	The aim of the Guidelines is to **promote Trustworthy AI**. These Guidelines set out a framework for achieving Trustworthy AI.
EU legislation					
26	Directive 90/385/EC	European Council	1990	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31990L0385	approximation of the laws of the Member States relating to active implantable medical devices
27	Directive 93/42/EEC	European Council	1993	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31993L0042	concerning medical devices

28	Directive 98/79/EC	European Parliament and the Council	1998	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31998L0079	in vitro diagnostic medical devices
29	Directive 2001/20/EC	European Parliament and the Council	2001	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0020	approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
30	Directive 2005/28/EC	European Commission	2005	https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1578314404983&uri=CELEX:32005L0028	laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
31	Regulation (EU) 536/2014	European Parliament and the Council	2014	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536	clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance