What Would It Take to Enable Germline Editing in Europe for Medical Purposes?

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Abstract

Commonly, the regulation on germline editing in Europe is described through the two prohibitions: the prohibition set out in Article 13 of 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 and the prohibition that is set out in the EU Clinical Trials Regulation. These prohibitions reflect the European regional position regarding the ethical and legal questions raised by the technology, and an unwillingness to enable such interventions in Europe. Simultaneously, these prohibitions have been shaped prior to the recent breakthroughs in the field, such as the discovery of the CRISPR-Cas technology, which has initiated a new era in the field. This contribution examines what it would take to enable human germline gene editing in Europe for medical purposes. It scrutinises in detail the content and context of the existing bans, as well as mechanisms to lift them. It argues that the bans that are prescribed by each of the European regional legal orders are embedded in strong structures, composed of values and principles. For the human germline gene editing to be enabled in Europe for health-related purposes, the approach to these values and principles needs to change. Only then can the machinery to lift the bans lead to a change.

Keywords

Biomedicine Convention Article 13 – Clinical Trials Regulation Article 90 – gene therapy – germline gene editing

1 Introduction

Commonly, the regulation on germline editing in Europe is described through the two prohibitions: one set out in Article 13 of 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 (Biomedicine Convention)[1] and the other set out in the EU clinical trials framework, Clinical Trials Directive and Clinical Trials Regulation repealing the directive.[2] These bans date back to 1997 for the Council of Europe and, at least in so far as the EU clinical trials framework is concerned, to 2001; moreover, they shape the national legal requirements and medical practice in European national legal orders.[3]

The recent scientific advances[4] as well as their extraordinary practical applications, resulting in the birth of the first children whose genomes have been edited despite a *consensus*[5] in the field, have led to a renewed discussion and positions on the moral acceptability of human germline editing and future directions of the field. While there is a general reservation towards premature use of technology on humans, there is also an interest in exploring and eventually harvesting the potential benefits that germline editing could offer. In the health context, it has the potential to correct disease-causing mutations early in the development of a human being when the mutation is present in one

1 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, ETS 164.

2 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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 OJ L 121, 1 May 2001, pp. 34–44, Article 9(6). Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance OJ L 158, 27 May 2014, pp. 1–76, Article 90.

3 In the EU, a reserved attitude towards interventions in human germline can be observed even earlier, for example, in 1998, in the Biotechnology Directive, Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions OJ L 213, 30 July 1998, p. 13–21, Article 6(2)(b).

4 Particular milestones are the work of Liang et al., published in 2015, which uses CrisprCas on non-viable human embryos to investigate the efficacy and specificity of the method, initiated an international debate on the permissibility of such research as well as future clinical. P. Liang, Y. Xu, X. Zhang, C. Ding, R. Huang, Z. Zhang, J. Lv, X. Xie, Y. Chen, Y. Li, Y. Sun 1, Y. Bai, S. Zhou, W. Ma, C. Zhou and J. Huang, 'CRISPR/Cas9-Mediated Gene Editing in Human Tripronuclear Zygotes', *Protein & Cell* 6 (2015) 363–372.

5 F. Baylis, 'Human Germline Genome Editing and Broad Societal Consensus', *Nature Human Behaviour* 1 (2017) 0103.

of few embryonic cells. Moreover, it promises to not only prevent passage of genetic disease to a child but also to break the genetic inheritance chain and prevent it from passing on to future generations.[6]

As with any issue in biology and medicine, arguments for and against the eventual use of human germline gene editing in humans are put forward. In support of germline interventions, such arguments as that society should not be deprived of the possibility of benefitting from scientific advances in the field are invoked.[7] Often, this argument is also accompanied by a proposed constrained application of the technology, e.g. for the cases where pre-implantation genetic diagnostics is not an adequate alternative,[8] or enable the use (at least) as far as pre-implantation genetic diagnosis is permitted.[9] Arguments such as the safety of the intervention and risks associated with,[10] for example, off-target edits and scientific uncertainties are invoked against the use of germline gene editing.[11] Other arguments are that alternative interventions for most of the cases are available and hence, there is a limited necessity for the interventions,[12] and that the intervention creates concerns of eugenics, and is problematic from a moral standpoint.[13]

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6 D.P. Wolf, P.A. Mitalipov and S.M. Mitalipov, 'Principles of and Strategies for Germline Gene Therapy', *Nature Medicine* 25 (2019) 890–897.

7 See, for example, H.I. Miller, 'Germline Gene Therapy: We're Ready', *Science* 348 (6241) (2015) 1325.

8 See, for example, G.Q. Daley, R. Lovell-Badge and J. Steffann, 'After the Storm — A Responsible Path for Genome Editing', *The New England Journal of Medicine* 380 (2019) 897–899. D. Cyranoski, 'The CRISPR-Baby Scandal: What's next for Human Gene-Editing', *Nature* 566 (2019) 440–442.

9 See A.L.V. Hammerstein, M. Eggel and N. Biller-Andorno, 'Is Selecting Better than Modifying? An Investigation of Arguments against Germline Gene Editing as Compared to Preimplantation Genetic Diagnosis', *BMC Medical Ethics* 20 (2019) 83.

10 C. Brokowski, 'Do CRISPR Germline Ethics Statements Cut It?', *The CRISPR Journal* 1 (2018) 115–125.

11 Hammerstein et al., *supra* note 9. Insight into uncertainties also here, National Academies of Sciences, Engineering, and Medicine, *Statement by the Organizing Committee of the Second International Summit on Human Genome Editing | National Academies* (28 November 2018), available online at https://www.nationalacademies.org/news/2018/11/statement-by-the-organizing-committee-of-the-second-international-summit-on-human-genome-editing (accessed 8 February 2022).

12 G. De Wert, B. Heindryckx, G. Pennings, A. Clarke, U. Eichenlaub-Ritter, C.G. van El, F. Forzano, M. Goddijn, H.C. Howard, D. Radojkovic, E. Rial-Sebbag, W. Dondorp, B.C. Tarlatzis and M.C. Cornel, 'Responsible Innovation in Human Germline Gene Editing: Background Document to the Recommendations of ESHG and ESHRE', *European Journal of Human Genetics* 26 (2018) 450–470.

13 On analysis of how eugenics relates to germline gene editing, see N. Agar, 'Why We Should Defend Gene Editing as Eugenics', *Cambridge Quarterly of Healthcare Ethics* 28 (2019) 9–19.

Different stakeholders, including law and policymakers, have also taken a stand on the issue. For example, in 2015, the National Academies of Sciences, Engineering, Medicine issued a statement emphasising that it would be irresponsible to proceed with any clinical use of germline editing until the intervention can be deemed sufficiently safe and is acceptable.[14] Three years later, in 2018, they emphasised that the time was not ripe for clinical trials in the field,[15] but the recent progress requires defining a rigorous, responsible translational pathway towards such trials.[16] In 2015, the UNESCO International Bioethics Committee issued the Report on Updating Its Reflections on the Human Genome and Human Rights and called for 'a moratorium on genome engineering of the human germline, at least as long as the safety and efficacy of the procedures are not adequately proven as treatment'.[17] In 2017, the Council of Europe Parliamentary Assembly urged the signatories of the Biomedicine Convention to proceed with a ratification or 'as a minimum, to put in place a national ban on establishing a pregnancy with germ-line cells or human embryos having undergone intentional genome editing'.[18] In 2021, the Council of Europe affirmed that a revision is not currently on the Council of Europe's agenda.[19] In comparison, in 2018, Nuffield Council on Bioethics report Genome

14 National Academies of Sciences, Engineering, and Medicine, *On Human Gene Editing — International Summit Statement | National Academies* (3 December 2015), available online at https://www.nationalacademies.org/news/2015/12/on-human-gene-editing-international-summit-statement (accessed 8 February 2022).

15 'Statement by the Organizing Committee of the Second International Summit on Human Genome Editing | National Academies' *supra* note 11.

16 *Ibid*.

17 International Bioethics Committee, *Report of the IBC on updating its reflection on the Human Genome and Human Rights* (2015), p. 3.

18 Recommendation 2115 (2017) The use of new genetic technologies in human beings. Parliamentary Assembly Origin — Assembly debate on 12 October 2017 (35th Sitting) Text adopted by the Assembly on 12 October 2017 (35th Sitting), available online at https://assembly.coe.int/nw/xml/XRef/Xref-XML2HTML-en.asp?fileid=24228&lang=en, 5.1.

19 The Committee on Bioethics of the Council of Europe, *Genome Editing Technologies: Some Clarifications but No Revision of the Oviedo Convention* (7 June 2021), available online at https://www.coe.int/en/web/human-rights-rule-of-law/newsroom/-/asset_publisher/UORLPrekXNpu/content/genome-editing-technologies-some-clarifications-but-no-revision-of-the-oviedo-convention (accessed 8 February 2022). Later in 2022, a clarification was adopted. Steering Committee for Human Rights in the fields of Biomedicine and Health (CDBIO), Intervention on the human genome, Re-examination process of Article 13 of the Oviedo Convention, Conclusions and Clarifications https://rm.coe.int/cdbio-2022-7-final-clarifications-er-art-13-e-2777-5174-4006-1/1680a87953 (accessed 13 November 2022).

Editing and Human Reproduction: Social and Ethical Issues concluded that the intervention should be permitted under some restrictive circumstances.[20]

In the existing scholarly debates and policy documents, fundamental biomedical law principles and human rights, such as human dignity, right to health, and right to benefit from the scientific advances, are tweaked in both directions. Ultimately, once science has progressed and such central intervention-related practical issues like the safety of the intervention are no longer a concern, for example, due to off-target effects[21] and the interventions have established positive risk-benefit ratio, it could be argued to be a policy choice. At the core lies considerable, and potentially irresolvable moral questions — regarding enabling clinical trials and thereafter providing access to human germline genetic interventions and subordinated to that regarding the scope of that access as part of healthcare services.[22]

This contribution acknowledges the significant controversies regarding permissibility of human germline gene editing, and it sets aside the difficult question of whether and under what circumstances human germline gene editing should be permitted. It assumes that eventually the question of *removing* the hurdles for clinical trials and ultimately *enabling* the medical application of the technology could be put on the agenda of the two European legal orders more fiercely. It, thus, examines what it would take to enable human germline gene editing in Europe for medical purposes. To address this question, this

20 Nuffield Council on Bioethics in 2018 concludes that germline gene editing could be ethically acceptable if "reproductive cells that have been subject to heritable genome editing interventions are (should only be) only used for purposes that are consistent with the welfare of the future person" and if "the use of heritable genome editing interventions is (should be) consistent with social justice and solidarity so that it should not be expected to increase disadvantage, discrimination, or division in society" Bioethics, N. Co., *Genome Editing and Human Reproduction: social and ethical issues* (London: Nuffield Council on Bioethics, 2018).

21 See the ongoing discussions regarding off-target effects, M.V. Zuccaro, J. Xu, C. Mitchell, D. Marin, R. Zimmerman, B. Rana, E. Weinstein, R.T. King, K.L. Palmerola, M.E. Smith, S.H. Tsang, R. Goland, M. Jasin, R. Lobo, N. Treff and D. Egli, 'Allele-Specific Chromosome Removal after Cas9 Cleavage in Human Embryos', *Cell* 183 (2020) 1650–1664. These off-target effects could be passed on to the next generations, see I. Höijer, A. Emmanouilidou, R. Östlund, R. van Schendel, S. Bozorgpana, M. Tijsterman, L. Feuk, U. Gyllensten, M. den Hoed and A. Ameur, 'CRISPR-Cas9 Induces Large Structural Variants at on-Target and off-Target Sites in Vivo That Segregate across Generations', *Nature Communications* 13 (2022) 627.

22 For example, the right to benefit from scientific advances as protected under Article 15(1)(b) can be subject to limitations under Article 4 of the Covenant, such as through protecting from participation in scientific research that is deemed unethical, *see* UN General Assembly, International Covenant on Economic, Social and Cultural Rights, 16 December 1966, *United Nations, Treaty Series* vol. 993, p. 3.

chapter examines the existing prohibitions in detail to ascertain what specific interventions in the human genome are prohibited through the two bans. It scrutinises the context in which these bans operate as well as mechanisms to lift them within each of the European legal orders. This chapter shows the limited reach of these bans; furthermore, it argues that the bans which are prescribed by each of the European regional legal orders are embedded in strong structures composed of values and principles. For the human germline gene editing to be enabled in Europe for health-related purposes, the approach to these values and principles needs to change. Only then can the machinery to lift the bans lead to a change.

2 On the Two Bans in European Regional Legal Fora

The Biomedicine Convention is a universal human rights instrument in the area of biology and medicine. It provides a common framework for the protection of human dignity and human rights to its contracting parties. While its effects could stretch beyond the borders of the Council of Europe, to this day, there is no country outside the Council of Europe that would have acceded to the convention.[23] It has 29 ratifications[24] and thus unites only slightly more than half of the members of the Council of Europe. However, the limited number of ratifications does not do justice to the impact of the principles set out in the convention across the Council of Europe. The powerful adjudication under the ECHR established by the ECtHR, and the structured approach crafted by the Council of Europe, whereby sectorial treaties and soft-law tools are anchored in the rights protected by the ECHR, render the ECtHR an indirect enforcer of the convention.[25] Although the ECtHR has not had a chance to consider on Article 13 of the Biomedicine Convention yet, given the important human rights questions that interventions in human genome pose, it cannot be precluded that a question will eventually land before the court.

23 See Article 34 of the Biomedicine Convention and Council of Europe, *Chart of Signatures and Ratifications of Treaty 164*, status as of 8 February 2022, available online at https://www.coe.int/en/web/conventions/full-list?module=signatures-by-treaty&treatynum=164 (accessed 8 February 2022).

24 *Ibid*. Seven countries have signed the convention and have not proceeded with the ratification.

25 See F. Seatzu and S. Fanni, 'The Experience of the European Court of Human Rights with the European Convention on Human Rights and Biomedicine', *Utrecht Journal of International and European Law* 31 (2015) 5–16.

The EU does not possess any general powers regarding health care. However, health matters trigger diverse competences of the EU.[26] Through the principle of conferral, the Member States have entrusted the EU to legislate for setting high standards of quality and safety for medicinal products.[27] As stipulated in declaration 32 attached to the Lisbon treaty, the EU shall be acting on quality and safety matters where national standards affecting the internal market would otherwise prevent a high level of human health protection being achieved. However, this provision is not in itself sufficient for enacting comprehensive legislation on clinical trials and regulation of the market-related aspects for medicinal products generally or advanced therapy medicinal products specifically. Central to the regulation of the medicinal products are rules on internal market, and consequently, the legal basis set out in Article 114 TFEU. These are also the two legal bases on which the Clinical Trials Regulation rests,[28] and which are examined in greater detail in the subsequent sections.

Generally, gene therapy falls within the scope of the EU Regulation on Advanced Therapy Medicinal Products.[29] However, the rules pertaining to clinical trials are set out in the Clinical Trials Regulation. The regulation applies to all clinical trials in the EU, whereby an integral part of a clinical trial is presence of a medicinal product for investigation in a clinical study.[30] This suggests that the EU Clinical Trials Regulation applies only to such gene editing that satisfies the definition of a medicinal product. What is a medicinal product and thus is captured under this ban is examined in the next section. Here, it suffices to note that other interventions that do not fall within the scope of Clinical Trials Regulation can be regulated differently, for example, under the general product safety requirements.[31]

For the national legal orders, the Biomedicine Convention as well as the EU law place different obligations. The Biomedicine Convention is an

26 For an insight into the EU competences, *see* K.P. Purnhagen, A. De Ruijter, M.L. Flear, T.K. Hervey and A. Herwig, 'More Competences than You Knew? The Web of Health Competence for European Union Action in Response to the COVID-19 Outbreak', *European Journal of Risk Regulation* 11 (2020) 297–306.

27 Article 168(4)(c) Consolidated version of the Treaty on the Functioning of the European Union OJ C 326, 26.10.2012, pp. 47–390.

28 Clinical Trials Regulation *supra* note 2.

29 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) OJ L 324, 10 December 2007, pp. 121–137.

30 Clinical Trials Regulation, *supra* note 2, Article 1 and Article 2(2).

31 See Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety (Text with EEA relevance), OJ L 11, 15 January 2002, pp. 4–17.

international treaty, and its effectiveness at the national level rests on the effectiveness of measures taken by the national legal orders in order to give them effect. Although Article 13 of the Biomedicine Convention is a non-derogable prohibition,[32] and the signatories are required to provide appropriate sanctions for infringements,[33] its effect can be compromised by the countries failing to take measures to give full effect to the provisions. Generally, from the international law perspective, a distinction can be drawn between monism and dualism traditions.[34] The monist school regards international and national law in a system of unity, whereas the dualist school sees them as a separate system. Additional challenges relating to implementation could emerge in the dualist traditions and limited direct impacts that the convention could create. However, as a matter of international law, disregarding whether a state follows a monist or dualist tradition, it shall ensure that it lives up to its international commitments, and violations of the ban prescribed in Article 13 do not take place.

The EU law obligations are subsumed under the principle of primacy of EU law.[35] As the Clinical Trials Regulation takes a form of a regulation — a directly applicable legal instrument — and Article 90 is capable of meeting the requirements of direct effect as the norm is sufficiently clear, precise and does not require further implementation measures,[36] there is nothing from hindering its application in regard to each clinical trial. Hence, its effects can reach down to, for example, each sponsor responsible for a clinical trial. However, unlike, for example, in the area of data protection, the Clinical Trials Regulation does not prescribe uniform sanctions for violations. It merely requires the Member States to adopt 'effective, proportionate and dissuasive' penalties for the infringements of the regulation,[37] leaving it up to each Member State to define the content of these penalties.

3 What Is Prohibited and Why?

3.1 *Article 13 of the Biomedicine Convention*

Article 13 of the Biomedicine Convention reads as follows:

32 Biomedicine Convention, *supra* note 1, Article 26.

33 *Ibid.*, Article 15.

34 J.G. Starke, 'Monism and Dualism in the Theory of International Law', *British Year Book of International Law* 17 (1936) 66–81.

35 Case 6/64, *Flaminio Costa v E.N.E.L.*, ECLI:EU:C:1964:66.

36 See Case 26/62, *Van Gend en Loos v Administratie der Belastingen*, ECLI:EU:C:1963:1.

37 Clinical Trials Regulation, *supra* note 2, Article 94(1).

> An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants.

This provision only allows for 'modifications' of the human genome for 'preventive, diagnostic or therapeutic purposes', except for when such modifications seek to introduce any changes to the genome of any descendants. It is neutral to the genome editing technique that is involved in introducing the modification; instead, it focuses on the prohibited behaviour and its intention. The provision is intended to enable only somatic, health-related genome editing. However, it tolerates that somatic, health-related genome editing could have implications for germ cells, and it could result in heritable changes.[38] It does not put any hinders to the basic research in the field using surplus embryos.[39] However, in line with Article 18 of the convention, embryos for research purposes shall not be created. The ban that is set forth in Article 13 becomes applicable if the potential of life is attempted to be realised, for example, through using gametes that have been subject to editing interventions in *in vitro* fertilisation or through insemination of a fertilised edited egg in a woman's body.

At the time this provision was adopted, it was the first of its kind. Work on this provision within the Council of Europe took place from November 1992 to June 1996, and the preparatory works provide an insight into central considerations that lie behind the wording of the provision. They include reluctance to assume risks that human beings could differ from one generation to the next,[40] interest to enable diagnostic and therapeutic somatic interventions and acceptance of eventual risks in that regard to the germline,[41] acknowledgements of the limitations relating to science underlying interventions in the human genome at the time of drafting the convention, as well as some

38 Explanatory Report to 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, para. 91.

39 See Steering Committee on Bioethics (CDBI) Convention on 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 (Ets No. 164), Preparatory Work on the Convention, CDBI/INF (2000) 1, pp. 63–68.
See also I. de Miguel Beriain, E. Armaza and A. Duardo Sánchez, 'Human Germline Editing Is Not Prohibited by the Oviedo Convention: An Argument', *Medical Law International* 19 (2–3) (2019) 226–232.

40 Preparatory Work on the Convention, *supra* note 38, ORED 9-12/11/92, p. 63.

41 See *ibid.*, pp. 63–68.

openness to the revisions of the wording of the provision.[42] While the interest in the openness to the revisions is traceable in the preparatory works at the early stages of the development of the convention, the preparatory works following November 1995 are silent on this issue.[43] *Expressis verbis* rejection of the idea that the provision could be revised is not documented. It might well be that some parallels can be drawn regarding the discussions on the state of scientific knowledge and state of art and the needs to revise the provision in that light, which had taken place at the earlier stages of the development of the provision, versus the principle-based discussions regarding the permissibility of interventions in the human genome.[44] One could also speculate that the revision consideration has some parallels with the development of Article 32 of the convention that focuses on the amendments to the convention, but the preparatory works are silent on that.[45] More conclusive answers from the preparatory works regarding the intentions are difficult to draw.

Explanatory Report to the Biomedicine Convention, on the other hand, emphasises only the fear of misuse that could endanger not only individuals but also the human species. As the ultimate fear in that regard, it points out the fear 'to produce individuals or entire groups endowed with particular characteristics and required qualities'.[46] It addresses safety of the interventions to the extent that they are allowed under Article 13, and in so far as they are part of scientific research, wherein they should be conducted accordingly. It could be argued that the Explanatory Report to the Biomedicine Convention addresses the central concern motivating the prohibition set out in Article 13. Since that is a matter of principal concern, the question of safety then was no longer relevant.

3.2 *Article 90 of the Clinical Trials Regulation*

Article 90 of the Clinical Trial Regulation states:

> No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.

42 See *ibid.*, in particular CORED 14-16/12/92, pp. 63–64, CDBI 27/06-1/07/94, pp. 65–66, and CDBI 20-22/1195, p. 66.

43 See Preparatory Work on the Convention, *supra* note 39, pp. 63–68. See also preparatory works regarding Article 32, pp. 124–125.

44 See nature of discussions and the transition to the agreement on the substance of the issues, *ibid.*, CDBI 26/02-1/03/96, p. 67.

45 *Ibid.*, pp. 124–125.

46 Explanatory Report to the Biomedicine Convention *supra* note 38, para. 89.

This provision contains a prohibition that has existed in the EU law for a considerable time.

In its predecessor, Article 9(6) of the Clinical Trials Directive, it was included in the second reading, following the recommendation of the Committee on the Environment, Public Health and Consumer Policy on the Council, giving a common position for the directive.[47] Justification of the inclusion was motivated with at that time the existing EU policy in the field. More specifically, it was argued that '[t]he prohibition of germ line gene therapy is in line with stated EU policy'.[48] No further information is provided regarding the policy that the committee refers to. It was then adopted in the 2nd reading.[49] In 2012, the European Commission launched a proposal for the Clinical Trials Regulation, and this proposal did not contain any consideration regarding the germ line. However, already in the first reading, this was rectified, and the ban set out in the Clinical Trials Directive found also its place in the proposed regulation, with a motivation that '[t]he regulation may not fall behind the existing directive. Therefore, we should adopt the formulation of the present directive'.[50] The available preparatory works are silent on whether this was a mere administrative slip, or the European Commission had a particular intention of not including the ban in its proposal. The context of EU law in the field, however, speaks of the former.[51]

One of the central features of the EU legal framework in the field is that it applies to medicinal products. This is a general rule, taming the EU competences and the application of the Clinical Trials Regulation, as well as the

47 European Parliament Recommendation for Second Reading Final A5-0349/2000, 22 November 2000.

48 *Ibid*., amendment 19, p. 17.

49 See European Parliament legislative resolution on the Council common position for adopting a European Parliament and Council directive 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 (8878/1/2000—C5-0424/2000—1997/0197(COD)), Amendment 42.

50 On the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012)0369—C7-0194/2012—2012/0192(COD)), Amendment 257.

51 Such a ban is also set out in other EU legal acts, for example, on EU funding for scientific research, *see* Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe — the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (text with EEA relevance) PE/12/2021/INITOJ L 170, 12.5.2021, pp. 1–68, Article 18(1)(b). Another example is Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions OJ L 213, 30.7.1998, pp. 13–21, Article 6(2)(b).

Regulation on Advanced Therapy Medicinal Products.[52] Consequently, it is also a limitation on the application of Article 90 of the Clinical Trials Regulation and the interventions that can be subjected to the ban on heritable genetic changes set therein.

The Clinical Trials Regulation applies to all clinical trials conducted within the EU.[53] From Article 2(2) of the Clinical Trials Regulation derives that in order for a clinical trial to be subject to the regulation, it shall involve assessment of a medicinal product or a 'therapeutic strategy' that falls outside the normal clinical practice in a Member State, or 'diagnostic or monitoring procedures' falling outside the normal clinical practice, whereby the 'therapeutic strategy' as well as 'diagnostic or monitoring procedures' relate to a medicinal product. The regulation does not define what a medicinal product is, but it indicates that the definition of a 'medicinal product' that is set out in Directive 2001/83/EC applies.[54] There, in Article 1(2), a medicinal product is defined as

> Any substance or combination of substances presented for treating or preventing disease in human beings.
>
> Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.

If a product falls within any of the two definitions (i.e. can be regarded as a medicinal product by presentation or by function), the product shall be regarded as a medicinal product.[55] However, the assessment of whether a particular substance shall be classified as a medicinal product is not straightforward. As explained by the Court of Justice of the European Union (CJEU), this assessment lies with the national authorities, acting under the supervision of the courts, to 'decide on a case-by-case basis, taking account of all the characteristics of the product, in particular its composition, its pharmacological, immunological or metabolic properties, to the extent to which they can be established in the present state of scientific knowledge, the manner in which it is used, the extent of its distribution, its familiarity to consumers and the risks which its use may entail'.[56] In regard to the advanced therapy medicinal

52 See recitals 2 and 3 in Advanced Therapy Medicinal Products Regulation, *supra* note 29.

53 Clinical Trials Regulation, *supra* note 2, Article 1.

54 *Ibid.*, Article 2(1). *See* C-27/08, *BIOS Naturprodukte GmbH v Saarland*, ECLI:EU:C:2009:278, paras 17–22.

55 See, for example, Joined Cases C-358/13 and C-181/14, *Markus D. and G.*, ECLI:EU:C:2014:2060, paras 26–28.

56 *Ibid.*, para. 42.

products, such as particular interventions in the human genome, however, this assessment lies with the European Medicines Agency.[57]

The assessment of a substance's classification as a medicinal product by presentation is rather straightforward — if a substance is presented as being intended for treating or preventing a disease in human beings, it shall be regarded as a medicinal product. However, the assessment of a substance being classified as a medicinal product by function is less straightforward. It requires a more sophisticated judgment, examining the central elements enlisted in the definition. More specifically, while restoration and correction are rather straightforward in the health context, questions emerge in regard to the meaning of the word modify, and consequently, what types of modifications are captured under the Clinical Trials Regulation.

The CJEU has explained that, in everyday language, the word modify appears neutral in terms of its effects, whether they are harmful or beneficial.[58] However, in the context of the EU objectives and competencies, and in particular, in the area of public health, as well as with due regard to the legal framework, in which this term is located, and associated terms in the definition imply the beneficial nature of the modification.[59] In a similar way, restoration and correction of functions are intended to capture the beneficial effects. In *Upjohn*, early on, the CJEU indicated that this wording covers 'all substances capable of having an effect on the actual functioning of the body'.[60] Thus, products, which alter physiological functions in the absence of disease, such as contraceptive substances, also fall within the scope of that definition.[61] More recently, in the joined cases *Markus D. and G.*, the CJEU clarified that this wording reflects the legislature's intention to capture substances producing 'beneficial effects … on the functioning of the human organism and, as a consequence — be it immediately or over a period of time — on human health, even in the absence of disease'.[62] Thus, the wording modify 'must be

57 See the role of Committee for Advanced Therapies under Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance) OJ L 324, 10.12.2007, pp. 121–137.

58 Joined Cases C-358/13 and C-181/14, *Markus D. and G.*, *supra* note 55, para. 31.

59 *Ibid.*, paras 30–37.

60 C-112/89, *Upjohn Company and Upjohn NV v Farzoo Inc. and J. Kortmann*, ECLI:EU:C:1991:147, para 21.

61 *Ibid.*, para 19. Though, obviously, this is an outlier in the medicinal products regime, similarly as abortifacients. Joined Cases C-358/13 and C-181/14, *Markus D. and G.*, *supra* note 55, paras 40–41.

62 Joined Cases C-358/13 and C-181/14, *Markus D. and G.*, *supra* note 55, para 36.

interpreted as not covering substances whose effects merely modify physiological functions and which are not such as to entail immediate or long-term beneficial effects for human health'.[63] Thus, for example, interventions in the human genome that do not produce this effect fall outside the scope of the application of the respective ban.

4 Lifting the Ban Set Out in Article 13 of the Biomedicine Convention

4.1 *On the Procedure of Lifting the Ban*

Biomedicine Convention is an international treaty, concluded under the auspices of the Council of Europe. A treaty may be amended by agreement between the parties.[64] Vienna Convention on the Law of the Treaties of 1969,[65] a treaty governing treaties, allows that treaty amendment rules are set forth in a respective treaty. Article 32 of the Biomedicine Convention sets forth a 4-stage mechanism to make it happen.

To begin with, there are only three actors that are entitled to submit a proposal for a treaty amendment. It can be done by any party of the convention, the Steering Committee for Human Rights in the fields of Biomedicine and Health (CDBIO),[66] or the Committee of Ministers.[67] Thereafter, the text needs to be examined by the CDBIO. If the CDBIO is the one submitting, this step can be viewed as futile on the condition that two-thirds majority of the votes are present for the submission of the proposal. The CDBIO is composed of experts of the highest rank on matters pertaining to the areas of the Biomedicine Convention, and in that committee, each Council of Europe member state may be represented and have one vote.[68] If the proposal is approved by a two-thirds majority of the votes cast, it proceeds to the next step, the Committee of

63 *Ibid.*, para. 38.

64 Vienna Convention on the Law of Treaties (United Nations (UN)) 1155 UNTS 331 VCLT, Vienna Convention 1969, Article 39.

65 *Ibid.*

66 Council of Europe, *The Committee on Bioethics (DH-BIO) Becomes the Steering Committee for Human Rights in the Fields of Biomedicine and Health (CDBIO)* (13 December 2021), available online at https://www.coe.int/en/web/bioethics/news/-/asset_publisher/EV740sp47zWZ/content/the-committee-on-bioethics-dh-bio-becomes-the-steering-committee-for-human-rights-in-the-fields-of-biomedicine-and-health-cdbio- (accessed 8 February 2022).

67 Biomedicine Convention, *supra* note 1, Article 32(5).

68 *Ibid.*, Article 32(2).

Ministers, for approval.[69] The Committee of Ministers is the organ that acts on behalf of the Council of Europe, and it consists of Ministers for Foreign Affairs of the Council of Europe member states.[70] Each member of the Council of Europe is entitled to one representative on the Committee of Ministers, and each representative shall be entitled to one vote.[71] It is required that the decision is made by a two-thirds majority of the representatives casting a vote and a majority of the representatives entitled to sit on the Committee of Ministers.[72]

As evident from the above, there must be a considerable interest in furthering the changes, and this interest needs to stem from different directions and reach a considerable threshold. To begin with, there needs to be an interest among one of the key actors to proceed with amendments. Thereafter, there needs to be a majority of the Member States of the Council of Europe experts working at the CDBIO in favour of the amendment. Thirdly, it needs to pass the threshold assigned to the ministers of foreign affairs of the Council of Europe states, representing the political view at the national level. Only thereafter can it proceed to the ratification stage, and the lifting of the ban can get the full effect.

4.2 *On the Context of Lifting the Ban*

The ban on human germline editing rests on a number of pillars of the Biomedicine Convention. Among its cornerstones is 'need to respect the human being both as an individual and as a member of the human species' and wish to tackle the fact that 'the misuse of biology and medicine may lead to acts endangering human dignity'.[73] Substantively, the convention seeks to protect the dignity and identity of all human beings with regard to the application of biology and medicine.[74] Moreover, '[t]he interests and welfare of the human being shall prevail over the sole interest of society or science'.[75] Any intervention shall be 'carried out in accordance with relevant professional obligations and standards'.[76]

The context in which Article 13 is placed indicates that germline interventions can be argued to be disrespectful to an individual, be incompatible with dignity, and endanger the humanity. In that regard, it is not in the interests and

69 Biomedicine Convention, *supra* note 1, Article 32(6). The participation in the CDBIO is open also to parties to the convention that are not Members of the Council of Europe.
70 Statute of the Council of Europe, European Treaty Series No. 1, Article 14.
71 *Ibid.*, Article 14.
72 *Ibid.*, Article 20.
73 Biomedicine Convention, *supra* note 1, preamble.
74 *Ibid.*, Article 1.
75 *Ibid.*, Article 2.
76 *Ibid.*, Article 4.

welfare of the individual that such interventions, as part of research or care, take place.

The view behind these strong values and fundamental principles of the European bio law is somewhat complex. One of the significant critiques that the Biomedicine Convention has received is the fact that it places human dignity at its core, and dignity is informing different solutions presented in the convention. However, at the same time, nowhere in the convention is this notion defined.[77] It is true that the concept of human dignity is notoriously difficult to define.[78] However, failure to elaborate, at least in a functional way regarding values it accounts for, opens up room for questions and uncertainties regarding exactly what facets of human dignity that the ban set out in Article 13 upholds.

Regarding the respect of an individual as one of the central pillars of the Biomedicine Convention, at least two facets emerge. First, that of the gamete donor and prospective parent. Second, that of the prospective child. As the norms of the convention apply to everyone, the protection of a prospective child is not precluded.[79] However, then, freedom from a particular genetic condition is ranked lower as a possibility to be born with a particular genetic condition.[80] This line of reasoning could easily be rejected through systemic interpretation of the convention in regard to genetic conditions to which other biology and medicine applications are permissible under the convention.[81] What remains then is that this respect anchors in the control over gametes and embryos, as well as an embodiment of collective values — such as avoidance of eugenics — in the notion of "respect" and allowing that to trump any interest in making individually beneficial decisions, which could be at the detriment of society, on whatever scale.

Additionally, the Biomedicine Convention is not only an instrument to safeguard individual rights in the application of biology and medicine. It is also an instrument that seeks to safeguard humanity, at least, within the European regional fora. In this light, heritable interventions in the human genome, as banned by Article 13, are regarded as a risk to humanity, even if the application is health-related and thus entails positive individual health effects on the

77 V.L. Raposo, 'The Convention of Human Rights and Biomedicine Revisited: Critical Assessment', *The International Journal of Human Rights* 20 (8) (2016) 1277–1294, p. 1283.

78 For insights *see* C. McCrudden, 'Human Dignity and Judicial Interpretation of Human Rights', *European Journal of International Law* 19 (4) (2008) 655–724.

79 See Biomedicine Convention, *supra* note 1, Article 1; and Explanatory Report to the Biomedicine Convention, *supra* note 37, paras 16–19.

80 It should be noted that this question is fundamentally different from abortion debates.

81 See permissibility of predictive genetic tests under the convention. Biomedicine Convention, *supra* note 1, Article 12.

prospective child. If, however, the endangerment relates to, for example, concerns over eugenics, they are qualitatively different from restrictive applications of technology in isolated cases. This begs the difficult question added here as a side note, on the chosen means to tackle the challenges, and in particular, whether carefully regulated applications of the technology could lead to the materialisation of these fears.

Additionally, the convention sets forth a number of principles and rights relevant for scientific research and medical care. It is not sufficient that health-related gene editing interventions could be anchored into the abovementioned pillars, they also need to comply with other norms. One such is the requirement for the health research and care to be in line with professional standards.[82] Thus, anchoring the health-related interventions in the fundamental pillars of the convention will not, in itself, be enough for enabling the interventions in research or care. Also, key actors, researchers and medical doctors need to be of the view that the intervention is compatible with the professional standards. Ultimately, it needs to be compatible with the research participant's and the patient's perspective under the clauses of informed consent or assent, so that the interventions can be applied in scientific research or care. While these largely relate to the application of techniques, once the ban is lifted, a lack of acceptance of the intervention, among the researchers, medical doctors and patients, risks depriving the lifting of the ban from its purpose.

5 Lifting the Ban Set Out in Article 90 of the Clinical Trials Regulation

5.1 *On the Procedure of Lifting the Ban*

Deregulation of a field is not regulated in the EU law in any particular way. Even though this phenomenon is rather unique, as it essentially requires the EU to take a step back from the depth of the integration, it has previously happened. An example of this is the area of genetically modified organisms.[83] Generally, there could be different reasons for deregulation of a field. One such reason is that the EU integration measure has not yielded the intended results. Another such reason is an arguable oversight of the legislature in failing to accommodate

82 Biomedicine Convention, *supra* note 1, Article 4.

83 See Directive (EU) 2015/412 of the European Parliament and of the Council of 11 March 2015 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory Text with EEA relevance, OJ L 68, 13.3.2015, p. 1–8 , recital 6.

in the secondary law the freedom that the Treaty on the Functioning of the European Union (TFEU) allows for the Member States. Another could be changes in reasons that underpin the ban. Even though the reasons behind lifting a ban could affect modalities within the procedure,[84] both of the basis of the Clinical Trial Regulations require a measure within the ordinary legislative procedure.

Within the ordinary legislative procedure, the European Commission has the task to submit a proposal to the European Parliament and the Council.[85] Additionally, in regard to the measures under Article 168(4)(c) TFEU, a consultation with the Economic and Social Committee and the Committee of the Region shall take place.[86] The European Commission, as a watchdog of the treaties and as the actor of furthering EU interests, shall put forward a proposal when it believes that it is in the interest of the EU that a ban on clinical trials involving germline gene editing be lifted.[87]

Following the proposal of the European Commission, the European Parliament — the representatives of the EU citizens — begins by adopting its position and communicating it to the Council — representatives of the EU Member States.[88] The Council can then either approve the Parliament's position motivating its reasons,[89] or adopt its own position.[90] In both instances, the Commission shall be informed. The adoption of its own position leads to the second reading and further dialogue between the two actors. That process can take up to three readings and involves a Conciliation Committee as a platform to work out the disagreements between the two parts.[91]

The European Parliament is composed of representatives of the EU's citizens, and it has the mandate to act in their interests.[92] The Council, however, has been assigned the task of carrying out policymaking and coordinating functions as laid down in the Treaties. It consists of a representative of each Member State at the ministerial level, who may commit the government of the Member State in question and cast its vote.[93] So, there should also be a

84 C-482/17 *Czech Republic v Parliament and Council*, ECLI:EU:C:2019:1035, para. 42.
85 Consolidated version of the Treaty on the Functioning of the European Union OJ C 326, 26.10.2012, pp. 47–390. Article 294(2) TFEU.
86 *Ibid.*, Article 168(4)(c).
87 Consolidated version of the Treaty on European Union OJ C 326, 26.10.2012, pp. 13–390, Article 17.
88 TFEU, *supra* note 85, Article 294(3).
89 *Ibid.*, Article 294(4) and (6).
90 *Ibid.*, Article 294(5)–(6).
91 *Ibid.*, Article 294(10)–(12).
92 TEU, *supra* note 87, Article 14.
93 *Ibid.*, Article 15.

prevailing opinion that lifting the ban set out in the Clinical Trials Regulation is the way to go. There must be a considerable interest in furthering the changes, and this interest needs to stem from different directions and reach a considerable threshold. Firstly, there needs to be an interest from the EU for this to happen. Secondly, there must be a support of the "people's representatives," and also the EU's policy agreement steered by the representatives of the Member States sitting in the Council.

5.2 *On the Context of Lifting the Ban*

Article 114 TFEU enables the EU to legislate in order to remove actual potential hinders to the internal market,[94] and in the context of germline editing, particularly, free movement of goods and services is of interest. Any measure that is prepared by the European Commission under this provision is required to have as a base a high level of protection in the fields of health, safety, environmental protection and consumer protection.[95] This needs to be done, considering particularly any new development, which is to be based on scientific facts.[96]

According to the established jurisprudence of the CJEU, legislation through Article 114 TFEU has some particularities that need to be accounted for. Since *Tobacco Advertising 1* case, it is well-established that the provision cannot be used to harmonise non-market objectives, if a market objective is lacking.[97] However, it is equally well established that if the divergences in the market exist (actual or potential), i.e. if the market precondition to engage Article 114 TFEU is met, the legislature can also make choices under Article 114(3) TFEU, including if those choices are decisive.[98] Once the field has changed, the EU legislature is not prevented from amending the existing legislation, to account for those changes.[99]

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94 C-482/17 *Czech Republic v Parliament and Council supra* note 83 para 35. On the insufficiency of mere disparities between the national laws, *see* para 58 (and cited case law therein) in C-547/14 *Philip Morris Brands SARL and Others v Secretary of State for Health*, ECLI:EU:C:2016:325.

95 TFEU, *supra* note 85, Article 114(3).

96 *Ibid*., Article 114(3).

97 C-376/98 *Federal Republic of Germany v European Parliament and Council of the European* Union, ECLI:EU:C:2000:544.

98 C-482/17 *Czech Republic v Parliament and Council, supra* note 83, para. 36.

99 *Ibid*., paras 38–39. See also C-491/01 *The Queen v Secretary of State for Health, ex parte British American Tobacco* (*Investments*) *Ltd and Imperial Tobacco Ltd.*, ECLI:EU:C:2002:741 paras 77 and 78, as well as C-58/08 *The Queen, on the application of Vodafone Ltd and Others v Secretary of State for Business, Enterprise and Regulatory Reform* (*Vodafone and Others*), ECLI:EU:C:2010:321, para. 34. *See* also C-477/14 *Pillbox 38* (*UK*) *Limited, trading*

The consideration of lifting the existing ban on human germline gene editing in the EU, thus, requires at least two acknowledgements. First, tolerance of the possibilities that could be opened up through the divergences. This stems from two considerations. The already noted inherent nature of Article 114(1) TFEU that allows legislation in that regard. Interlinked to that, the possibilities of the Member States to invoke, for example, health or morality-related considerations for the purposes of putting obstacles to the free movement nationally.[100] Secondly, acceptance of the measure under Article 114(3) TFEU, and in particular that the lifting of the ban is considered compatible with the requirement for a high level of health and safety protection. While it is well-established that the EU legislature enjoys discretion under this provision,[101] it is difficult to see that a measure that is contrary to this standard would be tolerable under the legislature's discretion. In so far as health would be concerned, such a measure would be incompatible with the high level of health within the EU under Article 168(1) TFEU[102] as well as health as protected under Article 35 of the CFREU,[103] and general principles of EU law.[104]

Article 168(4)(c) enables measures for setting high standards of quality and safety for medicinal products. A possibility to legislate under this provision is a public health asset of the Lisbon Treaty and could be said to reflect the until-Lisbon established praxis to address public health concerns through an internal market regulation. At its very basic level, it required that the germline editing not pose risks to safety. In healthcare, it is not a question of an absolute safety, but a question of positive risk-benefit ratio that needs to be demonstrated.

Any EU law measure shall comply with the fundamental principles of EU law and the rights and principles set out in the CFREU. For example, the CFREU does not mention human germline gene editing, however, prohibits

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as Totally Wicked v Secretary of State for Health, ECLI:EU:C:2016:324, para. 116, where the CJEU notes that the EU could be required to act in the changing circumstances.

100 See in that regard, e.g., TFEU *supra* note 84 Article 36, morality concerns, e.g., C-36/02 *Omega Spielhallen- und Automatenaufstellungs-GmbH v Oberbürgermeisterin der Bundesstadt Bonn*, ECLI:EU:C:2004:614. *See* also TFEU, *supra* note 84, Article 114(4).

101 See B. de Witte, 'Non-Market Values in Internal Market Legislation', in: N.N. Shuibhne (ed.), *Regulating the Internal Market* (Cheltenham: Edward Elgar, 2006), pp. 61–86.

102 For an explicit link between Article 114(3) TFEU and Article 168(1) TFEU see para. 61 in C-547/14 *Philip Morris Brands SARL and Others v Secretary of State for Health*, *supra* note 88.

103 See Charter of Fundamental Rights of the European Union OJ C 326, 26 October 2012, pp. 391–407, Article 51(1).

104 C-547/14 *Philip Morris Brands SARL and Others v Secretary of State for Health*, *supra* note 96, para. 62.

'eugenic practices, in particular those aiming at the selection of persons'.[105] Moreover, Article 1 of the CFREU safeguards human dignity. Hence, similar to the Biomedicine Convention, both of these values would need to be interpreted in a way to be compatible with germline gene editing for health-related purposes. Unlike Article 13 in the Biomedicine Convention, the prohibition of eugenic practices is set out much more broadly and vaguely in the context of germline gene editing. Hence, one could argue that the EU legislature is in a somewhat better position to push for changes than the Council of Europe is.

6 One at a Time or Both at the Same Time?

Both of the European regional legal orders set considerable restrictions for human germline gene editing to enter into the domain of clinical research and, subsequently, care. At the same time, neither the ban set out in Article 13 of the Biomedicine Convention, nor Article 90 of the Clinical Trials Regulation is set in stone. There are rather straightforward procedures within each of the legal orders that allow for the two bans to be lifted. The procedural requirements in both of the European regional legal orders require considerable agreement between different representatives of the states, representing different groups. There is room for tensions at the national level and between indifferent actors in the same country, and between states, and between states and institution representatives. Additionally, as the analysis in this chapter shows, the bans are located in a rather complex legal environment, and there are considerable thresholds that need to be met in order for the bans to be lifted.

Under the Biomedicine Convention, the ban *inter alia* seeks to uphold interest in safeguarding humanity. Hence, it is required that the understanding of risks associated with how heritable genome editing challenges that are reassessed, and a diametrically opposite conclusion of that which is valid today, is reached. Such an approach will inevitably open up discussions regarding the point of adopting the bans in the first place, and justification of the early critique of the bans. There is, however, a contra-argument to it, namely, the increased knowledge about the intervention, and consequently also control over it as well as minimisation of the negative effects it could create for the society.

The EU legal order, at least *expressis verbis*, does not prescribe such strong values that lie at the core of the prohibition. What has been traceable is that the prohibition reflects EU policy in the field. This, however, does not lead to a conclusion that the procedure for lifting the ban is much more straightforward.

105 CFREU, *supra* note 103, Article 3(2)(b).

To begin with, the intervention needs to be regarded as safe. Additionally, the Member States enjoy certain room for managing issues that can be anchored in the morality arguments, and the EU can be expected to tolerate that, provided, however, that the national legislation is overall coherent regarding the moral values it seeks to uphold.[106] Moreover, a ban aiming at safeguarding the germline is also set out in other EU legal acts, such as the mentioned Biotech Directive and the Research Regulation.[107] It could be argued that a more comprehensive action, rather than merely de-regulation of the field of clinical trials, will be necessary, and the restrictions set out in those laws will also need to be reconsidered.

The two bans, which are in effect in both of the European regional legal orders, are not mutually related. Therefore, one could question whether it suffices that one ban is lifted, whereas the other remains in effect. There is no requirement that lifting of the bans shall occur simultaneously. It is, however, neither practical nor sustainable from the state external accountability point of view and the doctrine of legal pluralism. It also cannot be argued to be possible if an account of the strong but not expressly regulated ties between the two legal orders is given.

The Council of Europe and the EU share the same set of 27 Member States. Not all Member States of the EU are parties to the Biomedicine Convention, but a significant portion of them are parties. A choice not to coordinate the actions and lift the two bans simultaneously risks resulting in a situation where a state has conflicting legal obligations. Some conflicts can be easier to resolve, but some are not as easy. For example, if the Biomedicine Convention lowers the standard and the EU retains it, then the EU Member States have a chance to envisage a higher level of protection under the Biomedicine Convention. However, if the EU lowers the standard, a question emerges as to whether it would then allow Member States to retain higher standards to remain in line with the Biomedicine Convention obligations. On the one hand, as has been already noted, it is a question of moral values where the EU has been generous in leaving leeway to the Member States. On the other hand, it needs to be acknowledged that it will end up being a market question, which is the EU's interest. Considering the free movement possibilities even under differing national laws, there could be limited room for national unilateral exemptions. This could suggest that the question of human germline gene editing for healthcare purposes is of a European concern. Hence, urgent, fruitful, multilevel policy discussions are needed on top of the dialogue with stakeholders and society.

106 See in that regard C-165/08 *Commission of the European Communities v Republic of Poland* ECLI:EU:C:2009:473.

107 See *supra*, note 51.