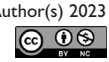
Article

MEDICAL LAW INTERNATIONAL

Medical Law International
2023, Vol. 23(1) 44–70



DOI: 10.1177/09685332231154586
journals.sagepub.com/home/mli


The EU legal framework on clinical trials directed to therapeutic germline gene alteration: A critical and systematic analysis

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Abstract

Interventions in the human germline, whether for purposes of therapy for a hereditary disease or for purposes of enhancement, are controversial. While enhancement is almost unanimously rejected, therapy-oriented intervention is not a priori regarded as unacceptable. The legal discussion so far has focused primarily on the questions of whether manipulation of the embryo's germline is permissible or whether the genetic manipulation of germ cells and the use of these germ cells for embryo generation is permissible. Up to now, the upstream questions regarding the systematic germline therapy development in clinical trials have been ignored, including questions as to whether the development of germline therapy would be legally permissible within the European Union framework of clinical studies. This article highlights the legal issues connected with the clinical development of germline intervention, provides an overview of the various answers to these legal questions, and indicates where further research and discussion are needed.

Keywords

Clinical trials, embryo status, enhancement, germline therapy, medicinal products

Received 3 February 2022; Revised 1 November 2022; Accepted 8 November 2022.

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Introduction

The advanced use of genome-editing methods has revitalized the debate on targeted intervention in the human germline. Compared to somatic gene therapies,[1] other medico-ethical and legal issues arise for germline therapies[2] because, for example, germline alterations are not limited to the treated individual. To the best of the authors' knowledge, officially, no clinical studies on targeted germline intervention have yet been applied for in the European Union (EU).

However, the question is whether the current EU legal framework is ready to face the challenge that will arise the day after appropriate animal experiments someone proposes a clinical trial involving a modification of the human germline accomplished by altering the DNA of embryos (sections 'Is regulation (EU) No 536/2014 in conjunction with directive 2001/83/ec applicable to germline gene interventions in embryos?' to 'The impossibility of legally binding informed consent as legal limit for germline interventions in embryos in vitro?'), using altered human germ cells (section 'Systematic development of germline interventions in adults'), or by targeted modification of the germline of born humans (section 'Development of germline therapeutics using genetically altered gametes'). Of course, this is unlikely to happen soon, since the available technology still suffers from serious issues related to safety and efficiency. The alleged germline interventions performed in China using CRISPR technology may draw attention to the topic but would not likely meet the current EU safety and quality requirements for gene therapy interventions.

However, once the technical obstacles disappear, respectively, provided that preclinical studies in animals suggest feasibility in humans as well, someone within the EU could ask for permission to use genetically altered germ cells, to transfer genetically modified embryos into a woman's womb, or to alter the germline of adults. These constellations therefore do not concern the legal issues in individual, singular therapeutic attempts, but rather the issues regarding the systematic development of such therapeutic efforts, especially in the context of clinical trials, which may contain both treated (verum) groups and control groups. In the context of germline interventions – comparable to all other pharmaceutical interventions – it is important to distinguish between the medicinal product, with which the germline intervention is specifically induced, and the result (successful germline therapy).

The discourse on the issue of germline intervention, however, has so far mainly focused on questions of the ethical justifiability of such interventions as well as on legal questions regarding single germline alterations in embryos, germ cells, and born

1. Somatic gene therapy is the method of introducing RNA or DNA into somatic cells (cells that do not produce the eggs or sperm) to change their genetic material and thereby cure genetically caused diseases causally. Somatic gene therapy aims to cure a disease only in the patient, not in the patient's descendants.
2. Germline therapy involves the modification of genes of germ cells or gametes (egg, sperm). Thereby, germline therapy alters the genome of future generations and could at least theoretically counteract hereditary diseases.

subjects.[3] The discussion has not dealt in the same depth with the upstream legal issues of whether or not the systematic development of germline gene therapeutic approaches would be permissible under the current EU pharmaceutical legislation. If this upstream technical, clinical development is already legally excluded, then this must be (legally) considered if one day germline therapy is to be permitted. The legal ability to authorize a therapy without the appropriate regulatory permissions required to develop that therapy would be useless, as the therapy in question could not be developed in compliance with the law. In a multi-level legal system such as the EU, it is also important that the relevant legal provisions in the individual competence areas and Member States do not conflict, as this would also prevent the actual provision of a therapy.

Considering the large number of publications on the one hand on ethical and legal issues concerning germline intervention and on the other hand on clinical trials, in particular on Regulation (EU) No. 536/2014 which is the central legal document for clinical trial requirements in the EU, it is surprising that neither the specific questions of the systematic development of germline therapeutic approaches within pharmaceutical legislation nor the significance of the legal status of the embryo does play a role in these publications. The ethical and legal discourse to date has been mainly limited to reciting the wording of Art. 90 Regulation (EU) No. 536/2014 'No gene therapy clinical trials may be carried out which result in modifications to the subject's germline genetic identity', but without examining the legal status of the embryo therein and thus the extent to which this prohibition actually prohibits clinical trials with embryos to develop germline interventions.

This article is meant first to address unanswered questions of the systematic development of germline therapy such as the legal status of embryos (in vitro) and the significance of this status for the legal feasibility of clinical trials. Second, this article aims to help answer these open legal questions by providing an analysis of the current EU legal framework relating to human germline gene altering in clinical trials. With regard to the merely ethical questions of germline interventions, reference is made to the extensive literature.[4] Ethical arguments – as well as, among others, also technical or legal

3. For example C. Brokowski and M. Adli, 'CRISPR Ethics: Moral Considerations for Applications of a Powerful Tool', *Journal of Molecular Biology* 431 (2019), pp. 88–101; I. Macpherson, M. V. Roqué and I. Segarra, 'Ethical Challenges of Germline Genetic Enhancement', *Frontiers in Genetics* 10 (2019), p. 767; G. de Wert et al., 'Human Germline Gene Editing. Recommendations of ESHG and ESHRE', *Human Reproduction Open* 26 (2018), pp. 445–449.
4. A. Caplan, 'Getting Serious about the Challenge of Regulating Germline Gene Therapy', *PLOS Biology* 17 (2019), e3000223; B. S. Coller, 'Ethics of Human Genome Editing', Annual *Review of Medicine* 70 (2019), pp. 289–305; Francois Bayleis, *Altered Inheritance: CRISPR and the Ethics of Human Genome Editing* (Cambridge, MA: Harvard University Press, 2019); I. De Miguel Beriain and T. Ishii, 'Should Gene Editing Replace Embryo Selection Following PGD? Some Comments on the Debate Held by the International Society for Prenatal Diagnosis', *Prenatal Diagnosis* 39 (2019) pp. 1170–1172; Macpherson et al., 'Ethical Challenges of Germline Genetic Enhancement'; T. Ishii, 'The Ethics of Creating Genetically Modified Children Using Genome Editing', *Current Opinion in Endocrinology, Diabetes and Obesity* 24 (2017) pp. 418–423; Jürgen Habermas, *The Future of Human Nature* (Cambridge: Polity Press, 2003); J. Harris,

arguments – in favour of or against a clinical trial are then taken into account, for example, in the context of the authorization application based on corresponding legal requirements (e.g. Art. 4 Regulation (EU) No. 536/2014).

Preliminary legal steps: identifying legislation and relevant jurisdiction on germline gene altering within the EU

Identifying the relevant international non-EU law

First, legal documents of the Council of Europe (CoE), here the 'Convention for the Protection of Human Rights and Fundamental Freedoms' (ECHR) as well as the 'Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine' (otherwise known and thereinafter as Oviedo Convention), could be relevant.[5]

With regard to the legal relevance for the development of germline therapy, it should be noted that the CoE, as an international organization, is legally independent of the EU. Although EU Member States are also Member States of the CoE and EU Member States have also ratified the ECHR, the EU has not yet joined the ECHR. Moreover, the ECHR itself does not contain provisions that explicitly address germline therapy. The ECHR includes a general provision in Art. 2(1), according to which the right to life of every human being is protected by law. Given the protective nature of this provision in favour of the citizen against the state, it could at most be asked to what extent this provision can justify legal prohibitions with regard to germline therapy in the Member States of the CoE, provided that germline therapy (as the only option) would be necessary for the survival of a specific person and/or to prevent this person from suffering due to illness. However, it is questionable whether such cases exist, since the corresponding genetic diseases can also be treated somatically, that is, without targeted germline intervention. Moreover, there is no question that therapies in which the alteration of the germline may occur merely as a side effect (radiotherapy, chemotherapy) are not prohibited because they (may) affect the germline.[6] Rather, such therapies are permissible if they pass the general risk-benefit assessment, taking into account the germline effect.

'Germline Manipulation and Our Future Worlds', *American Journal of Bioethics* 15 (2015), pp. 30–34; A. Berg, T. Minssen, S. Holm, M. Horst, K. Mortensen and B. L. Møller, 'Cutting Edges and Weaving Threads in the Gene Editing (Я)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns', *Journal of Law and the Biosciences* 5 (2018), pp. 35–83; E. Lanphier, F. Urnov, S. E. Haecker, M. Werner and J. Smolenski, 'Don't Edit the Human Germline', Nature, 519 (2015), pp. 410–411; B. D. Baltimore, P. Berg, M. Botchan, D. Carroll, R. A. Charo, G. Church, J. E. Corn, et al., 'Biotechnology. A Prudent Path Forward for Genomic Engineering and Germline Gene Modification', Science 348 (2015), pp. 36–38; J. Savulescu, J. Pugh, T. Douglas and C. Gyngell, 'The Moral Imperative to Continue Gene Editing Research on Human Embryos', *Protein & Cell* 6 (2015), pp. 476–479.

5. Tamara K. Hervey and Jean V. McHale, *European Union Health Law: Themes and Implications* (Cambridge: Cambridge University Press, 2015), pp. 30–70.
6. Council of Europe, 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 (European Treaty Series No. 164, recital 92, Oviedo, 1997).

The extent to which embryos in vitro (especially in the experimental stages for the development of germline therapies) are protected against destruction by Art. 2(1) ECHR has not yet been finally resolved.[7] In previous proceedings relating to the protection of embryos against destruction, the European Court of Human Rights (ECtHR), as the court of the ECHR, has left open the legal question of when human life begins for the purposes of Art. 2 ECHR and also whether embryos are entitled to human dignity. Due to the different views of CoE Member States on the legal status of embryos (both in vitro and in vivo), the ECtHR has emphasized that legislation on this is within the sovereignty of the Member States and that no common position on this can be established by the ECtHR.[8] Therefore, the ECHR and the ECtHR case law have no practical relevance to the development of germline therapy, and in particular do not result in prohibitions on germline intervention.

In response to the progress of medical research, the CoE has developed the Oviedo Convention, which serves as international instrument aiming to prohibit the misuse of innovations in biomedicine and to protect human dignity.[9] Its scope in human medicine covers, among other things, genetic engineering procedures and reproductive medicine. According to Art. 13 of the Oviedo Convention, an intervention seeking to modify the human genome may be carried out only for preventive, diagnostic, or therapeutic purposes and only if this intervention is not aimed to cause a change in the genome of descendants. Research on embryos in vitro is permitted (Art. 18(1)), while only the generation of embryos for research purposes is prohibited (Art.18(2)). Thus, research on donated supernumerary embryos is permitted in accordance with the requirements of the Oviedo Convention. Moreover, since there is no explicit prohibition in the Convention with regard to targeted germline modification in such embryos, this means that targeted germline manipulation is permissible in in vitro embryos.[10] The question that then follows is whether Art. 13 of the Oviedo Convention prohibits any gene modification of embryos that would be passed on to future generations. To answer this, the following question should be asked: What legal reasons could forbid a preventive genetic (germline) therapy on an embryo, if just by this intervention the born human being emerging from the embryo would be spared from a disease. Since targeted (preventive, diagnostic, and therapeutic) germline intervention in born human being is already not permitted (cf. Art. 13), then in the same legal system this can legally be denied to the embryo if the born human being and the embryo have the same legal (subject) status. If both have the same status, then the transmission of a germline change to descendants needs to be denied in both scenarios.

7. M. M. Spaander, 'The European Court of Human Rights and the Emergence of Human Germline Genome Editing', *European Journal of Health Law* 29 (2022), pp. 458–483.
8. Cf. ECtHR, Case of Vo v. France, Application no. 53924/00, Judgement 8 July 2004, recital 82.
9. R. Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law', *Journal of International Biotechnology Law* 2(4) (2005), pp. 133–143.
10. 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), pp. 226–232.

Moreover, the protection of the 'human genome' of the Oviedo Convention is not limited to born humans. This is due to the fact that the protective provisions of the Convention are not limited to born human beings.[11] According to the Explanatory Report, the Oviedo Convention aims to address concerns about biomedical developments at three levels: the level of the individual; the level of the society; and the level of the human species.[12] Therefore, Art. 13 can also protect the human genome of prenatal developmental stages against unwanted changes in the sense of the Oviedo Convention by basing the protection upon the human species (and its human genome). In this case, the legal status of the embryo as a prenatal developmental form is irrelevant. However, if the protection of the human genome is to be motivated by the level of the individual, one cannot avoid thinking about the legal status of the embryo. In doing so, one will then have to assume, as outlined in the following text, that the embryo must be a subject to be protected as an individual; an individual that is not also a subject is contradictory.

However, it must be taken into account that the Oviedo Convention has not yet been ratified by all Member States of the CoE.[13] States that have not ratified the Convention are therefore not committed to the Convention's exclusion of germline intervention. In addition, any state party can terminate the convention at any time – without giving reasons (Art. 37) and would thus no longer be bound. Furthermore, any state intending to ratify the Oviedo Convention in the future may, in accordance with Art. 36, declare reservations with respect to individual rules of the Convention – thus also, for example, with respect to Art. 13 – whereby their content in the state concerned also does not come into effect. In sum, this means that the Oviedo Convention does not permit the systematic development of germline therapy. Therefore, if states that have ratified the Oviedo Convention want to develop germline therapy, these states would either have to withdraw from the Convention or at least formulate a reservation regarding Art. 13 of the Convention.[14] Another option would be to amend the Oviedo Convention to allow the development and use of germline therapy. Thus, the question of the legal admissibility of germline therapy under the Oviedo Convention is an example of a legal question on germline therapy that is upstream of the questions on germline therapy under pharmaceutical law and clinical trial law.

Finally, the UNESCO's 'Universal Declaration on the Human Genome and Human Rights' (1997) should be mentioned. Its Art. 24 says that interventions in the human germline may contradict human dignity. However, it does not explicitly state a violation

11. B. C. van Beers, 'Rewriting the Human Genome, Rewriting Human Rights Law? Human Rights, Human Dignity, and Human Germline Modification in the CRISPR Era', *Journal of Law and the Biosciences* 7(1) (2020), pp. 1–36, p. 25.
12. Council of Europe, 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.
13. https://www.coe.int/en/web/conventions/full-list?module=signatures-by-treaty&treatynum=164 (accessed 17 October 2022).
14. V. L. Raposo, 'The Convention of Human Rights and Biomedicine Revisited: Critical Assessment', *The International Journal of Human Rights* 20(8) (2016), pp. 1277–1294.

of human dignity, nor does it prohibit germline intervention. Merely a review request to the International Bioethics Committee (IBC) is expressed. In October 2015, this committee recommended a moratorium on germline modification through genome editing by the Member States.[15] However, neither the mentioned UNESCO Declaration nor the Report of the IBC is legally relevant for the systematic development and application of germline therapy. This is due to the fact that this UNESCO document is 'only' a declaration that is not binding under international law. Therefore, also the IBC Report cannot have any legal effect on grounds of this UNESCO declaration.

Identifying sources of EU law applicable to systematic germline gene altering

The legal analysis of the EU law must begin with Art. 3(2)(b) of the EU Charter of Fundamental Rights (CFR), which bans, in general, eugenic practices in human beings. However, the (limited) scope of the Charter must be respected. According to Art. 51 CFR, the Charter only binds EU institutions, bodies, and agencies. According to this, the legislation and action of the Union must be measured by the standard of the CFR. Furthermore, the CFR binds the Member States only insofar as they are implementing and executing EU law. Therefore, the CFR does not apply to purely national issues governed by national law. Here, only ratified international law and the constitutional rights of the Member States as well as of the Member States' duly made laws are the standard of assessment.

Second, the restriction mentioned in the CFR regarding eugenics only applies to a specific application of germline gene altering, that is, altering aimed at enhancement.[16] But the question of when a deliberately induced genetic change counts as an enhancement can and must be debated. Is the correction of the genetic basis for a hereditary disease (already) a eugenic measure – an enhancement – or are eugenic measures only those that go beyond the typical characteristics of today's humans? However, this debate does not need to be addressed here, as this article deals only with interventions in the germline that are undisputedly related to the therapy of a genetic disease. Therefore, it should be pointed out that the CFR – if it would be applicable as such at all – does not include an explicit prohibition for therapeutic interventions into the germline.

Within the EU secondary legislation neither the EU Release Directive (2001/18/EC) on the release of genetically modified organisms (GMOs) nor the System Directive (2009/41/EC) on the contained use of genetically modified microorganisms (GMMs) prohibits germline therapy as such or germline therapeutics. The legal significance of both directives

15. International Bioethics Committee, Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights (Paris, 2015); A. Nordberg et al., 'Regulating Germline Editing in Assisted Reproductive Technology: An EU Cross-Disciplinary Perspective', *Bioethics* 34(1) (2020), pp. 16–32.
16. I. De Miguel Beriain, 'Legal Issues Regarding Gene Editing at the Beginning of Life: An EU Perspective', *Regenerative Medicine* 12 (2017), pp. 669–679.

– if necessary together with the provisions of the pharmaceutical legislation[17] – is limited to the risk analysis of GMOs and/or GMMs that may be contained in a medicinal product.[18] Rather, the Release Directive clarifies in Art. 2(2) that humans are not GMOs in the sense of this Directive, even if the human organism contains genetically modified cells. By this exclusion, the provisions of the Release Directive may not be applied to humans. In addition, the Release Directive contains further exemptions in Art. 5(1), so that, for example, medicinal products containing GMOs do not require a release authorization under the Release Directive.

The System Directive (2009/41/EC) establishes measures by which human health and the environment are to be protected. The System Directive does not explicitly exclude humans in its GMM definition. However, the Directive excludes humans because the Directive only covers microorganisms. In addition, the Directive specifies in Art. 2(e) that humans are users of GMMs. With regard to the development and application of germline therapy, both directives therefore relate at most to genetic engineering of individual cells, in particular of germ cells in vitro. However, as soon as these cells are transferred to a human being, the above-mentioned provision must be considered, according to which the human being is never a GMO or GMM in the legal sense.

But what about embryos in vitro that have been genetically modified, especially with regard to their germline? Are these legally GMOs or GMMs? The law does not explicitly address this. Directive 2001/18/EC explicitly excludes humans, and Directive 2009/41/EC refers only to microorganisms and embryos can hardly be considered microorganisms. However, this question can remain unanswered at this point, because at the latest with the transfer of a genetically modified embryo into the uterus, the autonomy of this embryo in the context of the genetic engineering legislation is missing. The focus is only on the pregnant woman, who is neither a GMO nor a GMM. Moreover, this question also no longer arises for the person born later due to the mentioned exemption rule. Even if a (in the germline) genetically modified embryo was considered a GMO or GMM, its transfer to a woman to create a pregnancy would not be covered by the Release Directive, since Art. 5(1) generally excludes the application of its provisions for the release of medicinal substances and compounds for human use consisting of, or containing, a GMO or combination of GMOs.

Furthermore, Regulation (EC) No 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products (ATMPs, ATMP Regulation), with which, among other things, Directive 2001/83/EC on the Community code relating to medicinal products for human use has been amended, does not contain any prohibitions on germline therapy or germline therapeutics, but establishes the technical requirements for safety, quality, and efficacy for the approval of medicinal products for human use

17. A. Mahalatchimy et al., 'Framing and Legitimating EU Legal Regulation of Human Gene-Editing Technologies: Key Facets and Functions of an Imaginary', *Journal of Law and the Biosciences* 16 (2021), p. 9.
18. EMA – Committee for Medicinal Products for Human Use (CHMP), *Guideline on Environmental Risk Assessments for Medicinal Products Consisting of, or Containing, Genetically Modified Organisms (GMOs), Doc. Ref. EMEA/CHMP/BWP/473191/2006 – Corr.* (London, 2006).

(and thus also for germline therapeutics). Regulation (EC) No 1394/2007 and Directive 2001/83/EC do not prohibit germline therapy as such, nor germline therapeutics,[19] but establish, with respect to the medicinal product used, the legal character of that medicinal product (i.e. 'ordinary' medicinal product, gene-therapy medicinal product, etc.).[20] Based on this, the specific technical requirements for entering the market, including the requirements for clinical trials, are set out.

Furthermore, one can consider whether the alteration of the germline would fall under the umbrella of the EU Tissues and Cells Directive (Directive 2004/23/EC). However, this is also not the case. Art. 1 of the EU Tissues and Cells Directive sets forth standards of quality and safety for human tissues and cells intended for human applications to ensure a high level of protection of human health. According to Art. 2, this directive shall apply to the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications.

However, the procedures for modifying the germline do not fulfil the conditions for the application of this Directive in cases of germline gene altering in embryos in vitro. One would first have to argue that embryos in vitro fall within the scope of the Directive. However, this is not compatible with recital 7 of the Directive, which speaks only of embryonic stem cells (thus pluripotent entities), but not of embryos (totipotent entities). Even if embryos were included within the scope of the Directive, their genetic modification would have to (a) constitute a processing of these entities and (b) be intended for the medical treatment of a human being. The transfer of an embryo to a woman should therefore be considered as 'medical treatment'. The woman would have to be cured of a disease by the transfer of the embryo. What disease would this be? If one interprets cases of unwanted childlessness as sickness (within the meaning of the Directive), then the pregnancy brought about with medical assistance may be medical treatment. It should be noted that the medicinal product would be an embryo, that is, a legal entity (cf. section 'Wrong status – the embryo as a legal subject and not as a legal object?'). All this should already show that this argument is absurd. It is all the more absurd if one considers the case of a medically assisted induced pregnancy that is only undertaken to carry out germline editing, with no pathological indication of unwanted childlessness among the parents and no indication of a hereditary disease in the embryo. This is where the cases of enhancement might be located.

Apart from this, there are only two EU legal documents that address the issue of germline alterations in a more direct way by ordering legal consequences in connection with germline interventions. The first is the EU Directive on Biotechnological Inventions

19. Mahalatchimy et al., 'Framing and Legitimating EU Legal Regulation of Human Gene-Editing Technologies', p. 26.
20. T. Faltus, 'Medicinal Genome Editing in Germany – Tensions between Safeguarding and Circumventing Ethical and Legal Standards', *Loyola of Los Angeles International and Comparative Law Review* 43 (2021), pp. 227–249; S. Slokenberga, 'What Would It Take to Enable Germline Editing in Europe for Medical Purposes?', *European Journal of Health Law* 29 (2022), pp. 521–542.

(Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions). Its Art. 6(b) states that 'processes for modifying the germline genetic identity of human beings shall be considered unpatentable'. Second, Art. 90 of 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 (Regulation (EU) No 536/2014 thereinafter) reads as follows: 'No gene therapy trials may be carried out which result in modifications to the subject's germline genetic identity'. The provisions of the Directive have been incorporated into the EU Member States in their respective national legislation, and the provisions of the Regulation are directly applicable in all EU Member States.[21] In accordance with CFR requirements, EU Member States must therefore comply with the CFR when carrying out the requirements of the Directive and the Regulation, and EU authorities must comply with them. In contrast to the CFR, neither the Directive nor the Regulation refers to eugenic interventions, but only to modifying the germline identity of human beings. It therefore needs to be investigated whether these two different wordings regarding germline alterations of the CFR on the one hand and Directive 98/44/EC and Regulation (EU) No 536/2014 on the other hand also permit different forms of (therapeutic) germline interventions in embryos, born humans, and germline cells.

Is Regulation (EU) No 536/2014 in conjunction with Directive 2001/83/EC applicable to germline gene interventions in embryos? Analysing a preliminary objection

Exposition

One might argue that Regulation (EU) No 536/2014 should not be applicable to germline gene alteration trials when performed on embryos, since it seems that no medicinal products in the legal sense are concerned. In other words, such gene altering practices do not create any 'medicinal substance' (this means something separate from the human being in question that is used by or administered to such a human being with a view to restoring, correcting, or modifying physiological functions).[22] 'The EU legislation on clinical trials concerns clinical trials "on medicinal products for human use," whereas gene editing in an embryo involves the application of a process or technique. Therefore, 'editing the DNA of an embryo does not create a "product," still less a "medicinal product," because it does not create any "substance or combination of substances"[23] which could then be governed by the pharmaceutical legislation.

21. Mark L. Flear, Governing Public Health: EU Law, Regulation and Biopolitics (Oxford: Bloomsbury, 2018).
22. Cf. J. L. Davies, 'The Regulation of Human Germline Genome Modification in the United Kingdom', in Andrea Boggio, Cesare Romano and Jessica Almqvist, eds., *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (Cambridge: Cambridge University Press, 2020), pp. 217, 236.
23. Davies, 'The Regulation of Human Germline Genome Modification in the United Kingdom', pp. 217, 236.

Thus, this type of argument concedes that the action certainly involves the application of a process or technique, but it holds that this does not mean that its result must be considered a medicinal product. Consequently, since according to this view no medical products are involved, then the Regulation should not apply.

Missing legal systematic considerations

First, we must concede that no (medicinal) product is produced by the *application* of the (genetics-altering) therapeutic substances to an embryo (nor to germ cell, nor to born humans). However, the substances applied to facilitate the genetic alteration, that is, substances with a therapeutic effect, are in general already medicinal products according to Regulation (EU) No 536/2014 in conjunction with Directive 2001/83/EC. As a result, legal requirements for any use (including the *application*) of these therapeutics must be observed. Such germline gene-altering substances are rather medicinal products. It can be assumed that these medicinal products are legally considered ATMPs under Regulation (EC) No 1394/2007 in conjunction with Directive 2001/83/EC. According to Art. 1 No 4a of Directive 2001/83/EC, ATMPs are also included in the scope of Directive 2001/83/EC (introduced by Art. 28(1) of Regulation (EC) No 1394/2007).

This finding is of legal importance because the use of medicinal products within the meaning of Directive 2001/83/EC in clinical trials – according to Regulation (EU) No 536/2014 – must be carried out in accordance with statutory provisions as set forth in Directive 2001/83/EC and Regulation (EU) No 536/2014. When assessing and approving clinical trials, the Member State authorities or EU authorities must then also comply with both CFR rules and CJEU case law on the interpretation of the EU law, as EU law is applied within the appraisal and approval processes of clinical trials.

Wrong status – the embryo as a legal subject and not as a legal object?

On the other hand, it is necessary to point out that one can only neglect the application of Directive 2001/83/EC and Regulation (EU) No 536/2014 by assuming that the embryo undergoing the germline alteration is an object and not a subject in the context of the EU legal framework.[24]

If the embryo in vitro was not a subject (=human being in the legal sense), but an object, then the testing of substances to induce specific germline changes in embryos would not be a clinical trial for a new medicinal product, because from a dogmatic legal

24. The consequences of the *Brüstle* and *ISCO* case law of the EUCJ on pharmaceutical legislation were first described in: T. Faltus, 'No Patent–No Therapy: A Matter of Moral and Legal Consistency within the European Union Regarding the Use of Human Embryonic Stem Cells', *Stem Cells and Development* 23(S1) (2014), pp. 56–59; T. Faltus, 'Keine Genehmigungsfähigkeit von Arzneimitteln auf der Grundlage humaner embryonaler Stammzellen', *Medizinrecht (MedR)* 34 (2016), pp. 250–257. On the question that embryos are legal persons and not things, see, inter alia: L. Bortolotti and J. Harris, 'Stem Cell Research, Personhood and Sentience', *RBM Online* 10(Supp 1) (2005), pp. 68–75; R. Müller-Terpitz, 'Der Embryo ist Rechtsperson, nicht Sache', *Zeitschrift für Lebensrecht* 15(2) (2006), pp. 34–42.

point of view, clinical trials for medicinal products are only carried out on humans (or on animals in the case of veterinary medicinal products). If the embryo is an object in the legal sense, then the systematic development of germline therapy for embryos would not be covered by current pharmaceutical legislation (at most as a preclinical study), whereas the investigation of the same substances for the same purpose in born humans would in any case be a clinical trial.

In case therapeutic germline intervention is considered permissible and embryos in vitro are regarded as objects, another problem arises. In this case, such therapies and the associated therapeutics could not – legally and conceptually – be developed in clinical trials. In today's legal understanding, however, clinical trials are a mandatory prerequisite for the approval of medicinal products (e.g. Art. 8(3)(i) Directive 2001/83/EC) and thus also for therapeutics for germline intervention. This dilemma has so far been ignored in the legal discourse on therapeutic germline intervention. Therefore, those who want evidence-based, effective, safe medicinal products (for germline intervention in embryos) must either consider the embryo as a subject or develop a new regulatory system for germline therapeutics with different regulatory requirements than those currently in effect.

Rather, one must keep in mind the case law built by the CJEU in the Cases C-34/10 (*Brüstle*) and C-364/13 (*ISCO*). Even though both judgements were indeed legally binding only within the scope of patent law, their significance for the issues discussed here arises from the fact that these patent judgements were based on EU law, namely on Directive 98/44/EC, and dealt – among other things – with the legal status of the human embryo in the EU context.[25]

Within the *Brüstle* and *ISCO* cases, the CJEU has defined the term *embryo* within the meaning of EU-harmonized patent law.[26] As a result, the CJEU has also commented on the question of the beginning of human life in the legal sense and its protection against destruction and other uses for purposes not supporting the embryo itself. According to this case law, every cellular human entity that has the inherent ability to develop into a human being[27] is an embryo in the meaning of the law.[28] In addition, the CJEU has emphasized that even a just-fertilized egg cell showing such ability to develop into a human being should be regarded as a human embryo within the meaning of Directive 98/44/EC.[29] The word 'embryo' is therefore a linguistic operator designating a human being in certain, prenatal stages of development; according to Art. 5 of Directive 98/44/

25. S. Davey, N. Davey, Q. Gu, et al., 'Interfacing of Science, Medicine and Law: The Stem Cell Patent Controversy in the United States and the European Union', *Frontiers in Cell and Developmental Biology* 3 (2015), 71.
26. A. Mahalatchimy, P. L. Lau, P. Li and M. Flear, 'Framing and Legitimating EU Legal Regulation of Human Gene-Editing Technologies: Key Facets and Functions of an Imaginary', *Journal of Law and the Biosciences* 8(2) (2021), lsaa080.
27. CJEU: Case C-364/13 Judgement of 18 December 2014, recital 38, operative provisions of the judgement.
28. A. Mahalatchimy, E. Rial-Sebbag, A. Duguet, F. Taboulet and A. Cambon-Thomsen, 'The Impact of European Embryonic Stem Cell Patent Decisions on Research Strategies', *Nature biotechnology* 33(1) (2015), pp. 41–43.
29. CJEU: Case C-34/10, Judgement of 18 October 2011, recital 35.

EC, the human body in its individual phases of formation does not represent a patentable invention. The embryonic phase is therefore nothing other than one of these stages of development.[30] The developmental phases covered by this operator are then legally to be treated like born human beings. There are no apparent legal reasons why embryos should not be granted this status in view of current legal conditions and case law.

Finally, in the *Brüstle* judgement, the CJEU pointed out that it can already be deduced from Directive 98/44/EC that the exploitation of biological material must respect fundamental rights and, above all, human beings.[31] In particular, recital 16 of Directive 98/44/EC emphasizes the point that patent law must be executed in compliance with the fundamental principles that guarantee the dignity and integrity of human beings.[32] However, if patent law has to respect such fundamental (EU) rights, then it cannot be logically explained why such fundamental (EU) rights should not also apply in the fields of medicinal products law or clinical trials law: same legislator, same entity, same status.

The destruction *or* use of embryos, that is, of humans, for purposes that solely benefit others, has in any case been found by the CJEU to be incompatible with the EU *ordre public* as laid down in Art. 6(1)(c) of Directive 98/44/EC. Based on this consideration, the CJEU has excluded the patenting of inventions based on such acts.[33]

From the rulings of the CJEU on the definition of 'embryo' in EU patent law, as well as the CJEU's comments on the uses of embryos that are incompatible with EU *ordre public*, it must therefore be concluded that the entity referred to in EU patent law as an *embryo* ultimately must be a legal subject, not just an object dominated by subjects. This has significant consequences for the further consideration of the question of the admissibility of clinical studies on germline changes in embryos[34] and, of course, it definitively dismisses the assumption that embryos are not legal subjects: if embryos are regarded as legal entities/subjects with rights that protect them against damage, destruction, and/or uses in the interests of others, then it is unclear why, for example, this rating should apply only to the EU's Directive 98/44/EC and not uniformly – and thus also in EU pharmaceutical or tissue law. Again: same legislator, same entity, same status.

This result does not change if the European Patent Convention (EPC) is also included in the analysis, because the EPC represents an independent legal system alongside EU law. Therefore, the legal cases concerning (embryonic) stem cells and/or embryos, which have been filed in the EPC so far, do not have legal relevance for the pharmaceutical law issues examined in this article. Moreover, according to Art. 53(a) EPC, Rule 28 EPC-Implementing Regulations and Rule 26(1) EPC-Implementing Regulations, the EU Directive 98/44/EC (and thus the CJEU case law on this subject) shall be used as a

30. Faltus, 'Stammzellen', pp. 250–257.
31. I. De Miguel Beriain, 'Patenting hESC in the EU Context: An Updated Analysis of a Complex Issue', in Phuc Van Pham and Achim Rosemann, eds., *Stem Cells in Clinical Applications: Safety, Ethics and Regulation* (Heidelberg and New York: Springer, 2017), pp. 263–273.
32. CJEU: Case C-34/10, Judgement of 18 October 2011, recital 32.
33. CJEU: Case C-34/10, Judgement of 18 October 2011, para 52, operative provisions of the judgement; other opinion: J. Timke, *Die* Patentierung embryonaler Stammzellen *(Baden-Baden: Nomos*, 2014), pp. 349, 393.
34. Faltus, 'Stammzellen', pp. 250–257.

supplementary source for interpreting the EPC on questions of the legal status of embryos and not, vice versa, the EPC for interpreting EU law.[35]

Also, the European Unitary Patent and the European Unified Patent Court,[36] which are expected to start in early 2023,[37] do not change this assessment since these legal institutions do not change the aforementioned substantive requirements for patents.

Could embryos be study participants (subjects) instead of being study objects?

We would further argue that embryos are not study objects in clinical trials, but rather study participants, and are cell donors in terms of tissue law. This might sound odd at first. On closer examination, however, the reverse is true: to consider human embryos as legal subjects in patent law but as legal objects in pharmaceutical and tissue law, merely due to opportunistic considerations, is odd. Indeed, it would be hypocritical to grant embryos human rights and dignity, including protection against bodily harm, but then refuse to accept the further consequences of this view.[38]

Therefore, the CJEU's assessment of the protection of the human embryo as a legal entity – taking into account EU primary law[39] – must be observed in all areas of EU law relating to embryos, including EU pharmaceutical legislation and tissue law. This is supported by the fact that the assessments of the protection of embryos under secondary EU patent law are ultimately assessments that have been substantiated by the primary law of the EU for the protection of human beings. Since these assessments have been incorporated into secondary EU patent law from primary law, such assessments can also be incorporated into secondary EU pharmaceutical law, clinical trial law, and tissue law from primary law. Considering the embryo as a subject from a legal point of view is also in line with the subject definition of EU Regulation 536/2014. According to Art. 2(17), 'subject means an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control'.

Those who assume that the *same legislator, same entity, same status* rule followed here should only apply in patent law but should not apply to embryos in the medical field must justify this without contradiction. However, no such consistent justifications have yet been put forward. It is noteworthy that this assessment does not mean that all forms of abortion need to be redefined, since the specific conflict situations must be considered. According to the judgement of the CJEU, however, a different legal interpretation may

35. U. Storz and T. Faltus, 'Patent Eligibility of Stem Cells in Europe: Where Do We Stand after 8 Years of Case Law?', *Regenerative Medicine* 12 (2017), pp. 37–51.
36. EPO, 'Regulation (EU) No 1257/2012, Regulation (EU) No 1260/2012', *Official Journal EPO* (2013), pp. 287–364.
37. Unified Patent Court, 'The Administrative Committee takes significant steps towards the setting up of the Unified Patent Court', 14 July 2022, https://www.unified-patent-court.org/news/administrative-committee-takes-significant-steps-towards-setting-unified-patent-court (accessed 17 October 2022).
38. Faltus, 'Stammzellen', pp. 250–257.
39. CJEU: Case C-34/10, Judgement of 18 October 2011, para 3 (referring to No 43 of the preamble of Directive 98/44/EC, para 32.

apply regarding the placing on the market of products for post-conception prevention of pregnancy.[40] This is because the legal prerequisites for placing a product on the market are also determined by EU pharmaceutical law (e.g. Art. 6(1) Directive 2001/83/EC; Art. 3 Regulation (EU) No 726/2004; Art. 5(1) Regulation (EU) No 2017/745). If one considers that the embryo (i.e. from fertilization and before implantation) is already a person with rights of his or her own, then it is also questionable whether 'killing' this embryo without a conflict situation is legally permissible. If there is no conflict situation and if abortion (i.e. hereby preventing the implantation) is initiated using the above-mentioned post-conceptive methods only because the child is not wanted, then it could be questionable whether this is legally compatible with the CJEU's assessment that embryos can be legally protected against destruction. Further investigations will have to clarify this in the future.

Relevance of Member State prohibitions for the applicability of the regulation

Art. 3(1) CFR states that every person (i.e. every legal subject, which must, we have argued, include human embryos) has the right to physical integrity. These requirements of the CFR must be considered in relation to clinical studies on germline gene alteration. This is the case because the EU Member States apply EU law in the area of pharmaceutical law. These are EU Directives that have been implemented in the laws of the EU Member States (e.g. 2001/83/EC). In addition, the application of EU regulations, such as the approval of clinical studies under Regulation No 536/2014 by Member State authorities and the market authorization of medicinal products under Regulation (EC) No 726/2004 by the EU or by the Member States, is again subject to EU law. Therefore, if the CJEU, by considering EU primary law, has defined viable embryos as embryos within the meaning of EU patent law and thus as human beings from the moment of the fusion of egg and sperm cell, then Art. 3(1) CFR needs to be considered in all fields of EU law relevant to the question of how embryos may be used. Those who wish to attribute different rights to the embryo in different legal matters under the same legislator must give reasons for this without contradiction: it is not clear why the same entity should be a subject in patent law matters, but just an object when it comes to clinical trials. Therefore, if one follows the CJEU's assessment and adheres to the consistent view of the embryo as a subject, then an embryo must not be destroyed or otherwise used for purposes not in the interest of that specific embryo itself. To do otherwise would be to violate the right to physical integrity of the embryo.

These options, however, find their limits in the legal regulations of the respective EU Member States, since the EU has no authority to prohibit certain therapies that are not specifically enshrined in EU law, rather in the national laws of each Member State. In Germany, genetic modification of the embryo's germline – whether in a clinical trial or as specific medical treatment – would be prohibited by the Embryo Protection Act

40. Manfred Spieker, Christian Hillgruber and Klaus Ferdinand Gärditz, *Die Würde des Embryos – Ethische und rechtliche Probleme der Präimplantationsdiagnostik und der embryonalen Stammzellenforschung* (Paderborn: Ferdinand Schöningh, 2012), p. 104 (overall for medical research, which includes clinical trials).

(Embryonenschutzgesetz) without exception. For Germany, the question of whether such interventions in the germline would be permissible or prohibited at the EU level is moot. In Spain, the dominant opinion is that basic and clinical research and clinical application of germline editing to human gametes, pre-embryos, and embryos are prohibited by the combined effect of Art. 13 of the Oviedo Convention and Art. 74 of Law 14/2007 on Biomedical Research. This view has had a paralysing effect on Spanish researchers, who, currently, are not engaging in research in this direction.[41]

The questions regarding the feasibility and admissibility of clinical studies on germline therapy under EU law are therefore pressing only in those Member States in which such interventions are not already excluded by Member State law. As shown, in such states, EU law would have to be observed to conduct (germline changing) clinical trials. Further consideration of the rights of the embryo in vitro leads one to examine the individual rights of embryos in the context of clinical trials to see what influence these rights have on the conduct of clinical trials on germline gene alteration.

The need to interpret Art. 90 of Regulation (EU) No 536/2014 for germline interventions in embryos in vitro

Historical and literal interpretation for the verum group

As mentioned, Art. 90 reads: 'No gene therapy clinical trials may be carried out which result in modifications to the subject's germline genetic identity'. The main problem is that this wording opens the gate to a discussion of what exactly constitutes the 'germline genetic identity' and under which conditions it shall be deemed 'modified' to apply Art. 90.[42] This interpretation suggests that clarification is required as to whether the modification of the DNA in the germline for the purpose of avoiding the manifestation of a hereditary disease in the later born person represents a modification of the subject's germline genetic identity. In other words: does the genetic basis of a hereditary disease belong to the subject's germline genetic identity?[43]

The historical background of the clause does not clarify this issue.[44] Indeed, the ban on germline intervention was not included in the original drafts of either the Directive 2001/20/EC or the current Regulation, but only added during the legislative process. In

41. An alternative interpretation can be found here: I. De Miguel Beriain and C. Romeo Casabona, 'The Regulation of Human Germline Genome Modification in Spain', in Andrea Boggio, Cesare Romano and Jessica Almqvist, eds., *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (Cambridge: Cambridge University Press, 2020), pp. 358–379.
42. I. De Miguel Beriain, 'Should Human Germ Line Editing Be Allowed? Some Suggestions on the Basis of the Existing Regulatory Framework', *Bioethics* 33 (2019), pp. 105–111.
43. I. De Miguel Beriain and A. M. Marcos del Cano, 'Gene Editing in Human Embryos. A Comment on the Ethical Issues Involved', in Marta Soniewicka, ed., *The Ethics of Reproductive Genetics. Between Utility, Principles, and Virtues* (Cham: Springer, 2018), pp. 173–187.
44. Slokenberga, 'What Would It Take to Enable Germline Editing in Europe for Medical Purposes?'.

the old Directive, the reason given for the ban was simply the following: 'The ban on gene transfer into germline cells is in line with the EU's declared policy'.[45] In the current Regulation, the justification for the ban is that the 'regulation may not fall behind the existing directive. Therefore, we should adopt the formulation of the present Directive'.[46] Under these circumstances, a number of possible interpretations find room, all of them with totally different legal consequences.[47] One might, for instance, hold that it was never an objective of the Regulation to totally ban germline gene alteration, but only those alterations that change the germline, as previously stated. Changes that do not cause this final result could be allowed. However, what does this mean, precisely? This is quite hard to know, since the concept of (germline) genetic identity is fuzzy.[48] It is hard to know whether a specific intervention will cause such result or not.

However, it is relevant to note that some elements of the wording (specifically: 'which result in modifications to the subject's germline genetic identity') seem to leave open the possibility that some types of interventions in the germline might be permitted (obviously, those that do not alter the genetic identity). If the legislature had intended to ban all types of germline modification, it presumably would have used an alternative wording, including only 'which result in modifications to the subject's germline' and omitting any reference to the alteration of genetic identity. Therefore, one might conclude that germline gene alteration is not banned once certain – to be determined – circumstances apply. One might also note that some interventions aimed at restoring the embryo's (genetic) health and which are not generally taken to constitute a change in its genetic identity are permissible within the EU legal framework. In addition, this interpretation would at least not be a priori incompatible with the legal status of the human embryo (in vitro) represented here.

As previously stated here, the embryo (in vitro) is considered a legal subject with same legal status as a born person. Thus, the embryo is worth protecting from harm and treating with healthcare interventions if technically possible. This seems to suggest that if an embryo has a genetic condition that will indisputably trigger a genetic disease (a situation that would typically condemn it not to be transferred into a woman under ordinary assisted-reproduction circumstances), germline gene intervention might, from an ethical perspective, be seen as a beneficial initiative that serves the embryo's interests.

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45. European Parliament, *Recommendation for Second Reading, 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 (8878/1/00 – C5-0424/00 – 1997/0197(COD))*, Amendment 19, pp. 17, 24.
46. European Parliament, *Report 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, pp. 129,263.
47. Mahalatchimy et al., 'Framing and Legitimating EU Legal Regulation of Human Gene-Editing Technologies'.
48. B. M. Knoppers and H. T. Greely, 'Biotechnologies Nibbling at the Legal "Human"', *Science* 366 (2019), pp. 1455–1457; H. Widdows, 'Between the Individual and the Community: The Impact of Genetics on Ethical Models', *New Genetics and Society* 28 (2009), pp. 173–188; R. Klitzman, '"Am I My Genes?": Questions of Identity among Individuals Confronting Genetic Disease', *Genetics in Medicine* 11 (2009), pp. 880–889.

Admissibility and acceptability of control studies

However, caution is required regarding this argument, as it is only applicable to embryos that are actually treated in the aforementioned meaning (i.e. embryos in the verum group of a clinical trial, embryos being factually altered in their germline by the medicinal product to be evaluated). A typical two-arm clinical study requires a comparison group in addition to the verum group. In principle, three different control constellations are (technically) possible: (a) comparison with a group that is not treated at all, but only observed; (b) a control preparation that has no therapeutic effect (placebo); and (c) a comparison group that is treated with another, already established, effective treatment. The legal assessment of these options in the case of embryonic germline interventions raises a number of concerns.

The following examples refer to germline treatment of embryos in vitro, which are transferred to a female after the respective treatment. This approach was chosen because, according to the current state of technology and knowledge, germline treatments would typically be performed on embryos in vitro due to the additional genetic examinations required, for example, with regard to the successful modification of DNA, and due to the technical accessibility of the embryo. Germline treatment of embryos in utero would be an additional technical complication from today's point of view. To what extent the legal considerations regarding germline modifications in vitro can then be applied to embryos in utero must be investigated by future ethical and legal discussion.

No treatment comparison, embryos in a placebo group, and the benefit of others. The evaluation of the control groups 'No Treatment' and 'Placebo' can be combined, because in both control groups the same questions arise with regard to the embryo as well as the human being emerging from the embryo. In both comparison groups, the embryo does not receive effective germline therapy. In both scenarios, proof of the effectiveness of germline therapy could be provided by the fact that people born from genetically modified embryos do not suffer, or suffer less, from symptoms typically associated with the hereditary disease being treated, compared to people born from genetically untreated embryos. However, it is questionable whether this comparison groups can actually be established. The reason for this is that after a genetic germline alteration, an embryo could be transferred for gestation; without germline alteration, the same embryo would not be transferred but discarded. If one assumes that embryos are legal entities with their own rights, implying that embryos with genetic defects are also entitled to such rights, then the legality of germline therapy for these embryos must be assessed in the same way as the embryos in the verum group. Moreover, the deliberate omission of a possible treatment (of symptoms) after birth is neither legally permissible nor ethically justifiable if undertaken only to artificially create a comparison group. The comparison to no-treatment scenario is therefore only considered if there is no treatment available at all, even not for symptoms which are specific to the respective hereditary disease. In this constellation, the most that can be done for the born individual in the control group is treatment of general health impairments (e.g. general pain treatment).

In conclusion, embryos in the no-treatment and in the placebo group would receive no individual benefit and would as a comparative figure at most be useful to others. The

question of the admissibility of such a research utilization is decided based on legal norms that take such ethical aspects into account and also consider and weigh up technical and legal reasons. Therefore, the claim that the embryo, because of its moral and corresponding legal status, is worth protection against harm and the offer of healthcare must meet legal requirements such as the legal provisions governing informed consent to participation in a clinical trial. However, since the embryo itself cannot consent to participate in a clinical trial with it as a study participant, the question arises to what extent these factual, ethical, and legal aspects, namely that at least certain embryos would only serve the benefit of others, would affect the permissibility of a proxy consent (see section 'The impossibility of legally binding informed consent as legal limit for germline interventions in embryos in vitro?').

Comparison with other effective treatment. In the case of physiological hereditary disease, only the symptoms of the disease can be treated after birth. In individual cases, somatic gene therapies can already be used at present. From a legal point of view, these 'control treatments' do not require an in-depth legal and/or ethical assessment (here), as they are all officially approved treatments. However, for a future debate it is worth asking whether it is ethically justifiable for the individuals in the control group born from the embryos without intervention in the germline to be instructed to undergo treatment with medicinal products for the rest of their lives if germline therapy was available.

For ethical evaluation, the question is not whether it can be assessed ex ante that germline therapy in the verum group has a more favourable benefit–risk ratio compared with existing treatment of symptoms, but rather the (ethical) question of whether this control group should be allowed to be established with the health consequences described. It is true that control groups are also established for classical, symptom-treating medicinal products, possibly even control groups that only receive a placebo. However, this situation is not (ethically) identical to the separation into individuals who receive germline therapy and individuals who do not receive this treatment. In studies on classical medicinal products, individuals from the placebo group can be treated with the possibly more effective medicinal products from the verum group after the end of the study (and vice versa). In germline studies, on the other hand, it is certain from the outset that in the event that the germline therapy has a more favourable benefit–risk ratio compared with the existing treatment of symptoms, the individuals from the control group cannot receive this treatment because the germline intervention with its effects on the typically systemic symptoms of the hereditary disease must take place at the embryonic stage to affect all body cells.

Fundamental legal problems of control groups in minors, respectively embryos. With regard to control groups, further fundamental legal problems arise from the current legislation on minors. According to Art. 32(1) of Regulation No 536/2014, a clinical trial with minors may be conducted only if, in addition to the conditions set out in Art. 28, all the additional conditions as stated in Art. 32 are met. Inter alia, Art. 32(1)(e) of Regulation No 536/2014 provides that clinical studies with these persons may be performed only if the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors to validate data obtained

in clinical trials on persons able to give informed consent or by other research methods. According to this provision, clinical studies on germline alteration in embryos would therefore be permitted only if the corresponding phenotypic disease pattern were to be observed solely among minors. However, as hereditary diseases also manifest themselves in adults, this provision is likely to represent a significant limitation. Art. 32(1)(f) of Regulation No 536/2014 could possibly help in overcoming this limitation, provided that the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors.

In addition, clinical trials with minors need to comply with Art. 32(1)(g) of Regulation No 536/2014. According to Art. 32(1)(g)(i), clinical trials may be carried out on minors only if there are scientific grounds for expecting that participation in the clinical trial will produce a direct benefit for the minor concerned outweighing the risks and burdens involved. According to this provision, the legality of control studies could be questionable if inclusion in the control study would have no benefit for the embryo concerned. In answering this question, it is therefore necessary to determine the specific benefit to the embryo as a subject to be included in the control group.

If the planned procedure does not benefit the treated embryo, Art. 32(1)(g)(ii) may be relevant – though there are scientific grounds for expecting that participation in the clinical trial will produce some benefit for the population represented by the minor concerned, and that such a clinical trial will pose only minimal risk to, and will impose minimal burdens on, the minor concerned in comparison with the standard treatment of the minor's condition. Irrespective of the answer to the question of what a 'minimal risk' or a 'minimal burden' is, one will have to assume – at least given the current state of our knowledge – that the risks of germline gene alteration for the individual are indefensible. Therefore, one will not be able to describe this risk as 'minimal'.

The impossibility of legally binding informed consent as legal limit for germline interventions in embryos in vitro?

Consent in the verum group

The central element of clinical trials is the informed consent of the full-age study participant after his or her information, legally set forth in Art. 28(1)(b)–(c) and Art. 29 of Regulation No 536/2014. Since the prenatal embryo as a legal subject is obviously not of age and also cannot express consent due to lack of communicative abilities, the embryo as a legal entity – and therefore in the systematics of EU pharmaceutical legislation, including the legislation governing clinical trials – is a *consent-incapable minor*. Can such a minor legally become a participant in a clinical trial, particularly a clinical trial on germline gene alteration?

Since the law of clinical trials, including information and consent, is EU law, all authorities in all Member States as well as the EU authorities must comply with the relevant EU legislation as well as with the interpretations of these provisions by the CJEU. In particular, this is the case law of the CJEU, *in concreto* the definition of *embryo* derived from primary law and patent law. In addition, pursuant to Art. 51 CFR, the requirements of Art. 3(1) CFR with regard to the protection of the integrity of the person

must be observed, as well as the requirements of Art. 3(2)(a) CFR, according to which, in the context of medicine, the information and consent requirements must be observed.

Also, with regard to embryos as participants in a clinical trial within an EU Member State (e.g. in a germline intervention study), the relevant Member State authorities approve the clinical trial on the basis of EU law. This must not be confused with the question of whether the use of human embryos in basic research is permitted or prohibited in an EU Member State. This question is only decided according to the law of the respective Member State, as the legislative competence on this question lies exclusively with the Member States.

However, in the case of the authorization of clinical studies, the relevant Member State authorities would have to determine whether there is informed consent with regard to the embryo as a study participant, either from the embryo itself or through a legally designated representative.[49] Art. 32(2) of Regulation No 536/2014 requires that a minor shall take part in an informed consent procedure in a way adapted to his or her age and mental maturity. The informed consent of an embryo in vitro is obviously impossible. Does that mean that in this constellation consent – because it is impossible – is unnecessary?

Since the embryo is obviously incapable of giving consent, the embryos participating in the trial would have to have the rights granted to them exercised by other persons – persons who are able to consent, and in particular, legal representatives, as far as this would be legally permissible. Regardless of whom this legal representative is, his or her proxy consent to the inclusion of a specific embryo in a clinical trial could, given the legal requirements and the interpretation of the CJEU, at first only be possible for embryos in the verum group (cf. section 'Admissibility and acceptability of control studies'). These embryos (strictly speaking, only the resulting born human beings in whom the disease is not manifested due to the germline intervention) would, at least theoretically, have the possibility of benefiting from germline intervention. For this, however, it must first be clarified whether this merely theoretical possibility is sufficient to fulfil the legal requirements for permissible intervention on the embryo.

Consent in the no-treatment group and in the placebo group

For embryos in a control group (cf. section 'Admissibility and acceptability of control studies'), there are even more complicated medico-ethical and legal questions regarding the necessary informed consent. As shown, for embryos in the control group (strictly speaking, the resulting born human beings in whom the disease is manifested), it is questionable whether inclusion in the control group constitutes a benefit or to what extent it is ethically justifiable to create such control groups at all.

In connection with the question of whether an embryo can participate in the control group, we would need to clarify whether it is ethically or legally significant that the embryo would simply be discarded if it did not participate in the control group. However, the proxy consent in the control cases could be abusive, as the legal status of the embryo as it has been set forth in EU law, notably Art. 3(1) CFR, is precisely to prevent an embryo from being used for the sole benefit of others. Therefore, it must be questioned

49. E. C. Jonlin, 'Informed Consent for Human Embryo Genome Editing', *Stem Cell Reports* 14 (2020), pp. 530–537.

whether this protection can be undermined by circumventing the embryo's inability to consent by supplying the consent of a representative legally empowered to enter the embryo into a placebo or no-treatment study.

This question of research for the benefit of a group has not only been raised with embryos but is also an issue in clinical studies of adults, in particular incapacitated subjects. Incompetent persons have a higher protection status due to their greater vulnerability compared to persons who are fully capable. If incapacitated subjects are given increased protection, then one must ask whether similarly increased protection should be extended to embryos, as legal persons. If (proxy) consent would be legally impossible for embryos in a control group, then maybe there could be no valid control group for a study involving embryos, and the scientific quality of any such study would be questionable. If, however, it is certain from the outset that this specific clinical study has no scientifically proven value, it is questionable whether such a study can be approved, since the study is still associated with risks to life and limb for the study participants.

Systematic development of germline interventions in adults

For reasons of conciseness, only constellations with adult persons capable of giving consent will be examined for the following legal analysis. For the additional questions in the case of born but minor persons, at least in principle, reference can be made to the above statements (cf. section 'The impossibility of legally binding informed consent as legal limit for germline interventions in embryos in vitro?').

First, it should be noted that the systematic development of germline therapeutics for intended, targeted germline intervention in the context of clinical trials is not to be confused with the question of the legal acceptability of unintended germline modification in the context of medical treatments. Such unintended germline alterations, as they can occur for example, in the context of oncological treatments by radiotherapy and/or chemotherapy, are typically considered ethically acceptable and legally permissible in view of the chances and risks of the specific therapy. In Germany, for example, this is explicitly regulated in the Embryo Protection Act (§ 5 para. 4 no. 3). In Spain, such interventions fall under the umbrella of Art. 13 of the Oviedo Convention, which does not rule out interventions for a somatic purpose which might have unwanted side effects on the germ cell line, according to recital 92 of its Explanatory Report.[50]

From a legal point of view, the systematic development of germline therapy in adults would have to be examined according to Regulation No 536/2014, in conjunction with Regulation (EC) No 1394/2007 and Directive 2001/83/EC. Regarding the questions to what extent such therapeutic modifications of the germline would be in compliance with Art. 90 Regulation No. 536/2014, reference can be made to the above interpretations of this provision, in particular whether the genetic basis of a possibly

50. Council of Europe, *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* (European Treaty Series No. 164, recital 92, Oviedo, 1997), at https://rm.coe.int/16800ccde5 (accessed 17 October 2022).

already manifested disease necessarily belongs to the genetic identity in the meaning of Art. 90 (cf. section 'Historical and literal interpretation for the verum group').

If one sees the development of therapeutic germline intervention as either already made possible by Art. 90 or if Art. 90 were to be reworded in such a way that systematic development therapeutic germline intervention in the context of clinical trials would be legally permissible, then, however, so far unresolved problems may arise in the multi-level legal system of the EU. This would affect Member States where genetic modification of germ cells or germline cells in vivo is prohibited by Member State law. In Germany, for example, it is argued – albeit controversially – that the Embryo Protection Act prohibits such interventions, regardless of whether the intervention is intended for therapeutic or merely enhancing purposes. In Spain, this topic is also controversial. The Spanish Code of Criminal Law states that

> Those who manipulate the human genes so as to alter the genome for purposes other than eliminating or decreasing serious flaws or diseases, shall be punished with a sentence of imprisonment from two to six years and special barring from public employment and office, profession or trade, from seven to ten years.[51]

Thus, manipulations aimed at eliminating or decreasing serious flaws or diseases are permitted. On the other hand, the regulation by the Oviedo Convention is ambiguous, as previously showed. However, Art. 74 of Spanish Law 14/2007 of Biomedical Research[52] imposes fines for the misuse of germline gene editing: 'the carrying out of any intervention aimed at the introduction of a modification in the genome of the descent' is considered as a very serious infraction that is punishable with a fine of between 10,001 and 1,000,000 Euros. However, this regulation refers to biomedical research. Instead, Art. 13 of the Spanish Law 14/2006 on Assisted Human Reproduction Techniques[53] allows interventions on pre-embryos (embryo in vitro) for therapeutic purposes if 'no modification of non-pathological hereditary traits or selection of individuals or the breed is sought' (letter c). Thus, it is unclear whether such intervention would be acceptable in Spain. Most authors tend to deny it, but there are some reasons to consider that it could be so, as merely showed.

If no consensus on the legal permissibility of this form of therapy can be achieved in the EU Member States, it is questionable how this therapy should then be legally constituted at EU level in view of a harmonized, common pharmaceutical market.

Development of germline therapeutics using genetically altered gametes

Germline therapeutic intervention can also be carried out by first genetically modifying germ cells and then using these modified germ cells to effect in vitro fertilization.[54]

51. Art. 159.
52. Ley 14/2007, de 3 de julio, de Investigación biomédica.
53. Ley 14/2006, de 26 de mayo, sobre técnicas de reproducción humana asistida.
54. Cf. G. De Wert et al., 'Responsible Innovation in Human Germline Gene Editing: Background Document to the Recommendations of ESHG and ESHRE', *European Journal of Human Genetics* 26 (2018), pp. 450–470.

Since the genetic intervention is not performed on embryos nor in born humans, the legal questions regarding the previously illustrated impact of the legal status of embryos on the permissibility of germline clinical trials do not arise.

Certainly, Art. 6(1)(2)(b) Directive 98/44/EC also excludes patenting of inventions based on genetically modified human germ cells. This exclusion, however, unlike the significance of the legal status of the embryo presented here, has no legal significance for the permissibility of clinical trials for germline therapy using genetically altered germ cells. In embryos, clinical trials on germline therapy can legally not be carried out because – in line with the case law of the CJEU in EU patent law – embryos are legally to be treated as born human beings, that is, as subjects. Thereby, the provisions for the protection of the subjects must be observed, which lead to the fact that clinical trials are legally not possible since embryos do not fulfil the legal requirements for study participants. Without clinical trials, however, the authorization of a medicinal product is legally excluded (cf. Art. 8(3)(i) Directive 2001/83/EC).

Unlike embryos, (genetically modified) germ cells are indisputably not subjects but objects, but nevertheless not patentable. However, clinical trials using genetically modified germ cells are not excluded because of this patent exclusion. First, at least theoretically, medicinal products can be developed and approved without an underlying patent. There is no legal requirement that only patented substances and processes may be tested in clinical trials or approved as medicinal products under the rules of pharmaceutical law. This would only be the case if there were an explicit legal regulation to this effect. Patent protection primarily concerns economic issues. Since patent law is irrelevant to the question of the admissibility of clinical studies on germline intervention using genetically modified gametes, it is also not necessary to examine what significance it has for the exclusion of patentability that (with similar wording as in Regulation 535/2014) according to Art. 6(1)(2)(b) Directive 98/44/EC only those inventions that concern 'the germline genetic identity' are not patentable.

Rather, clinical trials for germline therapy with genetically modified germ cells and their application to adult humans could legally also be excluded by Art. 90 of Regulation 536/2014 if 'the subject's germline genetic identity' is affected. However, also the requirement according to Art. 90 regarding the genetic identity has no meaning for the clinical application of genetically modified gametes.

In contrast to changes in the germline of embryos, the use of genetically modified germ cells does not change the genetic identity of a study participant, that is, a person, because in the latter case the genetic identity is only obtained by the merge of two germ cells. This resulting genetic identity is then not 'changed'. If therefore this genetic identity is not changed and if, among other things, appropriate informed consents (of gametes donors, woman to whom the embryo is to be transferred) and if the quality and safety requirements of the EU Tissues and Cells Directive (*Directive* 2004/23/EC) are met, there are no germline-specific legal grounds for rejecting clinical application for germline therapy at the level of EU law.

The question of whether it makes a difference that an embryo is derived from naturally occurring gametes or from genetically modified gametes – in both cases the embryo or the born human being that may develop later has no influence on its genetic

configuration – is mostly a question of medical ethics which does not need be examined here in detail due to the legal focus of this article.[55]

However, in general one has to ask whether the use of genetically modified gametes for the development of germline therapy would even be a clinical trial in the legal sense. From a legal point of view, in vitro genetic modifications of germ cells are not clinical trials, since germ cells are not subjects (not human beings), but cellular objects. In contrast, as outlined in here systematic studies of germline therapy on embryos in vitro would be clinical trials because embryos are subjects. As long as only germ cells in vitro are examined, this can be a preclinical study, but does not require regulatory authorization. But what should apply as soon as an embryo in the legal sense, that is, a subject, arises from the use of genetically modified germ cells in vitro? This embryo is not subjected to any further genetic (germline) manipulation. The embryo is simply grown in vitro with the genetic makeup resulting from the fusion of the used gametes and eventually transferred to a female. From this moment on, the approach is not different from established reproductive medical treatments. In addition, the transfer of an embryo (a subject, according to the view held here) to a human being (also a subject) cannot be considered a clinical trial within the meaning of Regulation 536/2014, since clinical trials typically concern the investigation of a medicinal product, according to Art. 2(2)(1). However, the transferred embryo as a subject cannot be a medicinal product (cf. section 'Identifying sources of EU law applicable to systematic germline gene altering').

This is followed by the question of what should apply if genetically modified germ cells were systematically transferred to humans. These could be clinical trials, with the individual being the study participant and the germ cells being the therapy objects. This raises the question of how long one can speak of a clinical study in this constellation, because at the latest with the formation (in utero) of the embryo in the legal sense, there would be no therapeutic object (such as a pill or genetically modified germ cells). Would this be the endpoint of the clinical trial? In any case, for the embryo that continues to develop in utero, it would not be a clinical trial in the sense of Regulation 536/2014, because again no genetic (germline) manipulation would be performed on this embryo.

EU-wide regulation of these questions would require that the EU is given the competence for this, which the EU does not have so far. Due to the different opinions on germline therapy within the EU states, there is likely to be a considerable need for legal research in this area as well.

For the sake of completeness, it should be mentioned that, targeted genetic modifications of germ cells for non-clinical research purposes are not regulated at the level of EU law but fall within the competence of the Member States (as described above). This is not to be confused with the provisions of the Tissue Directive 2004/23/EC, which only sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells, but does not contain any prohibitions on the genetic modification of germ cells.

55. On the issues regarding the moral status of naturalness and artificiality, see, among others: J. R. *Loftis*, 'Germ-Line Enhancement of Humans and Non-Humans', *Kennedy Institute of Ethics Journal* 15 (2005), pp. 57–76; A. Smajdor, D. Cutas and T. Takala, 'Artificial Gametes, the Unnatural and the Artefactual', *Journal of Medical Ethics* 44 (2018), pp. 404–408.

As shown, also other international law does not prohibit the therapeutic manipulation of germ cells (cf. section 'Identifying the relevant international non-EU Law'). The question to what extent the genetic manipulation of germ cells as such is legally permissible must therefore be determined in each individual EU Member State according to the law applicable there.[56] For example, the Spanish law does not include an explicit ban on clinical application of gene editing or similar procedures to human gametes. Moreover, Art. 13 of Law 2006 stipulates that an intervention for therapeutic purposes on a viable pre-embryo created in vitro may be acceptable if it is aimed at treating a disease or preventing its transmission, with reasonable and proven guarantee. However, one must always keep in mind that the Oviedo Convention has been ratified by Spain and, thus, its Art. 13 applies. Indeed, Art. 74 of Law 14/2007[57] (which is clearly related to the Convention) makes '[t]he carrying on of any intervention aimed at the introduction of a modification in the genome of the descendant' is a crime, punished with a fine from 10,001 to 1,000,000 Euros. In practice, the Spanish National Commission on Assisted Human Reproduction would hardly approve any kind of intervention that involves germline modification if the resulting entity is not destroyed in its first stages.

Similarly, in Germany, any genetic modification of germ cells is prohibited if these germ cells are to be used for reproductive purposes. Thus, whether this modification is a modification that affects the genetic identity is irrelevant. Violations can be punished with up to five years imprisonment. In contrast, in view of the constitutionally guaranteed freedom of research, it is permissible to genetically modify germ cells if it is excluded that the modified gametes will be used for reproductive purposes.[58]

Legal and actual bypasses

Not all medicinal products require authorization, even if they are intended for human use. At the level of EU law, marketing authorization is not necessary, for example, if the medicinal product concerned is not placed on the market in the legal sense. This is due to the fact that EU Regulation No. 726/2004, which regulates marketing authorization, and Directive 2001/83/EC only cover medicinal products that are to be placed on the market in legal terms (cf. Art. 3(1) Regulation (EC) No. 726/2004, Art. 2(1) Directive 2001/83/EC). The same applies to German and Spanish pharmaceutical law.

However, medicinal products manufactured and used by physicians in-house are typically considered not to have been placed on the market because the element of a transfer of power of disposition is missing. If the medicinal product that the physician has manufactured is

56. Description of the legal situations in different countries: Andrea Boggio, Cesare Romano and Jessica Almqvist, eds., *Human Germline Genome Modification and the Right to Science: A Comparative Study of National Laws and Policies* (Cambridge: Cambridge University Press, 2020); Jochen Taupitz and Silvia Deuring, eds., *Rechtliche Aspekte der Genom-Editierung an der menschlichen Keimbahn – A Comparative Legal Study* (Springer: Berlin, 2020).
57. Law 14/2007 of 3 July 2007 on Biomedical Research (*Ley 14/2007, de 3 de julio, de Investigación biomédica*), BOE No. 159, of 4 July 2007, available at https://www.boe.es/buscar/doc.php?id=BOE-A-2007-12945 (accessed 17 October 2022).
58. § 5 para. 2 and § 5 para 4 no. 1 Embryo Protection Act.

administered to the patient, the patient typically cannot pass this medicinal product on to another person; there is therefore no further disposal that goes beyond the application.[59]

Therefore, if changes in the germline – whether to embryos or germ cells – are carried out in medical practices or hospitals, these may not require marketing authorization and therefore do not require clinical studies. Another question here is whether the materials required to perform the intervention require an autonomous marketing authorization under pharmaceutical law or whether these materials also fall outside the scope of the marketing authorization because they have no therapeutic effect (since the actual therapeutically effective agent is manufactured by the physician in his or her practice using the materials). Whether such interventions that alter the germline are ultimately legally permissible is therefore determinable only according to the law of each Member State since there are no prohibitions on this at the level of the EU.

Outlook

When discussing a ban on germline therapy or the upstream clinical trials, one must ask whether such a ban is based on fundamental (normative, medico-ethical) considerations or is justified merely by the current legislation, without any ethical imperative. If the latter is the case, and if one believes that technical progress requires a change in the benefit–risk ratio of germline therapy, then one must consider whether the existing regulations need adjustment.[60] Until then, one must conclude that the ways Art. 90 of Regulation (EU) No 536/2014 will be adopted in practice are difficult to anticipate. Moreover, if we are to accept that clinical trials involving germline gene alteration of human embryos are permissible under the umbrella of the EU legal framework, we should wonder what the status of embryos in clinical trials should be. The Third International Summit on Human Genome Editing, to be held in 2023, would be an appropriate venue to address the international and interdisciplinary importance of the issues raised here.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: EU Commission, H2020 – 788039, German Federal Ministry of Education and Research (BMBF), 01GP1614A, and Government of the Basque Country, IT-1541-22.

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59. Faltus, ‘Medicinal Genome Editing in Germany’, pp. 227–249, BVerfG (= The German Federal Constitutional Court), Judgment of the First Senate of 16 February 2000, 1 BvR 420/97 -, paras. 39 & 40.
60. Cf. Slokenberga, ’Germline Editing’, pp. 1–22.