A Room with a View (and with a Gene Therapy Drug): Gene Therapy Medicinal Products and Genetic Tourism in Europe

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Abstract

In contrast to the extreme caution that has been imposed on genetic medical procedures, in European law genetic drugs, or medications, have found a legal loophole that allows flexible (perhaps too flexible) access to these drugs. In Europe, Gene Therapy Medicinal Products are a form of Advanced Therapy Medicinal Products and as such submitted to the marketing authorization procedure. However, there are legal mechanisms in place — such as compassionate use, named patient use, and hospital exception — that allow for their provision to patients without proper approval. This is not, de per se, problematic; the problem arises, though, because such mechanisms are neither properly regulated nor monitored, and their application differs substantially according to the jurisdiction. This disparity and lack of control have given rise to situations of genetic tourism, where patients in desperate need travel to so-called genetic paradises, looking for a miraculous, and extremely expensive cure. The outcome is sometimes tragic, endangering patients' safety and undermining confidence in genetic products.

Keywords

gene therapy medicinal products – advanced therapy medicinal products – compassionate use – named patient use – hospital use – genetic tourism

1 Introduction

European countries have traditionally had a very cautionary approach towards gene editing when it operates as a medical procedure,[1] not only because it is an innovative therapy,[2] but also, *et pour cause*, there are many unknowns in these therapies.[3] There is some acceptance of genetic interventions if they meet two criteria: i) that they are somatic (i.e., they do not affect any offspring) and ii) that they are therapeutic (even though the exact contour of the concept 'therapeutic' is unclear).[4] Such genetic procedures are allowed by Article 13 of the Oviedo Convention[5] and therefore by several European national laws.[6] Still, several restrictions are in place and medical procedures involving gene editing somatic therapies are highly regulated.[7]

However, gene therapy can also operate through medication rather than a medical procedure, and when that is the case the legal regime becomes much looser due to various loopholes on European pharma regulations. This chapter will address how the loopholes in pharma laws are allowing unproven genetic therapies to reach the market, exploiting the fragilities of vulnerable patients. Moreover, this scenario is harmful to the steady development of

1 European Group on Ethics in Science and New Technologies, *Ethics of Genome Editing* (Luxembourg: Publications Office of the European Union, 2021).

2 A. Loche, W. Mossmann, L. Van der Veken and G. Yang, 2020, 'COVID-19 and cell and gene therapy: How to keep innovation on track', *McKinsey and Company* (2020), available online at https://www.mckinsey.com/industries/life-sciences/our-insights/covid-19-and-cell-and-gene-therapy-how-to-keep-innovation-on-track, p. 2 (accessed 15 December 2021).

3 Reporting some of the uncertainties involved in gene therapies, S. Tunis, E. Hanna, P.J. Neumann, M. Toumi, O. Dabbous, M. Drummond, F.-U. Fricke, S.D. Sullivan, D.C. Malone, U. Persson and J.D. Chambers, 'Variation in Market Access Decisions for Cell and Gene Therapies Across the United States, Canada, and Europe', *Health Policy* 125 (12) (2021) 1550–1556, https://doi.org/10.1016/j.healthpol.2021.10.003.

4 This is a question discussed in V.L. Raposo, 'Gene Editing, the Mystic Threat to Human Dignity', *Journal of Bioethical Inquiry* 16 (2) (2019) 249–257, doi: 10.1007/s11673-019-09906-4; V.L. Raposo, 'When Parents Look for A "Better" Child (Reproductive Choices and Genetic Planning)', *BioLaw Journal/Rivista de Biodiritto* 15 (2021) 407–427, http://dx.doi.org/10.15168/2284-4503-796.

5 The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. Cf., V.L. Raposo, 'The Convention of Human Rights and Biomedicine Revisited: Critical Assessment', *International Journal of Human Rights* 20 (8) (2016) 1277–1294, doi: 10.1080/13642987.2016.1207628.

6 E.g., in Portugal, Article 8 of Law No. 12/2005, from 26 January; in Spain, Article 158 of the Criminal Code, together with Article 74 of Law No. 14/2007 from 3 July. In some other jurisdictions, it is not expressly allowed but also not expressly banned.

7 For an overview of EU laws in this regard, see http://www.genetherapynet.com/europe.html.

genetic technologies, jeopardizes funding and social credibility of legitimate gene editing drugs.[8]

2 The Qualification of Gene Therapies as Drugs

2.1 *ATMPs and Pharma Laws*

Usually, we tend to think about gene therapies as medical procedures. However, they are increasingly being provided as drugs. In Europe, Gene Therapy Medicinal Products (GTMPs)[9] are a form of Advance Therapy Medicinal Products (ATMPs).[10]

Commonly available drugs are able to treat the symptoms of genetic diseases, but they cannot cure them, whereas GTMPs can, by modifying and repairing the disease-causing gene. GTMPs involve the insertion of genetic material (DNA or RNA) into the target cell, using a carrier (the 'vector', usually modified versions of natural viruses), either in vivo or in vitro.[11]

As with any other drug, GTMPs are regulated by Directive 2001/83/EC, relating to medicinal products for human use,[12] and Regulation (EC) 1394/2007,[13] which introduced the ATMPs in the referred Directive. According to Part IV

8 J. Poulos, 'The Limited Application of Stem Cells in Medicine: A Review', *Stem Cell Research & Therapy* 9 (2018) 1, doi: 10.1186/s13287-017-0735-7.

9 It should be noted that these drugs are exclusively aimed at somatic (not germinal) gene therapy (not enhancement).

10 This chapter will only deal with GTPM's. However, many of the considerations presented apply to ATMPs in general, as GTPM's do not have relevant specificities regarding the issues here discussed. Likewise, several bibliographic references quoted in the chapter analyse other types of ATMPs (mostly stem cell products), but their consideration can easily be transposed to the GTPM discussion.

11 More details in A. Sinclair, S. Islam and S. Jones, 'Gene Therapy: An Overview of Approved and Pipeline Technologies'. in *CADTH Issues in Emerging Health Technologies* (Ottawa, ON: Canadian Agency for Drugs and Technologies in Health, 2016), at p. 171; K. Bulaklak and C.A. Gersbach, 'The Once and Future Gene Therapy', *Nature Communications* 11 (2020) 5820, doi: 10.1038/s41467-020-19505-2; X. Pan, H. Veroniaina, N. Su, K. Sha, F. jiang, Z. Wu and X. Qi, 'Applications and Developments of Gene Therapy Drug Delivery Systems for Genetic diseases', *Asian Journal of Pharmaceutical Sciences* 16 (2021) 687–703, doi: 10.1016/j.ajps.2021.05.003.

12 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28 November 2001, pp. 67–128, which rules ATMPs (hereafter, 'the Directive').

13 Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (hereafter, the 'ATMP Regulation').

of Annex I[14] of Directive 2001/83, GTMPs are 'a biological medicinal product which has the following characteristics: (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.[15] Gene therapy medicinal products shall not include vaccines against infectious diseases'.

2.2 *The Approval of GTMPs*

GTMPs (as all remaining ATMPs) follow the general drug approval procedure.[16] As with any drug, they are subject to the process of drug approval set forth in the 2001 Directive, which involves an assessment of the quality, safety, and efficacy of the product. If the assessment is positive a marketing authorisation (MA) is granted, and the drug can finally reach the market.[17]

A specificity feature of ATMPs is mandatory submission to the centralised approval procedure, i.e., it is up to the European Medicines Agency (EMA) to grant the respective MA and not to national drug authorities. Only some drugs are eligible for centralised approval:[18] these are the ones that are particularly risky and/or particularly innovative. ATMPs meet both requirements.

Centralised approval assures uniform assessment, to guarantee that all GTMPs provided in Europe follow the same standards of safety and efficacy. However, this apparent uniformity of criteria has a relevant loophole that

14 Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.

15 Note that the requisites are cumulative.

16 The first GTMP approved in Europe was Glybera, in 2012, a 'drug' aimed at treating adult patients with a condition known as familial lipoprotein lipase deficiency (S. Ylä-Herttuala, 'Endgame: Glybera Finally Recommended for Approval as the First Gene Therapy Drug in the European Union', *Molecular Therapy: The Journal of the American Society of Gene Therapy* 20 (10) (2012) 1831–1832, doi: 10.1038/mt.2012.194).

17 On the drug approval process in Europe see M.I. Manley and M. Vickers, *Navigating European Pharmaceutical Law* (Oxford: Oxford University Press, 2015).

18 This category included human medicines containing a new active substance to treat particular diseases; medicines derived from biotechnology processes, such as genetic engineering; advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines; orphan medicines (medicines for rare diseases); veterinary medicines for use as growth or yield enhancer (European Medicines Agency, *Authorisation of Medicines* (10 February 2020), available online at https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#scope-of-the-centralised-procedure-section (accessed 4 November 2021)).

allows patients to receive GTMPs even before the granting of the MA: the so-called early access pathways.[19] Even though a MA is required for the GTMP (or any other drug) to enter the market, there are legal mechanisms in place aimed at allowing patients in need to have earlier access to these medicines, under the discretion of national authorities, without an MA and consequently without the technical assessment of the drug authority in charge.

2.3 *Non-Approved GTMPs*

Early access to drugs — that is, before the MA is granted, while the drug is still under development — is not unusual in European Union (EU) law.[20] The 2001 Directive allows for that possibility in Article 5 (see also Article 83 of the ATMP Regulation), under the name of 'compassionate use',[21] based on humanitarian considerations. Similar to this one is the 'named-patient use', but while the former procedure is initiated by pharmaceutical companies for a group of patients in a selected clinic or hospital, the latter originates from a request presented by a physician on behalf of specific or 'named' patient directly to the manufacturer. In the case of ATMPs, there is an additional mechanism to allow early access to these drugs, which is the so-termed hospital exception. It refers to 'medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, to comply with an individual medical prescription for a custom-made product for an individual patient' (Article 3(7) of Directive 2001/83; Article 28 of Regulation (EC) 1394/2007).[22]

In all these cases — compassionate use, named patient use and the hospital exception — the procedure is such that national authorities are allowed

19 'Early access' pathways or schemes are common designation for these procedures that allow patients to have access to medicines before they obtain the respective MA. Cf. M. Mills, O. Efthymiadou, V. Tzouma, F. Grimaccia and P. Kavanos, 'PHP15 — Early Access to Medicines Pathways — Results of a Global Survey', *Value in Health* 20 (9) (2017) A654, doi: 10.1016/j.jval.2017.08.1548.

20 An overview in D.G.M. Coppens, J. Hoekman, M.L. De Bruin, I.C.M. Slaper-Cortenbach, H.G.M. Leufkens, P. Meij and H. Gardarsdottir, 'Advanced Therapy Medicinal Product Manufacturing Under the Hospital Exemption and Other Exemption Pathways in Seven European Union Countries', *Cytotherapy* 22 (2020) 592–600, doi: 10.1016/j.jcyt.2020.04.092, at 593.

21 Cf. J. Borysowski, H.-J. Ehni and A. Górski, 'Ethics Review in Compassionate Use', *BMC Medicine* 15 (2017) 136, doi: 10.1186/s12916-017-0910-9.

22 K. Yano and M. Yamato, 'Compassionate Use and Hospital Exemption for Regenerative Medicine: Something Wrong to Apply the Program for Patients in a Real World', *Regenerative Therapy* 8 (2018) 63–64, https://doi.org/10.1016/j.reth.2018.03.002.

some discretion in their decisions[23] and so the problem arises here: these mechanisms are applied quite differently among the Member States, providing European patients GTMPs with (very) different degrees of safety and reliability.[24] The hospital exception reveals an additional problem in this regard, caused by the fact that it targets medicines prepared for individual patients, or at least for a restricted circle of patients in a given hospital, under the exclusive professional responsibility of a medical practitioner (magistral formulas) and so the treatment is usually a custom-made product, prepared on a non-routine basis and adhering to specific quality standards.[25] The diverse 'composition' of every single product adds another layer of complexity, as they are so complex that even slight differences in their composition and/or structure can condition the respective safety profile of each one.[26] Another factor hampering the control over these genetic products is the fact that some of the concepts that materialise in the hospital exception — 'non-routine basis', 'industrial manner' and 'custom made' — have still to reach an agreed uniform definition among the Member States.[27] Let's take the example of 'non-routine basis'.[28] The

23 T. Ivaskiene, M. Mauricas and J. Ivaska, 'Hospital Exemption for Advanced Therapy Medicinal Products: Issue in Application in the European Union Member States', *Current Stem Cell Research & Therapy* 12 (1) (2017) 45–51, doi: 10.2174/1574888X11666160714114854, at pp. 46–49; J. Mansnérus, 'Encountering Challenges with the EU Regulation on Advance Therapy Medical Products', *European Journal of Health Law* 22 (5) (2015) 426–461, doi: 10.1163/15718093–12341369, at 442–444.

24 An analysis of how France and the United Kingdom interpret the requisites set up by the Regulation is provided in A. Dupraz Poiseau, and N. Thomas, 'The EU hospital Exemption Scheme for Advanced Therapies: A Valuable Tool to Support Innovation or a Regulatory Path Leading to a Fragmented Market? Examples of National Implementation in France and UK', *Cytotherapy* 16 (4) (2014) S52, doi: 10.1016/j.jcyt.2014.01.189.

25 C. MacGregor, A. Petersen and M. Munsie, 'Regulation of Unproven Stem Cell Therapies — Medicinal Product or Medical Procedure?', *EuroStemCell* (30 August 2015), available online at https://www.eurostemcell.org/regulation-unproven-stem-cell-therapies-medicinal-product-or-medical-procedure (accessed 5 December 2021).

26 D. Horgan, A. Metspalu, M.C. Ouillade, D. Athanasiou, J. Pasi, O. Adjali, P. Harrison, C. Hermans, G. Codacci-Pisanelli, J. Koeva, T. Szucs, V. Cursaru, I. Belina, C. Bernini, S. Zhuang, S. McMahon, D. Toncheva and T. Thum, 'Propelling Healthcare with Advanced Therapy Medicinal Products: A Policy Discussion', *Biomed Hub* 5 (3) (2020) 130–152, doi: 10.1159/000511678, at p. 140.

27 C. Eder and C. Wild, 'Technology Forecast: Advanced Therapies in Late Clinical Research, EMA Approval or Clinical Application Via Hospital Exemption', *Journal of Market Access & Health Policy* 7 (1) (2019), doi: 10.1080/20016689.2019.1600939.

28 A. Hills, J. Awigena-Cook, K. Genenz, M. Ostertag, S. Butler, A.-V. Eggimann and A. Hubert, 'An Assessment of the Hospital Exemption Landscape Across European Member States: Regulatory Frameworks, Use and Impact', *Cytotherapy* 22 (12) (2020) 772–779, doi: https://doi.org/10.1016/j.jcyt.2020.08.011, at p. 773.

British Medicines and Healthcare Products Regulatory Agency, for instance, issued a guidance note on the concept of 'non-routine basis', which recognises the difficulty in committing to a specific number of uses and states as an alternative that 'the scale and frequency of HE ['hospital exception'] ATMP production will be considered'. In Germany, following the guidance of the Paul Ehrlich Institute, the concept 'non-routine basis' is commonly understood as referring to drugs 'manufactured and used on such a small scale that it cannot be expected that sufficient clinical experience will be gained to enable the medicinal product to be fully evaluated'.[29] Most jurisdictions, however, shine no light on this issue. In essence, how many patients can be treated with the drug without it being considered a 'routine basis' is not defined.[30] Similar doubts involve the remaining concepts used to describe the hospital exception.

The flexibility that early access pathways provide for the rigid mechanism of MA approval is much appreciated. However, the extreme novelty and complexity of GTPM's cannot be underestimated. These features would require strict control on the way gene therapy drugs are provided to patients in the whole of European territory. This is not, however, what happens. Under the pretence of expediting medical care, GTMPs provided under early access pathways largely escape the required checks and controls.

3 The Risks of Unproven and Unregulated GTMPs

Medical procedures involving gene therapies are still a 'work in progress'. What we already know is that many potential hazards may take place: tumour formation, tissue rejection, autoimmunity, permanent disability and even death.[31]

29 Paul Ehrlich Institute, German Medicinal Products Act (Arzneimittelgesetz AMG) (2019), available online at at http://www.gesetze-im-internet.de/englisch_amg/englisch_amg.html#p0060 (accessed 23 November 2021).

30 Medicines and Healthcare Products Regulatory Agency, *Guidance on "Non Routine"* (2021), available online at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/397739/Non-routine_guidance_on_ATMPs.pdf (accessed 2 November 2021).

31 M. Carvalho, B. Sepodes, and A.P. Martins, 'Regulatory and Scientific Advancements in Gene Therapy: State-of-the-Art of Clinical Applications and of the Supporting European Regulatory Framework', *Frontiers in Medicine* 4 (2017) 182, doi: 10.3389/fmed.2017.00182; G. Műzes and F. Sipos, 'Issues and Opportunities of Stem Cell Therapy in Autoimmune Diseases', *World Journal of Stem Cells* 11 (4) (2019) 212–221, doi: 10.4252/wjsc.v11.i4.212; Z. Wang, X. Liu, F. Cao, J.A. Bellanti, J. Zhou and S.G. Zheng, 'Prospects of the Use of Cell Therapy to Induce Immune Tolerance', *Frontiers in Immunology* 11 (2020) 792, doi: 10.3389/fimmu.2020.00792.

When such therapies are used before being properly approved and certified, the risks dramatically increase.[32]

All around the world we can find alarming incidents related to the provision of unproven GTMPs without proper monitoring, based on a market logic and not on a healthcare logic. Europe is no exception.

An infamous episode in Europe involved the Stamina Foundation, a charitable entity based in Italy, which was providing allogenic intravenous injections — classified as an ATMP — to patients with different medical conditions, under the payment of 'generous' amounts.[33] The norms on compassionate use were invoked as a basis for the use of these drugs, but an inspection by the Italian drug authorities found out that the requirements had not been met, mostly because the ATMP lacked sufficient clinical evidence (the existing evidence was merely testimony from 'treated' patients). Surprisingly, and despite these findings, the Stamina Foundation managed to get a judicial ruling allowing its activity, later confirmed by a governmental decree.[34] However, later on, several individuals with connections to the Stamina Foundation ended up facing court proceedings and some of them were even arrested.[35]

Another example of what happens when ATMPs are not properly monitored refers to X-Cell, for long the largest stem cell clinical network in Europe, based in Germany. It built a name for itself by providing unproven transplantations of autologous bone marrow stem cells for neurological disorders, injecting them into the brain, spinal cord or other body parts of patients. The price of those treatments was around 26 000 euros. From the beginning, the practice of these clinics generated suspicions, but not even the entry into force of

32 P. Bianco, 'Don't Market Stem-Cell Products Ahead of Proof', *Nature* 499 (7458) (2013) 255, doi: 10.1038/499255a; P. Foong, 'Regulating Unproven Stem Cell Interventions: How Effective Are the ISSCR Guidelines?', *Biotechnology Law Report* 39 (3) (2020) 196–203; L. Richardson, 'Harms Linked to Unapproved Stem Cell Interventions Highlight Need for Greater FDA Enforcement', *PEW* (1 June 2021), available online at https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/06/harms-linked-to-unapproved-stem-cell-interventions-highlight-need-for-greater-fda-enforcement (accessed 12 December 2021).

33 Cf. Emmanuelle Rial-Sebbag, and Alessandro Blasimme, 'The European Court of Human Rights' ruling on unproven stem cell therapies: a missed opportunity?' *Stem Cells and Development* 23(1) (2014) 39–43, doi: 10.1089/scd.2014.0361, at 16–17.

34 C. Hornby, 'Scientists Criticize Italy for Allowing Unproven Stem Cell Therapy', *Reuters* (29 March 2013), available online at https://www.reuters.com/article/us-italy-stemcell-idUSBRE92R0UD20130328 (accessed 23 October 2021); P.J. Zettler, 'Compassionate Use of Experimental Therapies: Who Should Decide?', *EMBO Mol Med* 7(10) (2015) 1248–1450, doi: 10.15252/emmm.201505262.

35 A. Abbott, 'Disgraced Stem-Cell Entrepreneur Under Fresh Investigation', *Nature* 539 (2016) 340, doi: 10.1038/539340a.

the ATMP Regulation (in 2009 in Germany) managed to shut them down, as the Regulation came with an 18-month transition period. After that period the clinics failed to ask for a license to operate and they were finally shut down, but they moved to Lebanon, where they continue with their doubtful 'therapeutic' procedures. Its medical practice was mired in scandal: severe internal bleeding in the head of a 10-year-old boy following cell injections into the brain; and the death of an 18-month-old infant after receiving a stem cell treatment with brain injections.[36] Money was a central element in the clinics' daily practice and they were managed more as a tourist destination than a medical one (e.g., X-Cell representatives were waiting for patients at train stations or airports to drive them to their hotel).

These two cases specifically relate to stem cell drugs, but the legal framework that facilitated its occurrence is the same one that rules gene therapy drugs, and thus it is fair to assume that it can lead to the same results. Up until now, specialised literature has not revealed high profile cases with genetic unauthorised drugs.

4 Are Pharmaceutical Norms Promoting Unsafe Genetic Tourism?

All the three early access pathways — compassionate use, named patient use and the hospital exception — fall under the competence of national authorities, which decide their requirements without the desired consistency.[37] Manipulated by less scrupulous providers of genetic 'treatments', the norms

36 A. Abbott, 'Notorious Stem Cell Therapy Centre Closes in Germany', *Blogs Nature* (9 May 2011), available online at http://blogs.nature.com/news/2011/05/notorious_stem_cell_therapy_ce_1.html (accessed 12 December 2021); C. MacGregor, A. Petersen and M. Munsie, 'Stem Cell Tourism: Selling Hope Through Unproven Stem Cell Treatments — Lessons from the X-Cell Center Controversy', *EuroStemCell* (30 April 2015), available online at https://www.eurostemcell.org/stem-cell-tourism-selling-hope-through-unproven-stem-cell-treatments-lessons-x-cell-center (accessed 3 January 2022); J. Yee, 'Europe's Biggest Stem Cell Clinic Shut Down After Baby's Death' *Bioedge* (14 May 2011), available online at https://bioedge.org/uncategorized/europes-biggest-stem-cell-clinic-shut-down-after-babys-death/ (accessed 4 December 2021).

37 An additional problem linked to the abuse of these special procedures is that they (especially the hospital exception) are being used to circumvent the drug approval procedure, discouraging investment in fully approved ATMPs. More details in Alliance for Regenerative Medicine, *Recommendations for the use of Hospital Exemption* (10 October 2020), available online at http://alliancerm.org/wp-content/uploads/2020/10/ARM-position-on-HE-final-Oct-2020.pdf (accessed 30 November 2021).

on early access pathways gave rise to genetic paradises, where control is loose and profits flow.

One would think that unapproved ATMPs were only possible in jurisdictions with little regulation in this area, but actually there are reports of clinics offering unapproved ATMPs in apparently highly regulated pharmaceutical jurisdictions, such as the ones we have in Europe.[38] Several reasons justify this regulatory loophole. Some national drug authorities — AIFA (Italy), AEMPS (Spain), ANSM (France) and IGJ (the Netherlands) — merely require ATMPs manufactured under a hospital exception to comply with the EU regulations for ATMPs. This may seem enough, but as those norms are based on a risk-based approach, they leave a wide margin of discretion for national authorities to assess what is being provided to patients and it remains unclear how demanding (or how flexible) the procedure is.[39] Moreover, in some jurisdictions — France, Germany, Italy, Poland, The Netherlands — regulatory authorities do not explicitly require ATMPs provided within the hospital exception to have been previously clinically tested.[40]

Disparities in the way ATMPs (including GTMPs) are provided have fostered a kind of 'genetic tourism' (a specific form of medical tourism)[41] in Europe, whereby desperate patients look for the more 'genetically-loose' jurisdictions, i.e., the ones in which access to ATMPs is simpler, cheaper and more loosely controlled. This phenomenon was identified long ago. Back in 2010, the Committee for Advanced Therapies expressed its concerns 'about a phenomenon known as stem-cell tourism[42] in which severely ill patients travel to clinics around the world where unauthorised stem-cell-based treatments are offered in the absence of rigorous scientific and ethical requirements. Some clinics offer these unauthorised therapies to desperate patients with incurable diseases at a high cost without ethics approval from independent bodies and potentially without documentation of adequate quality standards necessary for the protection of patients' safety'.[43]

38 Z. Master, K.R.W. Matthews and M. Abou-el-Enein, 'Unproven Stem Cell Interventions: A Global Public Health Problem Requiring Global Deliberation', *Stem Cell Reports* 16 (6) (2021) 1435–1445, doi: 10.1016/j.stemcr.2021.05.004.

39 Hills et al., *supra* note 28, at 773–774.

40 *Ibid*., at 775.

41 B. Gharaibeh, J. Anderson and B.M. Deasy, 'Combating the Threat of Stem Cell Tourism through Patient Education and Government Regulation', *Innovation and Entrepreneurship in Health* 3 (2016) 15–24, doi: 10.2147/IEH.S56239, at pp. 15–16.

42 The concerns about 'stem cell tourism' also apply top genetic tourism.

43 Committee for Advanced Therapies and CAT Scientific Secretariat, 'Use of Unregulated Stem-Cell Based Medicinal Products', *The Lancet* 376 (9740) (2010) 514, doi: 10.1016/S0140-6736(10)61249-4.

Patients in need, and frequently losing hope, are willing to leave their homes and travel to such dubious 'genetic resorts', many unaware of the lack of clinical data supporting their genetic adventure. They engage in procedures at best ineffective and possibly even unsafe.[44] Due to the lack of transparency — we do not have accurate data on how many ATMPs are being provided to patients nor about their safety and effectiveness[45] — only more serious outcomes become public, but it is fair to assume that several minor incidents might take place with these non-approved drugs.

5 Should We Abolish Unproven GTMPs?

GTMPs offer promising possibilities in terms of personalised medicine[46] and, overall, hope for many patients afflicted by serious diseases — either caused by one single gene or by multiple genes — for which there are no other therapeutic alternatives available.[47]

Even unproven ATMPs might bring benefits to patients and in some cases they are the only option. However, because of the long wait for the MA they might arrive too late on the market. All drugs (each and every one) require lengthy approval procedures; when genes are involved the assessment becomes even more complex.[48] Due to the particularities of GTMPs, the procedure for drug authorization cannot be as standardized as with other drugs. To circumvent some of the obstacles posed by these GRMP's (and ATMPs in general), EMA drafted a risk-based approach, 'based on the identification of various risks associated with the clinical use of an ATMP and risk factors inherent to the

44 S. Jawad, A. Al-Yassin, D. Herridge, W.K.L. Lai, N. Rozario and J. Hendy, 'Safeguarding Patients Against Stem Cell Tourism', *British Journal of General Practice* 62 (598) (2012) 269–270, doi: 10.3399/bjgp12X641591, at p. 269.

45 Cf. Al Alliance for Regenerative Medicine, *supra* note 37 (the Alliance urges doctors involved in these practices to collect more data to increase transparency).

46 Horgan et al., *supra* note 26.

47 Carvalho et al., *supra* note 31, at p. 182; A. Elsanhoury, R. Sanzenbacher, P. Reinke and M. Abou-El-Enein, 'Accelerating Patients' Access to Advanced Therapies in the EU', *Molecular Therapy: Methods & Clinical Development* 7 (2017) 15–19, doi: 10.1016/j.omtm.2017.08.005, at 15.

48 Coppens et al., *supra* note 21; A. Loche, N. Paolucci, N. Peters and L. Van der Veken, 'A Call to Action: Opportunities and Challenges for CGTs in Europe', *McKinsey and Company* (2021), available online at https://www.mckinsey.com/industries/life-sciences/our-insights/a-call-to-action-opportunities-and-challenges-for-cgts-in-europe (accessed 4 December 2021); S. Ylä-Herttuala, 'The Need for Increased Clarity and Transparency in the Regulatory Pathway for Gene medicines in the European Union', *Molecular Therapy* 20 (3) (2012) 471–472, doi: 10.1038/mt.2012.1.

ATMP with respect to quality, safety and efficacy'.[49] this strategy profiles each risk that is inherent to the product (not the general risk of a product),[50] and thus is quite complex and time-consuming. These barriers end up restricting access until drug authorities are satisfied with the scientific evidence, even in cases where sound data on these products' safety and efficiency are already available. For these reasons, an absolute ban on unproven GTMPs — that is, gene therapy drugs provided under early access pathways — would prevent patients in need from having easier and faster access to gene editing therapies that might save their lives.

6 Some Suggestions for the Future

There are several scenarios in which patients receive unproven gene editing therapies in a legitimate way. This usually happens in the framework of standardised, clinically sanctioned and legally based clinical trials. It might also happen within early access pathways. However, the very rules of those legal mechanisms give rise to practices in a grey area,[51] that might take advantage of the lack of control, raising a clear public health problem.[52]

This outcome is a complete subversion of the original intents of early access pathways. They were not created to break the strict rules on drug approval, but to confer some flexibility on their (most criticised) rigidity.[53] However, they should only operate regarding gene therapy drugs that, though still under development, have already proven to be reasonably safe to be used by humans. Otherwise, it is pure human experimentation and, more than that, economic exploitation of people in very fragile situations.

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49 European Medicines Agency, *Guideline on the Risk-Based Approach According to Annex I, Part IV of Directive 2001/83/EC Applied to Advanced Therapy Medicinal Products* [*EMA/CAT/CPWP/686637/2011*] (2013), available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139748.pdf (accessed 12 December 2021), at p. 3.

50 *Ibid.*, at p. 4.

51 Claiming for more regulation, P. Bianco, '"Commercial Stem Cells" Damage Medicine: Medicine is Aware', *Recenti Progressi in Medicina* 106 (11) (2015) 538–539, doi: 10.1701/2074.22484.

52 Master et al., *supra* note 38.

53 European Federation of Pharmaceutical Industries and Associations, *The Root Cause of Unavailability and Delay to Innovative Medicines: Reducing the Time Before Patients Have Access to Innovative Medicines* (2020), available online at https://www.efpia.eu/media/554527/root-causes-unavailability-delay-cra-final-300620.pdf (accessed 11 December 2021).

The problem is not so much the fact that these therapies are unproven, but the fact they are unregulated.[54] When regulated, even therapies without the entire set of clinical evidence can be beneficial. The original aim guiding the implementation of early access pathways was, in my perspective, to allow access to unproven therapies, but in a regulated manner. However, the regulation part of the equation was lost along the way. National states, which run these mechanisms of early access, failed to establish clear practices and adequate control in this regard.

The provision of GTMPs within early access pathways should not be banned due to the benefits referred to in the previous sections. However, I do advocate two types of measures to circumvent potential health hazards: i) transparency and specific information duties; ii) proper monitoring by the different entities in charge.[55]

6.1 *Trustworthy Information*

6.1.1 A Duty to Provide Transparent Information

In the medical field in general there can be no misinformation, no false expectations, no deception. Right now, many cases of early access pathways involving GTMPs are pure quackery and non-enlightened patients are an easy target. Therefore, patients should be provided with trustworthy information about what they can expect from non-approved GTPM's.[56]

Studies show that patients who have received clear explanations and who have informed participation in medical decision making are less willing to accept risky treatments.[57] However, often patients do not realise that drugs provided under these early access pathways are still experimental procedures, as they have not been fully tested and assessed by the competent drug

54 The distinction between the two in L. Riva, L. Campanozzi, M. Vitali, G. Ricci and V. Tambone, 'Unproven Stem Cell Therapies: Is It my Right to Try?', *Annali Istituto Super Sanita* 55 (2) (2019) 179–185, doi: 10.4415/ANN_19_02_10, at 181.

55 Other measures that have been suggested to circumvent medical tourism (and that can also be applicable to genetic tourism) is patent law to restrict the use of technology. See J.S. Sherkow, E.Y. Adashi, and I.G. Cohen, 'Governing Human Germline Editing Through Patent Law', *Journal of the American Medical Association* 326 (12) (2021) 1149–1150, doi: 10.1001/jama.2021.13824.

56 A. Zarzeczny, H. Atkins, J. Illes, J. Kimmelman, Z. Master, J.M. Robillard, J. Snyder, L. Turner 7, P.J. Zettler, and T. Caulfield, 'Stem Cell Market and Policy Options: A Call for Clarity', *Journal of Law and the Biosciences* 5 (3) (2018) 743–758, doi: 10.1093/jlb/lsy025, at pp. 753–756.

57 L. Fraenkel and E. Peters, 'Patient Responsibility for Medical Decision Making and Risky Treatment Options', *Arthritis and Rheumatism* 61 (12) (2009) 1674–1676, doi: 10.1002/art.24947.

authorities. Moreover, patients are not able to fully understand the risks and benefits of such therapies,[58] and thus they create great expectations that in the end are frustrated, sometimes causing severe damage.[59]

Information in this regard has two dimensions: (a) the real benefits of gene editing treatments,[60] which at this moment are not totally clear, and the potential hazards involved, so that patients do not overestimate the outcomes; (b) the particular risks they incur when taking non-authorised drugs, for which there are not enough data available, any or not enough clinical evidence and no final assessment from a drug authority.

6.1.2 Should Informed Patients Still Be Protected from Their Own Decision?

A basic premise of modern health law is patients' self-determination regarding the treatments they want (or do not want) to receive. Therefore, informed patients should be allowed to use unproven medical treatments if that is their desire.

However, many have spoken out against the right of terminally ill patients to use risky treatments, such as non-approved drugs, even when there are no other therapeutic alternatives.[61] It has been stated that because patients who resort to these therapies are usually extremely vulnerable[62] — they have reached the end of the line — they should not be allowed to make such choices.[63]

Likewise, some court decisions have upheld this understanding. In Hristozov and others v. Bulgaria,[64] and in Durisotto v. Italy[65] (related to the Stamina

58 Therefore, patient education is a must. Cf. Z. Master and D.B. Resnik, 'Stem-Cell Tourism and Scientific Responsibility', EMBO *Reports* 12 (10) (201) 992–995.

59 Poulos, *supra* note 8.

60 Gharaibeh et al., *supra* note 41, at pp. 17–18.

61 See the considerations of Rial-Sebbag and Blasimme (*supra* note 33, at p. 41): 'The fact that a patient has exhausted all other therapeutic options is not enough to overlook those considerations'.

62 'Exposing the weakest people to unknown risks is ethically unacceptable', P. Bianco, R. Barker, O. Brüstle, E. Cattaneo, H. Clevers, G.Q. Daley, M. De Luca, L. Goldstein, O. Lindvall, C. Mummery, P.G. Robey, C. Sattler de Sousa e Brito and A. Smith, 'Regulation of Stem Cell Therapies Under Attack in Europe: For Whom The Bell Tolls', *EMBO Journal* 32 (11) (2013) 1489–1495, doi: 10.1038/emboj.2013.114, at 1491.

63 'There should not be a "right to try" something that is unsafe but rather approved treatments and in line with good clinical practic' (Riva et al., *supra* note 54, at p. 179). It is not clear from the paper if the authors would be willing to accept the so called 'right to try' if these therapies present more safety tests or if patients were more enlightened.

64 *Hristozov and others v. Bulgaria*, 2013, nos. 47039/11 and 358/12.

65 *Durisotto vs Italy*, Application no. 62804/13, European Court of Human Rights (HUDOC), 2014. A comment to this case in Rial-Sebbag and Blasimme, *supra* note 33.

Foundation) the ECHR gave precedence to the patient's protection (including from their own 'reckless' decisions) rather than personal self-determination. In Durisotto, the ECHR was asked to ascertain whether a governmental decree could establish the conditions under which the compassionate use of ATMPS could be provided to new patients (that is, patients not previously included in the treatment). The case was presented as a violation of the ECHR's norms — Article 2 (right to life), Articles 8 (right to respect for private life) and 14 (prohibition of discrimination) — to sustain the person's right to freely decide what experimental treatments to receive (more specifically, the right of the father to decide about the experimental treatments to be provided to the daughter, of whom he was the legal guardian). The Court, however, dismissed the claimants' arguments. As regards the right to private life, the Court stated that 'the interference with the right of the applicant's daughter to respect for her private life may therefore be considered necessary in a democratic society' (para. 41) and that the judicial decision preventing access to the Stamina treatment 'pursued the legitimate aim of protecting health and was proportionate to it (…) the scientific value of the method in question has not been established at the present time' (para. 48).

If this premise were true, informed consent would have to be abolished for a myriad of medical acts performed on severely ill patients. I believe that the particular vulnerability of these patients justifies further protection than in normal situations, but the law cannot be paternalistic. Additional protection from reckless decisions cannot lead to a ban on their free choice, even when it comes to risky treatments.[66]

6.2 *Greater Control by Authorities in Charge*

The different authorities in charge — drug authorities, health regulatory agencies and medical associations — should exercise greater control over the provision of GTPM's under early access pathways. This cannot be under the pure responsibility of the medical practitioner, nor be purely dependent on national governments decisions. There are recommendations from the EMA

66 In the US the so called 'right to try' — that is, the patient's right to use drugs under development — was claimed for a long time and it was finally passed in law in 2018. Cf. R. Agarwal and L.B. Saltz, 'Understanding the Right to Try Act', *Clinical Cancer Research* 26 (2) (2020) 340–343, doi: 10.1158/1078-0432.CCR-19-2015.

More radically, Flanigan (J. Flanigan, 'Three Arguments Against Prescription Requirements', *Journal of Medical Ethics* 38 (2012) 579–586) argued in favour of a right to self-medicate oneself based on personal autonomy. In this paper I speak in favour of personal autonomy, but not to the extent that the patient should be allowed to medicate himself/herself.

on compassionate use (including the type of patients who can benefit from it), but when it comes to the other mechanisms the EMA's intervention is almost nil. It is crucial to set up guidelines/recommendations, or, eventually, binding documents, which, therefore, would hold those in non-compliance responsible. Such scientific guidelines should establish minimum thresholds of demonstrable safety for GTMPs to be provided to patients, which, in turn, require a certain amount of clinical evidence to base such threshold. Right now, there are no minimum requirements regarding the safety and efficacy of GTMPs under early pathways procedures, so, in theory, even gene editing products without any clinical evidence can be provided.

In addition to monitoring the gene editing product itself, the physicians who prescribe it should also be under stricter control by the authorities in charge of regulating the medical profession. These authorities should quickly identify and stop medical practitioners carrying out deceitful practices involving GTMPs.[67] A strict ban on misleading adverting should also be in place.

Up until now, disciplinary medical boards have acted reactively to sanction doctors, but failed to act proactively to monitor such practices, perhaps due to the lack of resources, namely, of staff with expert knowledge in the particular domain of gene editing products.[68]

Control and sanctioning by medical professionals has the advantage of allowing a technical assessment of each case by experts in the field, instead of leaving matters to a court of law. The appearance of expert witnesses might not be enough to assist judges — laymen in the matter — in such complex and technical (in scientific terms) issues, for which specific expertise is required.[69] There is, however, a downside: professional regulation tends to vary a lot across jurisdictions, so we might end up with the very same problem raised by early access pathways, that is, disparity in assessment, giving rise to very different practices.

7 Concluding Notes

The use of unproven GTMPs under a fragmentary legal framework is leading to genetic paradises and 'genetic no man's land', which threaten patient

67 A. Zarzeczny, T. Caulfield, U. Ogbogu, P. Bell, V.A. Crooks, K. Kamenova, Z. Master, C. Rachul, J. Snyder, M. Toews and S. Zoeller, 'Professional Regulation: A Potentially Valuable Tool in Responding to "Stem Cell Tourism"', *Stem Cell Reports* 3 (2014) 379–384, http://dx.doi.org/10.1016/j.stemcr.2014.06.016, at pp. 381–382.

68 *Ibid.*, at pp. 381–382.

69 *Ibid.*, at p. 381.

safety and discredit genetic therapies by spreading a general mistrust about them. The lack of clear regulation and proper monitoring of these early access mechanisms leaves desperate patients unprotected from unscrupulous health care providers.

To avoid this outcome the simplest solution would be to abolish any provision of GTMPs that are not duly approved and only allow GTMPs with their respective MA. However, by doing so we would be depriving patients in extreme need of what could be their last chance of survival. Not all non-authorised GTPM's are dangerous. The key is not to simply to abolish early access pathways, but to impose more reliable information requirements and more checks and controls.