

LIMITING ACCESS TO UNAPPROVED THERAPIES: A PATERNALISTIC PRACTICE?¹

LIMITANDO O ACESSO A TERAPIAS NÃO APROVADAS: UMA PRÁTICA PATERNALISTA?

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Abstract: The aim of the article is to answer the question of whether the limitations of the access to unapproved therapies outside of clinical trials are permissible in light of the modern paradigm of health care which is based on the patients' autonomy of will. We only focus on the therapies consisting in the provision of unregistered medicinal products. The law is often restrictive in allowing patients to be provided with experimental therapies even if they grant fully informed consent. The Czech law and a recent Czech case of an unapproved stem cell therapy provide a basis for the analysis of the problem with universally applicable conclusions. We argue that the regulation of access to unapproved therapies serves an important public interest of the protection of public trust in the health system and hence is justified. The law should only permit access to experimental therapies that have sufficient scientific justifications. Under certain conditions, the patients can be allowed to cover the costs of the therapy.

Keywords: Health law. Unapproved therapies. Stem cell therapies. Medical paternalism. The Czech Republic.

Resumo: O objetivo deste artigo é responder sobre se são permitidas as limitações do acesso a terapias não aprovadas fora dos ensaios clínicos, à luz do paradigma moderno dos cuidados de saúde, que se baseia na autonomia de vontade dos pacientes. O debate do texto se concentra nas terapias que consistem no fornecimento de medicamentos não registrados. A lei é muitas vezes restritiva ao permitir que os pacientes recebam terapias experimentais, mesmo que concedam consentimento totalmente informado. A lei tcheca e um recente caso tcheco de terapia com células-tronco não aprovada fornecem uma base para a análise do problema com conclusões universalmente aplicáveis. Argumentamos que a regulamentação do acesso a terapias não aprovadas atende a um importante interesse público da proteção da confiança pública no sistema de saúde e, portanto, é justificada. A lei deve permitir apenas o acesso a terapias experimentais com justificativas científicas suficientes. Sob certas condições, os pacientes podem cobrir os custos da terapia.

Palavras-chave: Legislação sanitária. Terapias não aprovadas. Terapias com células-tronco. Paternalismo médico. República Tcheca.

Recebido em 18 de outubro de 2019

Aceito em 18 de outubro de 2019

¹ The article was written with the support of the Charles University Grant Agency (GA UK) research project no. 910319 *Legal Paradigm of Medical Research: Civil Liability for Death and Bodily Harm*.

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Introduction

In a certain way, the medical research progresses both quickly and very slowly. With the pharmaceutical industry searching for new active substances—and the new uses of the previously known ones—there often arises hope for more effective cures of many serious health conditions. On the other hand, most medicinal products do not succeed in clinical trials and even if their potential becomes proven in the end, the process of clinical trials takes many years. At the same time, each clinical trial is designed to involve a certain number of participants who must fulfil the defined criteria (i.e. certain age or stage of progress of the disease). As a result, there are patients suffering from life-threatening or debilitating diseases who are not allowed to participate in clinical trials of medicinal products that could help them. It is very understandable that these people often try to get access to the new—and not yet registered—medicines any other way.

During the last decades, the paradigm of health care shifted from paternalism to the autonomy-based approach.³ It would seem that willing patients should be allowed to try unapproved therapies if they represent their last hope. The denial of access to these treatments could be understood as unduly limiting the patients' autonomy of will and their right to health. However, the situation is rather complex.

Unfortunately, the vulnerability of such patients can be abused by the rogue vendors of unapproved cures. And to make the situation even worse, it is often not easy to recognise whether a certain provider of unregistered medicines is a deceiver or a well-meaning person who wishes to give the patients a spark of hope. The rules for the provision of unapproved therapies are often not entirely clear and even more ambiguous is the ethical evaluation of such situations.

In this article, we will analyse several related ethical and legal problems in order to determine whether limitations of the access to unapproved therapies are permissible from the perspective of the contemporary paradigm of autonomy-based health care. On the general level, we will ask whether the limitations of the access to unapproved therapies represent a paternalistic approach and if so, whether they are permissible from the ethical point of view.

Then, we will focus on two possible criteria of access to unapproved therapies which might be controversial. First, we will ask whether the criterion of sufficient scientific justification of the use of unapproved therapy is suitable (and, of course, how to measure this justification). Second, we will analyse whether the patients should be allowed to pay for the therapy. The debate on both of these criteria can be illustrated by the recent Czech case of stem cell therapy of ALS.

³ For a Czech experience with the rather rapid change of medical paradigm, cf. Šustek (2018).

It may seem that the core of the problem is the conflict between the principle of non-maleficence and the principle of autonomy as two of the leading principles of medical ethics.⁴ However, we will argue that the problem is more complex since there must be also taken into account the public interest in a functioning health system.

It needs to be noted that while medical research encompasses also evaluation of medical devices and evaluation of new methods not yet established in clinical practice (Šustek, 2016b),⁵ this article focuses on the access to unapproved medicinal products. (p. 688).

1 International Perspectives

The debate on the rules for access to unapproved therapies is particularly strong in the USA nowadays, where there have been discussed the so-called *Right to Try* laws (Caplan, 2016). Nevertheless, the cases of provision of unapproved medicines are very usual in many countries. Most often, these controversies are connected to stem cell therapies:⁶ we can recall the vast numbers of clinics providing these therapies in the legal shadow in many countries of the world. (Maron, 2016, & Šolc, 2018, p. 47-53).

An interesting example might be the Italian case of a stem cell therapy called the Stamina method provided by the private Stamina Foundation. The method was harshly criticised for being ineffective, for failing to secure patient safety, and for the ignorance of certain scientific findings. The Stamina treatment, nevertheless, could have been provided to the patients since Italian law allows the use of an unregistered medicinal product outside of a clinical trial in patients whose health or life is under threat and for whose health condition there exists no therapeutic alternative. The use of the Stamina method did not stop until the new legislation was enacted, practically prohibiting the application of stem cell therapies in most new cases. (Šolc, 2018, p. 92-93.) The controversy was finally solved by the European Court of Human Rights in its decision in case *Durisotto v. Italy* of 6 May 2014, application No. 62804/13 (*Durisotto v. Italy*, 2014). According to the Strasbourg court, the limitation of access to unapproved therapy represents an interference with the right to respect for private and family life but it can be considered necessary in a democratic society for the protection of health (in the sense of Article 8 (2) of the European Convention on Human Rights). Furthermore, the court stated that the level of permissible risk of unapproved therapy is to be set by the organs of particular states.

⁴ In their influential book *Principles of Biomedical Ethics*, Beauchamp and Childress (2013) identify four basic principles of medical ethics: respect for autonomy, nonmaleficence, beneficence, and justice. (pp. 101-301). Beauchamp and Childress (2013) aptly denote paternalism as a conflict between beneficence and autonomy. (pp. 214-215).

⁵ Under Czech law, the evaluation of medical devices is regulated by The Czech Republic Act No. 268 Coll., on Medical Devices (2014), and the evaluation of new methods not yet established in clinical practice is regulated by The Czech Republic Act No. 373 Coll., on Specific Health Services (2011b).

⁶ For an overview of the history of stem cell research in Brazil (Teixeira Zorzaneli, Speroni, Menezes, and Leibing (2017).

2 Legal Regulation in the Czech Republic

According to Article 8 (1) of The Czech Republic Act No. 378 Coll., on Pharmaceuticals (2007) (hereinafter “Act on Pharmaceuticals”), it is generally only legal to prescribe, put on the market, or use registered medicinal products. However, consistently with the EU law, there are several exemption from this rule.^{7,8}

The most practical and useful of these exemptions is the regime under Article 8 (3) and (5) of Act on Pharmaceuticals which is sometimes called *compassionate use*. This regime is also the only exemption which does not require the authorisation of either the State Institute for Drug Control (*Státní ústav pro kontrolu léčiv*, hereinafter “SÚKL”) or the Ministry of Health.

The compassionate use under Article 8 (3) and (5) of The Czech Republic Act No. 378 Coll., on Pharmaceuticals (2007) is always related to an individual patient. Since no official authorisation is required, the treating physician is only obliged to immediately inform the SÚKL about the prescription or the use of an unregistered medicinal product. There are several cumulative conditions for compassionate use under the law. There are certain conditions regarding the medicinal product intended to be used.⁹ There must be no medicinal product with the same composition or analogic therapeutic properties in the distribution or in circulation on the market in the Czech Republic. Furthermore, the use of the medicinal product must be sufficiently justified by scientific knowledge. The medicinal product cannot contain any genetically modified organism.

The physician is obliged to inform the patient (or their legal representative) about the intent to use an unregistered medicinal product and about the consequences of the treatment. If the patient cannot be informed due to their health condition, the physician will immediately provide the information when it becomes possible. The fact that the medicinal product is unregistered must also be noted in the prescription.

3 The Czech Case of an ALS Stem Cell Therapy

After Sweden, the Czech Republic was the second country in Europe where there was successfully derived a stem cell line. (Kuře, 2009, p. 67). It is not surprising that to this day, the

⁷ Apart from the below-mentioned regime under Article 8 (3) and (5) of The Czech Republic Act No. 378 Coll., on Pharmaceuticals (2007), these exemptions are the hospital exemption for advanced therapy medicinal products (Sections 49a and 49b of Act on Pharmaceuticals), the specific treatment programmes utilising unregistered human medicinal products (Section 49 of Act on Pharmaceuticals), and the temporary authorisation of the Ministry of Health in case of an exceptional situation (Section 8 (6) of Act on Pharmaceuticals).

⁸ For a more detailed analysis of the exceptions from the prohibition of the use of an unregistered medicinal product in the Czech Republic, cf. (in the Czech language). (Šolc, 2018, pp. 191-197).

⁹ It must either be registered in another state, or be an advanced therapy medicinal product whose manufacturer is a holder of a permission to manufacture the relevant dosage form in the scope corresponding to the permission to manufacture evaluated medicinal products issued by the SÚKL. Cf. Article 8 (3) of The Czech Republic Act No. 378 Coll., on Pharmaceuticals (2007).

country has seen several cases of controversial stem cell therapies. The most famous one regarded the application of experimental stem cell therapy of amyotrophic lateral sclerosis (ALS).¹⁰ The case was made public in a TV report broadcasted in November 2015 (Obchod, 2015) and immediately attracted wide media attention. A clinical trial of the therapy was undergoing at the Motol University Hospital in Prague, one of the largest hospitals in Europe.¹¹ At the same time, a team led by a Czech scientist Professor Eva Syková provided the therapy to the patients who were not eligible for the trial. From the legal perspective, the stem cells were applied under the regime of the compassionate use according to Section 8 (3) and (5) of Act on Pharmaceuticals. Syková's team allegedly informed the patients that it would be possible to apply stem cells outside the frame of the trial but that they would have to cover the costs of the cultivation of stem cells. Officially, patients were not allowed to pay directly for their treatment and their financial contribution was labelled as a donation for research. While stem cells were cultivated by the private company Bioinova, the donations were made to the non-governmental organisation *Buněčná terapie (Cell Therapy)* which was chaired by Syková and which had its registered office at the same address as Bioinova.

Syková later stated that nobody was promised the therapy based on the donation. Nevertheless, the donation was a necessary condition for the patients to be provided with the therapy. The amount of payment was approximately 150.000 CZK (approximately 5.750 EUR). While the sum could reflect the real costs of the cultivation of stem cells for one patient, many critics considered it highly unethical to demand money for the experimental treatment.

The case was a high-profile one not only because of the gravity of ALS. Eva Syková is one of the well-known faces of Czech science and the most cited Czech female scientist (“Žebříčku Nejcitovanějších“, 2018). At the time, Eva Syková held several important functions including a seat in the Senate and the position of the director of the Institute of Experimental Medicine of the Academy of Sciences of the Czech Republic. It might be noted that the Institute owned 43 per cent share in Bioinova. Furthermore, Bioinova was the sponsor of the clinical trial undergoing at the Motol University Hospital.

The Commission for the Scientific Integrity of the Academy of Sciences found an important violation of research ethics in the actions of Syková's team. The main problem, though, was not seen in the payments but in the insufficient scientific justification of the therapy. It had not yet completed a clinical trial anywhere in the world. The only promising results were achieved in testing on animals. Nevertheless, Eva Syková and other members of her team were not sanctioned.

In May 2016, a new TV report (Obchod, 2016) accused Syková's team of requesting the donation from several patients for inclusion in the clinical trial. The scheme was allegedly

¹⁰ Amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's Disease) is a motor neuron disease that leads to complete paralysis. Death usually comes in five years after the onset of disease. Physicist Stephen Hawking probably suffered from a very slowly progressing form of ALS. Cf. “Amyotrophic Lateral” (2019) and also (Harmon) 2012.

¹¹ In 2010, the Motol University Hospital was listed as the fourth largest hospital in Europe with its 2 410 beds. Cf. “Europe's 10” (2010).

supported by two Motol physicians. The situation was now even more alarming than before: payment for participation in a clinical trial represents a direct violation of Act on Pharmaceuticals and the fundamental rules of research ethics. The consequences were rather serious. Eva Syková was removed by the then President of the Academy of Sciences Professor Jiří Drahoš from her function of the director of the Institute of Experimental Medicine of the Academy of Sciences.¹² Syková also resigned from her position of the first vice-chairman of the Czech Government's Research, Development and Innovation Council. Her reputation was severely damaged. The NGO *Buněčná terapie* ceased to exist. An internal investigation in the Motol University Hospital concluded that it was not proven that participation in the trial was conditioned by the payment. Some patients—but not all of them—were given back their donations.¹³

The questions we are considering in this article are demonstrated in a very sharp light in the described case regarding the application of stem cells outside of the clinical trial. If the patients were given the last hope, was it not paternalistic to condemn the practice? From the ethical point of view, did the problem consist rather the insufficient scientific justification, or in the fact that the patients paid for the therapy?

Before we explore these questions, we might ask whether the ethical and/or legal evaluation of the case should be different if the patients' health really benefited from the therapy (which was not the case). Legal regulation of medical research—as well as the prevailing ethical approach to it—is largely categorical, assessing the permissibility of research practices on their inherent qualities and not on their consequences. That is a reasonable protection against attempts to justify highly unethical research by its possible benefits for mankind. The pioneer of medical research ethics Dr. Henry K. Beecher stressed that a clinical study is ethical or unethical from its start regardless of the value of its scientific contributions.¹⁴ We fully agree with this notion.

4 Limitation of Access to Unapproved Therapies as a Paternalistic Approach?

Generally, personal freedom is limited not only to protect the rights of others but, in cases of sufficiently intensive public interest, also to protect the person from their own decision. The latter category typically consists in situations when a person acts in a way which endangers certain personal value that also has crucial importance for the society and, therefore, is protected by the law. Even though it might seem that a fully capable person is protected from themselves by the law—which would arguably be an absurd effort—it is more accurate to say that a certain value which the person bears is protected as important for the society as a whole. For example,

¹² Ironically, Jiří Drahoš replaced Eva Syková in the Senate two years later.

¹³ For an analysis of the case, cf. Šolc (2018, p. 51-53). Cf. also, for example, Dostál (2014) and Rychlík (2016).

¹⁴ As cited (in Czech translation) in Munzarová (2005, p. 48). The quote is not original; it was translated back to the English language by the author of this article.

a person cannot relinquish their fundamental rights. Therefore, a person is not allowed to grant a completely free and informed consent to being killed, since human life is understood as one of the very basic values of our society. Even freedom in a more fundamental meaning is protected against an individual's free decision, for example, the decision to sell oneself to slavery. Among other highly protected values, there is, for example, the respect to the human body which results in the prohibition of its commercialisation so nobody is allowed to sell their organs¹⁵ or to undergo drastic cosmetic procedures that would be deemed mutilating by the society.¹⁶

It is, therefore, necessary to ask what value is protected by the limitations of access to unapproved therapies and whether this value is important enough to outweigh the autonomy of will. One of the protected values is, apparently, the health of the person seeking therapy. If we focused solely on the value of health, however, ethical and legal differentiation between the access to unapproved and approved therapies might prove very difficult.

Unapproved therapies are usually connected to a higher risk to the patient's health. Therefore, it could be argued that the law sets a certain limit on health risks a person is allowed to take. On the general level, this is true. In many instances, the law imposes an obligation on an individual to take measures to protect their own health. Examples of this approach are familiar from everyday life: obligatory seatbelts for drivers and passengers in cars and helmets for motorcyclists, the rules of employers' responsibility for harm which motivate them to force their employees to use protective equipment (such as helmets on construction sites) etc. In all these instances, the law seems to prefer an individual's health over their free will, while the proportionality between these limitations of autonomy of will and public interest on the protection of individual health can be questionable. At first sight, the limitation of access to unapproved therapies is just another of these cases.

However, unregistered medicinal products are not necessarily more risky in all cases. There might be medicinal products that are not yet approved but with less reasonably presumed risks than some registered medicines, especially those used to treat more serious health conditions. Even more importantly, the risk-benefit ratio¹⁷ might be more favourable in some unregistered medicines than in most of their registered counterparts. It can be even argued that for a patient who is dying from an incurable disease, the risk-benefit ratio is almost always positive,¹⁸ which is not true for many registered medicinal products. At the same time, the most controversial cases of denial of access to

¹⁵ For a brief analysis of the concept of commercialisation of the human body in relation to the selling of the body parts, cf. Šustek and Šolc (2018, pp. 201-208).

¹⁶ A recent example is an English body modification practitioner who was convicted for causing grievous bodily harm with intent which consisted in a tongue splitting, the removal of an ear and the removal of a nipple for willing clients. Cf. Pegg (2019).

¹⁷ The risk-benefit ratio can be best understood as a ratio between the probability and magnitude (importance) of an anticipated benefit on the one hand and the probability and magnitude (severity) of anticipated harm on the other hand. Cf. Beauchamp and Childress (2013, p. 230).

¹⁸ In the context of medical research, we agree with Resnik (2018) who believes that a dying patient may reasonably participate in a study even if they expect they might die as a result of participation. The prospect of treatment which was provided by the participation in the study might outweigh its very high risks. (p. 167).

unapproved therapies, understandably, involve the said category of patients. It is not easy to argue for this denial on the basis of the protection of the health of someone who has a prognosis of a very short life of poor quality. Therefore, it could be argued that in case of a positive risk-benefit ratio, even unapproved therapies should be accessible to fully informed patients under certain conditions.

Moreover, when compared to the participation in a clinical trial, the provision of an unapproved therapy outside the trial's frame might not be the worse option. While the investigators must strictly follow the protocol of the trial, the treatment based on compassionate use of the drug can be more individualised. Furthermore, the subject of the trial might undergo tests or procedures which aim is the collection of data and not the benefit to the subject. (Resnik, 2018, p. 182). While it might seem paradoxical, the patient's health can arguably be better protected by the provision of the unapproved drug outside the clinical trial in certain cases.

However, health and autonomy are not the only values that are protected by medical law. This can be demonstrated in a wider clinical context. The patient's consent is a necessary but not a sufficient condition for the legal provision of health services. Even with fully informed and free consent, health professionals are only allowed to provide their services in accordance with the professional standards.¹⁹ In the Czech Republic, compliance with medical professional standards is usually called the provision of health care *de lege artis* as opposed to the *non-lege artis* provision in breach of the said standards. The standard is defined in Article 4 (5) of The Czech Republic Act No. 372 Coll., on Health Services (2011a), as "the provision of health services according to the rules of science and acknowledged medical procedures with the respect to the individuality of the patient and with regard to the particular conditions and objective possibilities".

In other words, the patient cannot grant informed consent to services that would breach the professional standards and expect these services will be provided. For health professionals and providers of health services, such provision would represent a breach of law. If we tried to explain this by the protection of patients' health—provided the patients are fully informed—we would face once again the above-mentioned problems related to the protection of fully capable persons from themselves. Furthermore, it would conflict with the fact that activities of various natural and spiritual healers, none of which is evidence-based, are legal.²⁰

¹⁹ According to Section 30 of The Czech Act No. 40 Coll., Criminal Code (2009) the consent of the aggrieved party with personal injury does not exclude criminal responsibility with the exception of the consent with medical procedures which, at the time when they were carried out, were in accordance with the law and the standards of medical science and practice.

²⁰ Even though the healer can be held liable for the harm which was caused by the failure to proceed with due professional care. Since the healer undertakes to care for the health of the patient, she enters into the contract for health care with the patient under Section 2636 and following of the Civil Code (which applicability is broader than that of Act on Health Services). Therefore, the standard of due professional care (Section 2643 (1) of the Civil Code) can be applied to the healer. The healer's activity is, nevertheless, legal: the healer is only liable for the breach of contractual obligation. Cf. Šustek (2016c, p. 274).

The described limitations of the legal provision of health services are, in fact, required by the protection of the integrity of the medical profession, health systems, and medicine as such.²¹ Regular provision of health care not corresponding to the professional standards would significantly diminish patients' trust in health professionals. Even if providers of health services were fulfilling their obligation to inform the patients of the *non-lege artis* character of proposed therapy, patients might (and probably would) start to feel like the subjects of rather uncontrolled experiments.²² While in some cases a bold therapy approach might have very good outcomes, on average the numbers of cases of iatrogenic harm would inevitably increase. The overall confusion and the decrease of trust in the health system would indirectly endanger the health and lives of many patients who would be reluctant to seek health services. In the end, the libertarian approach to the *non-lege artis* therapies might result in a public health crisis.

We can conclude that the principle of limiting the access to unapproved therapies is no more paternalistic approach than the prohibition of the provision of health services in a *non lege artis* manner. On the general level, it is justified by an important public interest.

5 Sufficient Scientific Justification

For the above-outlined reasons, there is a strong public interest in prohibiting the provision of the *non-lege artis* health services. There could arise the question of whether the provision of unapproved therapies outside the frame of clinical trials should not be banned without exception.

For determination of whether the certain clinical procedure was in accordance with the professional standards, there are usually used recommendations issued by medical societies (professional societies of the Czech Medical Association of J. E. Purkyně) and other guidelines. Even though these documents are non-binding, they express important opinions of the expert community (or its significant part) on the safety, efficiency, and suitability of particular therapies. Any deviation from these guidelines can only be considered *de lege artis* if it is sufficiently justified. (Šustek, 2016c, pp. 276-277.)

It is the nature of unapproved therapies that they are not yet recommended in any guideline. It is also their nature that their safety, efficiency, and suitability is being tested and there can be no expert opinion on them other than hypotheses which are yet to be verified or falsified. It

²¹ Since these limitations are not based on grounds of the patient's benefit, it can be argued that they are actually not paternalistic. In a similar way, Beauchamp and Childress argue that a refusal to provide a certain health service with the aim of protection of the patient's health represents *passive paternalism*. However, the refusal to perform an intervention on the basis of the physician's conscience „*may not be a paternalistic decision*“. The difference lies in the fact it may not be paternalistic to deny certain intervention to the patient in order to protect values which exist outside of the patient. Cf. Beauchamp and Childress (2013, pp. 225-226).

²² As Resnik (2018) puts it with regard to medical research, “[r]isks that materialize can [. . .] undermine the public's trust in the scientific enterprise” (pp. 166-167).

could seem that unapproved therapies cannot be provided *de lege artis* since the standard of *lex artis* does not even apply to them.

However, we believe that the *lex artis* standard also has a broader meaning than the proven medical procedures. In Czech legal doctrine, there is known the term “*lex artis largo sensu*”, the *lex artis* in the broad sense, which encompasses organisational, communicational, or administrative aspects of the provision of health services. (Šustek, 2016c, p. 266). The requirement of the provision of health services on the appropriate professional level is, therefore, not limited to compliance with standard medical procedures. In a similar way, the concept of *lex artis* can be expanded with regard to medical research. It should be understood more broadly as any action which is reasonably required from a health professional in a certain situation based on relevant legal (and also extra-legal) norms. (Šolc, 2018, p. 207).

An unapproved therapy can arguably be provided *de lege artis* in this broad sense if certain conditions of its provision are defined and fulfilled. It is reasonable to believe that the fundamental criterion should be scientific justification as it is required in Czech law by Article 8 (3) of The Czech Republic Act No. 378 Coll., on Pharmaceuticals 2007. While it is legal for non-professionals to provide services allegedly improving health with no scientific basis, it should not be so for the providers of health services (as they are defined in Act on Health Services). The minimum scientific justification is, apparently, open for discussion. The very minimal level of justification is that the medicinal product has successfully undergone all phases of preclinical research (including the testing on tissues and animals) and is ready for a clinical trial on human subjects. It would be highly inconsistent and dangerous both for the patients and the integrity of biomedicine to consider a certain medicinal product not yet prepared for a clinical trial and, at the same time, ready for clinical use. For the reasons outlined above, this is true even in patients for whom the medicinal product would represent their (real or perceived) last hope.

We would argue that the readiness for a clinical trial is still not a sufficient criterion. The results in animal tests, even if promising, can be very misleading for the patients. The scientific knowledge which is necessary to justify the use of an unapproved drug should be related to the drug's basic effects on the human organism. Otherwise, the patients would be provided with therapies of only presumed effects on the human body and their hope would be based on illusion in the vast majority of cases.

There are three phases of clinical trial preceding the registration of the medicinal product. In Phase I, the basic functioning of the drug in the human organism is tested. In more detail, there is studied pharmacokinetics (the absorption, distribution, metabolism, and excretion of the drug²³), pharmacodynamics (the effects of the drug on the body and the relationship between the

²³ For the definition of pharmacokinetics, cf. Harvey, Clark, Finkel, Rey, and Whalen (2012, p. 1).

drug concentration and the magnitude of the organism's response²⁴), and the tolerability of the drug. Based on the results of Phase I, the dosing of the medicinal product is optimised for the next stages. (Cook, Hansen, Siu, & Abdul Razak, 2015, pp. 997-1007). The Phase I is usually based on a collaboration with healthy volunteers: for this reason, this is the only phase in which the participants can receive monetary remuneration. (Šustek, 2016a, p. 694). Patients suffering from the health condition which the medicinal product aims at are involved in cases when the provision of the drug to healthy volunteers would be unethical, such as in case of cytotoxic drugs intended for oncological patients. (Wiffen, Mitchell, Snelling, & Stoner, 2012, p. 110). The patients suffering from the disease are most often allowed to participate starting from Phase II of the trial when there is further assessed the safety and efficiency of the medicinal product. In Phase III, the drug is compared with medicinal products that are registered for the same indication.²⁵

We suggest that the most appropriate time to allow the provision of unregistered medicinal products is after the completion of Phase I. This approach has several advantages. Earlier use of the drug would be connected with an extreme level of uncertainty including its dosing. On the other hand, waiting for the completion of Phase II would exclude many patients from access to unregistered therapies. While the average time between the start of Phase I and the completion of Phase III is eight years, Phase I usually only takes several months. (Hlavatý, 2016, p. 67). The criterion of completed Phase I, therefore, seems to balance the proportionality between the threshold of minimum scientific knowledge justifying the use of the drug and the interest of the eligible patients to seek unapproved therapies. Furthermore, it ensures an equal approach to all the patients seeking the unregistered drug. Since clinical trials are most often open for them since the start of Phase II, it is arguably reasonable to allow those who cannot participate at the trial to access the drug at the same time and not earlier or later.

The criterion of scientific justification needs clarification. Each case is to a relatively high extent specific in this area, and no regulation can be expected to sufficiently anticipate all aspects that might be relevant in particular cases. Nevertheless, it would be recommendable if expert societies issued broad guidelines on the matter, which could be then used by the clinical practice to establish a more reliable standard of *lex artis*. In the beginning, it should be made clear that the use of an unregistered medicinal product is allowed after the completion of Phase I of the clinical trial.

Nevertheless, we might recall the case of stem cell therapy provided by Eva Syková's team to remind us that the mere fact that there is an ongoing clinical trial on patients suffering from the relevant disease does not suffice to justify the compassionate use of a medicinal product. There should be established a certain minimal standard of promising results in human patients.

²⁴ For the definition of pharmacodynamics, cf. Harvey et al. (2012, p. 25).

²⁵ For an introduction to the phases of clinical trials, cf. (in the Czech language) Šolc (2018, pp. 146-150). For a brief overview, cf. "Phases of" (2019).

This standard would primarily encompass the data on the efficacy of the therapy. In cases of therapies aiming at less grave health conditions, it would be necessary to wait longer for reliable data on safety. From this perspective, the proportionality between the risks and potential benefits of the therapy—given the nature and prognosis of the patients' health condition—will always be the crucial aspect.

6 Payment for Unapproved Therapies

If the use of unregistered medicinal products – under certain conditions – represents the *de lege artis* provision of health services, there needs to be clarified whether it can be legally paid by the patient. There are several options for payment for these therapies. We can think of the payment from the (public or private) health insurance,²⁶ the obligatory payment from the drug manufacturers who sponsor clinical trials, the payment from some special fund, etc. It is a very complicated question which cannot be analysed in this article. The problem arises when, for some reason, the provision of an unapproved therapy in an individual case is not covered and the only option for the patient is to pay for the therapy.

We demonstrated that the limitations of access to unapproved therapies do not only serve the aim of the protection of patient's health but also the integrity of medicine and the health system. With regard to the payment, the protected value on the side of the patient is rather their financial situation or, from a broader perspective, their right to private and family life. A very expansive therapy can in some cases endanger the patient's livelihood, housing, and their ability to pay for basic goods and services. This is the reason why modern society, especially in European countries which value social solidarity, shifts many costs incurred by unexpected and unfavourable events (such as a natural disaster or a disease) from the affected individuals to herself. However, if the society cannot cover the costs of unapproved therapy, or if it fails to do so for any other reason, it does not seem to be just to prohibit the patient from covering these costs. We will try to outline the reasons why we believe so.

It is obvious that the patient is, in a certain way, forced to pay for the therapy. Nobody would want to undergo an experimental medical treatment if it was not necessary (or, more precisely, the willingness to undergo an unnecessary medical treatment is itself a psychiatric diagnosis).²⁷ However, it would be inaccurate to conclude that the payment is forced upon the patient by the

²⁶ In the Section 16 (1) of Czech Republic Act No. 48 Coll., on Public Health Insurance (1997), states that “[in] exceptional cases, the respective health insurance company covers health services otherwise not covered by the health insurance company if the provision of such services is the only option from the perspective of health condition of the insured”. According to Section 16 (2), the prior consent of the health insurance company's review physician is required with the exception of cases when the delay could result in harm to the insured person.

²⁷ A person suffering from Münchhausen syndrome pretends to be ill in order to provoke sympathy of others and to being cared for by them. Sometimes, they seek medical treatment for their alleged health condition. Cf. “ICD-11 Diagnosis” (2019).

society's decision to allow the option of this payment. First of all, the patient still can make a fully informed decision not to make the payment: it is their right, not duty. The term *force* can only be used here in a weaker sense than actual coercion or another type of external force which eliminates the individual's will. Secondly, even in this weaker sense, the patient is forced to make the payment by their health condition (an objective situation in which they find themselves) and by the society's decision not to provide the payment, not by the option to pay for the treatment. It would be untenable to claim that it is the patient's *right* to pay for the treatment what diminishes their autonomy of will and unduly forces them to make the payment.

If the patient was to be protected against their own financial decisions based on their medical needs, it would have to be illegal to buy any health services, medicines, or medical devices which are not covered by the public health insurance or otherwise paid for by the society. It is easy to see that this approach is not empowering the patient's autonomy of will but, in fact, poses a significant restriction on it.

Nevertheless, it is crucial to ensure that the patient's decision making is based on the knowledge of true and sufficient facts regarding their health condition, prognosis, alternatives to the treatment, the nature of the treatment, and associated risks. It is vital that the patient is aware not only of the fact that the treatment is experimental but also of a low probability of the positive outcome. This fact must not be merely hidden among other information in an informed consent form. The provider of the treatment must make sure that the patient fully understands that while the treatment might be their last hope, it is, in fact, unlikely to significantly improve their health conditions. Some experimental treatments are objectively more promising than others, and this needs to be reflected too. If there are already available some exact data regarding the treatment's efficiency, they need to be disclosed to the patient. However, what is most important is the patient's understanding of the basic structure of the situation: there is hope but (in most cases) it is very uncertain and little. If the informed consent serves to at least partly equalize the information asymmetry in the physician-patient relationship (Salač, 2019), the information on the true probability of health benefits is crucial. Upon this knowledge, the patient can make their informed decision based on their personal values.

In order to protect the integrity of medicine and health systems, it is necessary to ensure that the direct payment from the patient will not lead to an enrichment of anyone involved. Therefore, it is imperative that the payment does not exceed the real costs of the treatment. Otherwise, it can never be guaranteed that the provider will not be financially motivated to misinform the patient or to unduly influence their decision. Both the real risk of these illegitimate practices and the suspicion in which all the providers of experimental therapies would find themselves arguably outweigh any positive impact of allowing the financial motivation to provide said therapies.

Looking back to the case of Eva Syková, we agree with the Commission for the Scientific Integrity of the Academy of Sciences' conclusion that the insufficient scientific justification of

therapy represented a more serious problem than the fact that the patients were required to pay for it. It was the combination of a very low probability of therapy's effect and the request for payment that made the behaviour of the therapy's providers highly unethical. In our opinion, the payment itself would be ethically permissible if there were promising results in humans and if the patients were fully informed regarding the probability of beneficial effects of the therapy.

Conclusion

This article was dedicated to the analysis of limitations of the access to unapproved therapies as a practice which seemingly contradicts the autonomy-based paradigm of health law and medical ethics. Under Czech law, the access to unregistered medicinal products usually takes the form of compassionate use according to Article 8 (3) and (5) of The Czech Republic Act No. 378 Coll., on Pharmaceuticals (2007). A recent case of unapproved ALS stem cell therapy provided by the team lead by Professor Eva Syková on the basis of compassionate use was presented as a glaring example of the most serious ethical questions: whether the limitations of the access to unapproved therapies are overtly paternalistic, whether (and how) the provided unapproved therapy has to be scientifically justified, and whether the patients should be allowed to pay for it.

We argued that it would be questionable to justify the limitations of the access to unapproved therapies based solely on the risks they pose to the patient's health. Even though unregistered therapies are usually riskier than registered ones, it may not be always the case; furthermore, the risk-benefit ratio might be better for some unregistered medicines, especially if they might help patients suffering from incurable life-threatening diseases. On the other hand, the unregulated use of unapproved therapies would jeopardize the integrity of the medical profession and public trust in the health system. From this perspective, the limitations of the access to unapproved therapies have the same aim as the prohibition of the provision of health services in breach of professional standards—that is to protect the public interest on ethically working and trusted systems of health care.

We further argued that the regulated use of unapproved therapies actually represents the provision of health services on the appropriate professional level. As a result, any breach of limitations of the access to unapproved therapies is nothing but a provision of health services not according to professional standards. While limitations of access to unapproved therapies might seem to be a unique relict of paternalism, they are in fact nothing but the application of professional standards in a broad sense. In this sense, they are not different from the rules limiting clinical practice in general.

Analysing suitable requirements for the use of unregistered medicines outside of clinical trials, we did not further focus on the non-existence of sufficient therapeutic alternative since it is a universally agreed condition. Nevertheless, we concluded that the use in a particular case must have sufficient scientific justification. The very minimum should consist in the completion of Phase I of

the clinical trial. The criterion of sufficient scientific justification needs to be clarified in more detail in the future. Guidelines issued by expert societies could prove very helpful in this regard.

We also focused on the question of whether it should be legal for the patients to pay for their experimental therapy outside of a clinical trial. While the answer is positive, it is necessary to ensure that the payment does not exceed the real costs of the treatment and that the patient was properly informed of the experimental nature of the treatment and real chances of improvement of their health condition.

References

- Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. (2019). *National Institute of Neurological Disorders and Stroke*. Retrieved from <https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Amyotrophic-Lateral-Sclerosis-ALS-Fact-Sheet>
- Beauchamp, T. L., & Childress, J. F. (2013). *Principles of Biomedical Ethics*. (7th ed.). New York: Oxford University Press.
- Caplan, A. (2016). Medical Ethicist Arthur Caplan Explains Why He Opposes “Right-to-Try” Laws. *Cancer Network*, 30(1). Retrieved from <https://www.cancernetwork.com/oncology-journal/medical-ethicist-arthur-caplan-explains-why-he-opposes-right-try-laws>
- Cook, N., Hansen, A. R., Siu, L. L., & Abdul Razak, A. R. (2015). Early phase clinical trials to identify optimal dosing and safety. *Molecular Oncology*, 9(5), 97-1007.
- Dostál, O. (2014). Poslední naděje za 150 000 korun. [The Last Hope for 150 000 CZK.] *Medical Tribune*. Retrieved from <http://www.tribune.cz/clanek/33793-posledni-nadeje-za-korun>
- Durisotto v. Italy, application No. 62804/13 European Court of Human Rights (the decision of 6 May 2014).
- Europe’s 10 Largest Acute Care Hospitals Have Sizeable Clinical Pathology Laboratories. (2010, April 23). *Dark Daily*. Retrieved from <https://www.darkdaily.com/europes-10-largest-acute-care-hospitals-have-sizeable-clinical-pathology-laboratories-423>
- Harmon, K. (2012, January 7). How Has Stephen Hawking Lived Past 70 with ALS? *Scientific American*. Retrieved from <https://www.scientificamerican.com/article/stephen-hawking-als/>
- Harvey, R. A., Clark, M. A., Finkel, R., Rey, J. A., & Whalen, K. (2012). *Lippincott’s Illustrated Reviews: Pharmacology*. (5th ed.). Baltimore, Philadelphia: Lippincott Williams & Wilkins, Wolters Kluwer.

Hlavatý, T. (2016). *Základy klinického výskumu. [The Basics of Clinical Research.]*. Bratislava, Praha: Grada Publishing..

ICD-11 Diagnosis of Factitious Disorder Imposed on Self. (2019). Retrieved from <https://icd.who.int/dev11/f/en#/http%3a%2f%2fid.who.int%2fid%2fentity%2f790764418>

Kuře, J. (2009). Human Embryonic Stem Cell Research in Central and Eastern Europe: A Comparative Analysis of Regulatory and Policy Approaches. In A. Plomer, & P. Torremans, *Embryonic Stem Cell Patents: European Law and Ethics*. Oxford: Oxford University Press.

Maron, D. F. (2016, June 30). Unproved Stem Cell Clinics Proliferate in the U.S. *Scientific American*. Retrieved from <https://www.scientificamerican.com/article/unproved-stem-cell-clinics-proliferate-in-the-u-s/>

Munzarová, M. (2005). *Lékařský výzkum a etika. [Medical Research and Ethics]*. Praha: Grada Publishing.

Obchod s nadějí. [The Business with Hope.]. (2015, November 9). Česká televize. [The Czech Television]. Retrieved from <https://www.ceskatelevize.cz/ivysilani/1142743803-reporteri-ct/215452801240037/obsah/434334-obchod-s-nadeji>

Obchod s nadějí II. [The Business with Hope II.]. (2016, May 30). Česká televize. [The Czech Television]. Retrieved from <https://www.ceskatelevize.cz/porady/1142743803-reporteri-ct/216452801240020/video/475045>

Pegg, S. (2019, February 12). Body modification – when consent is not a defence. *The Conversation*. Retrieved from <https://theconversation.com/body-modification-when-consent-is-not-a-defence-87816>

Phases of clinical trials. (2019). *National Comprehensive Cancer Network*. Retrieved from https://www.nccn.org/patients/resources/clinical_trials/phases.aspx

Resnik, D. B. (2018). *The Ethics of Research with Human Subjects*. Cham, Switzerland: Springer International Publishing AG.

Rychlík, M. (2016, June 1). Pád profesorky Evy Sykové. [The Fall of Professor Eva Syková.] *Lidové noviny*. Retrieved from <https://www.pressreader.com/czech-republic/lidove-noviny/20160601/281573764949024>

- Salač, J. (2019). Informovaný souhlas jako nástroj vyrovnání informačního deficitu ve vztahu lékař-pacient. [Informed Consent as an Instrument of Equalizing the Information Asymmetry in the Physician-Patient Relationship]. *Paneurópske právnické listy*, 2(1). Retrieved from <http://www.paneuropskepravnickelisty.sk/index.php/salac-j/>
- Šolc, M. (2018). *Právo, etika a kmenové buňky. [Law, Ethics and Stem Cells.]*. Praha: Wolters Kluwer.
- Šustek, P. (2016a). Klinický výzkum. [Clinical Research.] In P. Šustek, & T. Holčapek, *Zdravotnické právo. [Health Law]*. Praha: Wolters Kluwer.
- Šustek, P. (2016b). Medicínský výzkum. [Medical Research.]. In P. Šustek, & T. Holčapek, *Zdravotnické právo. [Health Law]*. Praha: Wolters Kluwer.
- Šustek, P. (2016c). Náležitý odborný postup (lex artis). Obecně. [Appropriate professional procedure (lex artis). In P. Šustek, & T. Holčapek, *Zdravotnické právo. [Health Law]*. Praha: Wolters Kluwer.
- Šustek, P., & Šolc, M. (2018). Selling and Owning Human Body Parts in the Light of Human Rights: the Ideal and the Current Practice in the Czech Republic. In P. Šturma, V. A. Mozetic, *Business and Human Rights*. Waldkirchen: rw&w Science & New Media Passau-Berlin-Prague.
- Šustek, P. (2018). Two Decades of the Convention on Biomedicine: Has It Been Any Good? In P. Šturma, *Czech Yearbook of Public & Private International Law. Česká ročenka mezinárodního práva veřejného a soukromého*. Praha: Česká společnost pro mezinárodní právo, 2018. Retrieved from <https://rozkotova.cld.bz/CYIL-vol-9-2018/276>
- Teixeira Zorzanelli, R., Speroni, A. V., Menezes, R. A., & Leibing, A. (2017, January/March). Pesquisa com células-tronco no Brasil: a produção de um novo campo científico. [Stem cell research in Brazil: the production of a new field of science.] *História, Ciências, Saúde – Manguinhos*, 24(1), 129-144.
- The Czech Republic Act No. 40 Coll., Criminal Code (2009).
- The Czech Republic Act No. 48 Coll., on Public Health Insurance (1997).
- The Czech Republic Act No. 268 Coll., on Medical Devices (2014).
- The Czech Republic Act No. 372 Coll., on Health Services (2011a).
- The Czech Republic Act No. 373 Coll., on Specific Health Services (2011b).

The Czech Republic Act No 378 Coll., on Pharmaceuticals (2007).

Wiffen, P., Mitchell, M., Snelling, M., & Stoner, N. (2012). *Oxford Handbook of Clinical Pharmacy*. (2nd ed.). Oxford: Oxford University Press.

Žebříčku nejcitovanějších českých vědců vládou chemici. [The List of the Most Cited Czech Scientists is Ruled by the Chemists.]. (2018, May 7). Česká pozice. Retrieved from http://ceskapozice.lidovky.cz/zebricku-nejcitovanejsich-ceskych-vedcu-vladnou-chemici-pel-/tema.aspx?c=A180504_110119_pozice-tema_houd