When a new disease emerges, there are at first no specific medicinal products to treat it. This has also been the case in the Covid-19 pandemic. Scientists and health professionals have been trying to establish the best treatments possible using the already-existing medicines that are normally used for different indications. The off-label use of medicinal products is a standard part of medical practice. If it meets certain criteria, it is not contradictory to the standard of care. Nevertheless, the urgency of the pandemic situation brings about new issues. What amount of data on efficacy and safety should be considered sufficient to scientifically justify the off-label use of a particular medicine? How should health professionals reflect the rapid scientific developments and high levels of uncertainty in their clinical practice? How can these factors be influenced by the politicisation of medicine? The paper deals with the outlined questions in order to analyse and concretise the criteria for off-label use of medicinal product in the specific context of the Covid-19 pandemic.
**INTRODUCTION**

In late winter and early spring 2020, the world suddenly found itself facing an unexpected crisis. The novel coronavirus infection, soon named COVID-19, was starting to spread swiftly around the continents. At first, little was known about the emerging disease. Its case fatality rate was usually believed to be on the scale of several percentage points, but sometimes the estimates even exceeded ten per cent. It was impossible to know whether there would be any long-term effects of the disease (today, we know that there really are such prolonged symptoms, often referred to as ‘long COVID’). The world started to work hard to find ways to slow the spread of the infection, mostly with the aim of flattening the epidemic curve to avoid the collapse of health systems and communities.

The other pressing question was how to treat COVID-19 most effectively. Some of the first clinical guidelines came from China in early February 2020, providing the first practical advice based on actual clinical experience with the novel disease. With time and growing experience, the treatment of COVID-19 has become more precisely adapted to the disease and more effective: for example, prone positioning of patients (when they lie on their chest down and back up)

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1 This paper was written with the support of the Charles University Grant Agency (GAUK) research project no. 910319 “Legal Paradigm of Medical Research: Civil Liability for Death and Bodily Harm”.


with severe acute respiratory distress\textsuperscript{8} and the preference for non-invasive mechanical ventilation when possible\textsuperscript{9} have become standard practice. Nevertheless, there has still been a pressing need for a crucial tool that would truly turn the tide of fatality rate: effective medicinal products.

There was no time to waste by waiting patiently for brand new drugs. Instead, physicians and scientists around the world set on the journey to identify already-existing medicines that could help COVID-19 patients. They would provide them to the patients under the so-called off-label regime, denoting the use of a medicinal product differently than for what it was registered and what is embodied in its Summary of Product Characteristics (SPC). In practice, it most often means that a medicinal product is used for a different indication or a different age group of patients, or that there is altered dosage, dosing frequency, duration of use, etc.\textsuperscript{10} Off-label use is a normal part of clinical practice, in many cases being necessary to help the individual patient’s need. It is perfectly legal—provided that it complies with the standard of care.\textsuperscript{11} Should the off-label use of a medicinal product breach the standard of care, there might arise a civil or even criminal liability for a potential resulting harm to a patient.

This paper will analyse the content and assessment of the standard of care related to the off-label use of medicines in the uncertain and rapidly evolving times of a pandemic. If not explicitly stated otherwise, all the dates relate to the year 2020.

\begin{center}
\textbf{I. Standard of Care}
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In medical malpractice cases, the breach of duty on behalf of a health professional or health facility usually consists in the failure to comply with the standard of care. It can be basically understood as the standard of the reasonably

\begin{footnotesize}
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\item[11] Vymazal and Šustek (n 10) 263.
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skilled and experienced doctor or another health worker in a particular professional field.¹² This standard must always reflect the current practice based on up-to-date evidence embodied in clinical guidelines, protocols, scientific papers, etc.¹³ However, what is the evidence-based practice of medicine regarding a new disease? In such cases, there can hardly be any specific evidence of the efficacy of any treatment.

We need to look for the answer in a more detailed definition of the standard of care. From its very nature, medicine is a creative enterprise. A skilled doctor does not only follow protocols step by step. She needs to understand how the disease affects the patient’s body, the reasons behind the protocol’s content, and under what circumstances it might be beneficial or necessary to modify it. Many experts stress that even in a seemingly mechanised medicine, a physician’s critical and creative approach is invaluable. Siddhartha Mukherjee makes it clear that ‘human decision making, and, particularly, decision making in the face of uncertain, inaccurate, and imperfect information, remains absolutely vital to the life of medicine (…) the medical revolution will not be algorithmized’.¹⁴ We may read that medicine is an ‘art of appropriately apply science in practice’.¹⁵ From the legal perspective, Margaret Brazier and Emma Cave note that ‘[b]lind adherence to guidelines or protocols would itself be negligent’.¹⁶

Using the same cognitive process, physicians are able to proceed even if there are no established protocols or guidelines. Like detectives, they can try to make sense of seemingly unrelated symptoms, deduce their probable causes in the human body’s inner functioning, and come up with possible remedies. Apparently, the level of uncertainty in similar situations is high. For this reason, the law does not allow resort to the off-label use of medicines completely freely (arguably except for a patient facing imminent death when a physician could act in the state of necessity).

European law does not explicitly regulate the off-label use of medicines, but there might be applied the regulation of the so-called compassionate use of medicines.¹⁷

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¹² See Margaret Brazier and Emma Cave, Medicine, Patients, and the Law (6th ed, Manchester University Press 2016) 199–200 or Imogen Goold and Jonathan Herring, Great Debates in Medical Law and Ethics (2nd ed, Palgrave 2018) 78.

¹³ See Brazier and Cave (n 12) 207–209.


¹⁶ Brazier and Cave (n 12) 208.
The compassionate use and the off-label use of medicinal products are, in a certain sense, similar to each other. While the former concerns drugs that have not yet been registered and the latter relates to drugs that have been registered for a different use, both concepts enable physicians to use such medicinal products directly for particular patients who need them, without having to wait for the results of clinical trials or any formal approval. In the absence of direct European off-label use regulation, the provisions on compassionate use might be applied.\textsuperscript{18} Therefore, it is possible to conclude that off-label use is only allowed in patients with a chronically or seriously debilitating disease or whose disease is considered life-threatening and cannot be treated satisfactorily by an authorised medicinal product.\textsuperscript{19} National legislators regulate the practice in more detail. For example, Czech law expresses two cumulative conditions for the off-label use of medicinal products. First, no sufficient equivalent with necessary therapeutic properties that could be used in accordance with its SPC shall be available. Second, off-label use must be sufficiently scientifically justified,\textsuperscript{20} as will be further analysed below.

On the other hand, no endorsement of public authority is necessary. It might strengthen the argument that the off-label use of a certain medicinal product complies with the standard of care, but it does not automatically secure the legality of such use in all possible cases. Even more importantly, the lack of a public authority endorsement does not mean that the off-label use is not appropriate. While the providers of health services have usually been eager to obtain the official approval to use off-label medicines that might provide hope during the COVID-19 pandemic, it was not strictly necessary to wait for these decisions. Quite the contrary: any drug could have been used off-label as soon as promising results of studies were published that were convincing enough to provide sufficient scientific justification. Another example might be found in the pre-pandemic discussion on the use of gadolinium-based contrast agents in magnetic resonance imaging of the brain. In 2017, the European Commission restricted the registration of several such agents. One of them was the drug marketed as Multihance, the registration of which was limited to the indication of


\textsuperscript{18} See Vymazal and Šustek (n 10) 263.

\textsuperscript{19} Vymazal and Šustek (n 10) 263, or Petr Šustek, Tomáš Holčapek, and Martin Šolc, ‘Doporučení pro tzv. off-label použití léčivých přípravků pro pacienty s COVID-19 [Recommendations for the So-Called Off-Label Use of Medicinal Products in COVID-19 Patients]’ (2020) 31(3) Anesteziologie a intenzivní medicína 120.

\textsuperscript{20} Section 8 (4) of Act No. 378/2007 Coll., on Pharmaceuticals.
liver imaging. The reason was the discovery of ganolinium deposition in the patients’ brains, even though there have been no known or suspected adverse neurological effects. Nevertheless, a part of the professional public considered the decision to restrict registration of gadolinium-based contrast agents premature and overly cautious. Papers and other sources usable to define the standard of care could arguably justify the use of the restricted contrast agent in brain scans where it is necessary because of its ability to achieve high-resolution images.

Since the off-label use of medicinal products is a part of clinical practice, all the general requirements for any health service must also be met. Health professionals are obliged to secure the patient’s informed consent before interfering with her integrity (or to provide the required information to the patient as soon as possible if she was unable to grant consent at the relevant time); informed consent is, anyway, the legal ground for the provision of health services in the vast majority of cases. The provider should explain to the patient the off-label nature of the intended medicinal product use, its reasons (i.e., the lack of adequate alternative that could be used according to its SPC), risks, and alternatives (however less effective they might be). Equally important is the obligation to comply with the standard of care in administering the drug and all aspects of related care.

Definitions of a standard of care in particular jurisdictions usually reflect the uncertain and creative nature of medicine. In the Czech Republic, the standard of care—known by the law as the *care on the appropriate professional level*, and in everyday practice usually called the *lex artis* standard—is defined in Section 4 (5) of Act No. 372/2011 Coll., on Health Services and the Conditions of Their Provision, 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’.

There are, therefore, three requirements or aspects that cumulatively form the standard of care:

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22 See Vymazal and Šustek (n 10) 263.


24 See Šustek, Holčapek, and Šolc (n 19) 120.

25 Ibid 120.
1) the objective requirement of the compliance with ‘the rules of science and acknowledged medical procedures’;
2) individualisation on behalf of the patient (‘with the respect to the individuality of the patient’);
3) individualisation on behalf of the health services provider (‘with regard to the particular conditions and objective possibilities’).26

The explicit mention of the objective possibilities makes the situation more favourable for the physicians, even though we might argue that even without its embodiment in the legal text, a similar rule would be set by the courts. When doctors have to treat their patients in the absence of reliable evidence, there must be accepted a higher level of uncertainty than under normal conditions. Furthermore, respect for the patient’s individuality makes it even clearer that physicians are allowed to be reasonably inventive in finding the most beneficial treatment for each of those they have in care.

Regarding the objective aspect of the standard of care, we must keep in mind that there are no acknowledged medical procedures when a novel disease strikes. Hence, only the criterion of the rules of science remains. It means that physicians need to engage in the above-outlined detective work and use the relevant scientific sources available to make their decisions. In fact, we are facing once again the question of how we can evaluate whether a doctor’s actions are sufficiently scientifically justified.

II. SUFFICIENT SCIENTIFIC JUSTIFICATION

The evaluation of scientific justification for the off-label use of a particular medicinal product in a crisis is, in principle, not very different from the evaluation of compliance with the standard of care under normal circumstances. In both cases, it is necessary to determine whether the relevant procedure is considered medically appropriate by a relevant part of the professional public.27 If there is not enough collective experience—such as in the case of a new disease—it is

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26 For the categorisation of the objective aspect and two individualised aspects of the lex artis standard, see Martin Šolc, ‘Možnosti umělé inteligence při hodnocení protiprávnosti v medicínskoprávních sporech [The Possibilities of Artificial Intelligence in the Assessment of Breach of Duty in Medical Negligence Cases]’ in Jozef Suchoža, Ján Husár, and Regina Hučková (eds), Právo, obchod, ekonomika [The Law, Commerce, and Economics] (Univerzita P. J. Šafárika v Košiciach 2020) 274—275.

required that among professionals, there is sufficiently represented opinion that the intended off-label use can potentially be beneficial for the patients.

We will look for this opinion in the same kind of sources as under normal circumstances: in scientific journals, guidelines (if there already are any), textbooks, etc. Nevertheless, the law must reflect that doctors often need to use less specific sources that do not describe the treatment of a particular disease but rather facilitate a deeper understanding of its symptoms and thus help doctors with the innovative process of finding treatment options.

If the sources are specific, they tend to be less reliable during the first months of a new disease. In the COVID-19 pandemic, we have witnessed a massive expansion of preprint papers. The term preprint in the academic context denotes a paper that has been posted on a public server prior to a formal peer review.\(^2\) Preprints have been posted by some of the world’s most prestigious medical journals, such as *The Lancet*\(^3\) or *The New England Journal of Medicine*.\(^4\) While preprints are tremendously useful in getting the new information and results of studies to the public and enabling debate,\(^5\) their reliability is lower in comparison with the papers that have already undergone rigorous peer review.\(^6\)

In a situation of acute lack of better sources, however, preprints are completely acceptable to scientifically justify a choice of treatment, including the off-label use of medicinal products.\(^7\) Furthermore, the requirements on the quality of the study used for the scientific justification need to be appropriately lowered. While small studies would not always suffice to justify off-label use of a drug scientifically, they should be considered acceptable if there are no available results of any more extensive studies.

As we have shown, the rigour of evaluating scientific sources may be somewhat relaxed in critical situations. In connection with the law’s imperative to consider the particular conditions and objective possibilities, the gravity of the crisis provides sufficient grounds for such an approach. It is also necessary to

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\(^7\) See Šustek, Holčapek, and Šolc (n 19) 121.
bear in mind that the safety of registered medicinal products, regardless of their original indication, was already proven in sound clinical trials.\textsuperscript{34} Furthermore, many of these medicines have been widely used in clinical practice for a very long time. Any potential health risks would have most likely been already identified.

The tendency to accept almost any serious scientific paper as a source of the standard of care in times of crisis is understandable and, in many cases, beneficial. However, it seems appropriate to balance it with a certain kind of safety check. Otherwise, the safety of the patients, as well as the public trust in health systems, might be compromised. The conditions outlined below were proposed by Šustek, Holčapek, and Šolc in their paper ‘Recommendations for the So-Called Off-Label Use of Medicinal Products in COVID-19 Patients’,\textsuperscript{35} which is based on Czech law, but we believe they are also widely applicable to different jurisdictions.

A medicinal product should not be used off-label if there is a scientifically based suspicion that it would be harmful to the patient. The scientific justification, but also the suspicion of potential harmful effects, do not necessarily have to originate from experience with the particular drug. It might also be based on the knowledge of or experience with medicines that have the same active substance or are otherwise comparable. Furthermore, a preprint should not establish scientific justification if its results have been subjected to a serious scientific doubt or if an average professional in the field finds them suspicious at first sight.\textsuperscript{36} We believe the same rule should also apply to very small studies, even if they have already been published after a successful peer review process.

While all these considerations are broad and vague, they might make a crucial difference in navigating the course of action between recklessness and hesitancy in a critical situation. We will illustrate them with a case that seems to be a nearly perfect example of the swift development of science in turbulent times—the rise and fall of hope in hydroxychloroquine (HCQ).

\section*{III. Case Study: The Story of Hydroxychloroquine}

It could have been the medicine everybody was waiting for. When the pandemic first hit European countries in early spring 2020, the promise of HCQ seemed to be great. The medicine has been successfully used for a long time to treat malaria and several autoimmune diseases such as rheumatoid arthritis or

\begin{flushright}
\textsuperscript{34} Ibid 121.
\textsuperscript{35} Ibid 119.
\textsuperscript{36} Ibid 121.
\end{flushright}
In March, several papers were published that suggested its potential efficacy in treating COVID-19 as well. *In vitro* (i.e., in a laboratory environment), HCQ inhibited infection with SARS-Cov-2, the virus that causes COVID-19.\(^3\) Furthermore, it seemed that HCQ could help real patients in clinical settings.

Important for spreading the hopes in HCQ was a preprint in the *International Journal of Antimicrobial Agents* released on March 20. Ironically enough, the paper was formally published in the journal in July after successfully completing peer review,\(^3\) but at that time, as we will see below, its results were hardly relevant anymore. This small French study (with only twenty patients treated) suggested that the administration of HCQ in combination with an antibiotic azithromycin significantly reduces viral load in COVID-19 patients.

The claim of the efficacy of HCQ against COVID-19 was only supported by laboratory experiments and a handful of small clinical studies. Under normal circumstances, the scientific justification of off-label use based on such a limited body of evidence would be at least questionable. However, the situation was anything but normal. The numbers of countries suffering from the pandemic were rapidly increasing, as well as the disease’s death toll. Anything that could help patients and save lives was desperately wanted.

Furthermore, HCQ has been a part of clinical practice since the 1950s,\(^4\) its active substance being used for many centuries.\(^5\) There has always been a certain risk of rare adverse cardiac effects of HCQ,\(^6\) but it seemed to be overridden by its potential benefits for COVID-19 patients (as it is for most patients suffering from conditions HCQ has been long used for). By the end of March, HCQ was used off-label for COVID-19 around the world, not excluding the Czech Republic.\(^7\)

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\(^8\) See Drugs.com (n 40).

\(^9\) See Šustek, Holčapek, and Šolc (n 19) 121.
However, doubts started to arise soon. A prime example of these concerns comes from the USA. Late in April, the Food and Drug Administration (FDA) issued a caution against the use of HCQ or a similar drug, chloroquine, for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Physicians were recommended to initially evaluate and subsequently monitor patients to whom HCQ was given to identify cardiovascular problems in a timely manner.\footnote{See FDA, ‘FDA Drug Safety Communication, Safety Announcement’ (24 April 2020) \url{https://www.fda.gov/media/137250/download} accessed 28 February 2021.}

Then, on May 22, a paper in \textit{The Lancet} was published that shattered all remaining dreams of HCQ COVID-19 treatment.\footnote{See Mandeep R Mehra and others, ‘Hydroxychloroquine or Chloroquine with or without a Macrolide for Treatment of COVID-19: A Multinational Registry Analysis’ (2020) \textit{The Lancet} \url{https://doi.org/10.1016/S0140-6736(20)31180-6} accessed 28 February 2021.} It suggested that HCQ (even in combination with a macrolide such as azithromycin) was not only ineffective; it actually decreased in-hospital survival and increased frequency of ventricular arrhythmias when used for the treatment of COVID-19. In fact, azithromycin seemed to worsen the outcomes. The study was reportedly based on an analysis of the data on 96,000 patients from many countries mined from multiple registries.

It is not a surprise that the paper became very influential. Published on Friday, it even prompted the World Health Organization (WHO) to halt its Solidarity Trial’s HCQ arm on Monday, May 25. With the involvement of thousands of patients, the Solidarity Trial was an important study aiming at discerning which therapies are truly effective and safe for COVID-19 patients. The halting of the HCQ arm consisted in a suspension of new patients’ enrolment until the WHO review had considered available data on the drug.\footnote{See Jason Beaubien, ‘WHO Halts Hydroxychloroquine Trial over Safety Concerns’ (NPR, 25 May 2020) \url{https://www.npr.org/sections/coronavirus-live-updates/2020/05/25/861913688/who-halts-hydroxychloroquine-trial-over-safety-concerns?t=1614538942824} accessed 28 February 2021.} On July 4, the HCQ arm was discontinued.\footnote{See WHO, ‘“Solidarity” Clinical Trial for COVID-19 Treatments’ (11 August 2021) \url{https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments} accessed 28 February 2021.} But at the time, the safety concerns were not as relevant as the lack of efficacy anymore.

The events in the meantime were probably the most remarkable scientific scandal related to COVID-19 treatments of the year. Just a few days after the publication of the above-outlined \textit{Lancet} paper, errors were found in its data. Serious concerns regarding the veracity of the data arose immediately. \textit{The Lancet} swiftly launched a third-party peer review ‘to evaluate the origination of the
database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper’.  

The data were collected and analysed for the purposes of the paper by the company Surgisphere, which did not agree with transferring the full data set, client contracts, and other necessary data for the third-party analysis. The company claimed that such actions would violate their client agreements and confidentiality requirements. Nevertheless, the reviewers found themselves unable to conduct an independent and private peer review and therefore were withdrawn from the peer-review process. In reaction to that, the paper’s co-authors themselves (with the exception of the co-author who owned Surgisphere) requested its retraction.  

Nevertheless, these events were no victory for the proponents of HCQ COVID-19 treatment. According to the later studies, HCQ is not significantly dangerous but also not beneficial for patients with COVID-19.  

Even in the face of growing evidence of HCQ inefficacy, the US President Donald Trump kept actively promoting the drug throughout the summer. It would be great if a relatively cheap and easily accessible medicine could reduce the severity of the pandemic—for the politicians, it would be an easy opportunity to gain popularity. Trump pushed for the use of HCQ even for COVID-19 prevention (something the FDA warned against in its above-mentioned document from April).  

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49 Ibid.

50 Characteristically for the COVID-19-related scientific communication, which has been largely taking place on social networks, we might cite here The Lancet’s tweet from 4 June 2020: <https://twitter.com/thelancet/status/1268613313702891523> accessed 28 February 2021.


Trump’s supporters saw HCQ as a badge of their political allegiance.\textsuperscript{54} On the other hand, the off-label use of HCQ was vocally criticised by many experts, including Anthony Fauci,\textsuperscript{55} a leading member of the White House Coronavirus Task Force and the director of the National Institute of Allergy and Infectious Diseases. The use of HCQ remained a highly contentious political issue in the USA for several months,\textsuperscript{56} being an almost unseen case of politicization of a particular medicinal product. The science, though, was clear on the matter by mid-2020.

The development of scientific justification of the off-label use of HCQ for COVID-19 can be roughly summarised as follows:

- **Late March to late April:** the off-label use of HCQ was scientifically justified on the basis of \textit{in vitro} data and early reports, especially the French study from March 20 (this limited evidence was considered sufficient due to the critical situation and the pressing need to find an efficient therapy).

- **Late April to May 22:** scientific justification was fading, but the off-label use was arguably still justified.

- **May 22 to June 4:** the off-label use was scientifically unjustified; furthermore, it seemed risky from the legal perspective if harm to the patient (especially ventricular arrhythmia) occurred, even though the causation would be very difficult to establish.

- **June 4 onwards:** the off-label use has been scientifically unjustified, even though it has not been necessarily risky from the legal perspective—based on the recent knowledge, HCQ is probably not dramatically unsafe for COVID-19 patients, but it is ineffective in treating the disease.

### IV. Races Continue: Emerging Off-label Use of Medicines, Emerging Standard of Care

In 2020, several other medicines registered for different indications were, at least for some time, seen as promising for COVID-19 treatment. For example, some studies suggest that an antiviral drug, favipiravir, shortens hospitalisation

\textsuperscript{54} See Rogers (n 41).


stays and fastens the alleviation of symptoms, but different trials seriously contest these results. Another antiviral medicine, remdesivir, was approved as a treatment for COVID-19 by the FDA, but the WHO issued a conditional recommendation against its use due to the lack of evidence of its efficacy in improving survival and other important outcomes.

On the other hand, dexamethasone, a cheap corticosteroid commonly used for many indications, has been particularly successful in preventing deaths in patients seriously ill with COVID-19 since spring 2020. In indicated patients, its use should now be considered a part of the standard of care, as confirmed, for example, by the official endorsement of the European Medicines Agency (EMA).

In the end, the COVID-19 indication was added to dexamethasone’s SPC, so its use is no longer off-label.

As of February 2021, there have been several other medicines used off-label against COVID-19. For example, trials suggest the efficacy of a rheumatoid

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arthritis drug tocilizumab and other interleukin-6 inhibitors, a gout medicine, colchicine, or an inhaled corticosteroid budesonide normally used against asthma. The future will show us whether some of these medicines will be as effective as, or perhaps even better than, dexamethasone. The legal certainty of their off-label use will follow the developments in science. The gravity of the pandemic situation still needs to be taken into account. On the other hand, as the number of drugs known to be effective has been slowly growing, the standard of evidence required for the scientific justification of off-label use of medicines has been arguably increasing as well.

Moreover, specific COVID-19 treatments—monoclonal antibodies such as bamlanivimab or their cocktails such as Regeneron’s REGN_COV2—have been tested for their efficacy in patients who do not yet need hospitalisation. Monoclonal antibodies already acquired Emergency Use Authorisation by the American FDA in November 2020 and have been reviewed by Europe’s EMA since early 2021. In the months or years to come, it can be expected that new medicines registered for use against COVID-19 will gradually replace many older drugs that are used now. If there will be a medicine registered for COVID-19, the off-label use of another drug for the same indication (i.e., patients with mild

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illness or patients who need respiratory support) will be contrary to the standard of care, unless it will be necessary because of the patient’s individual health needs or the objective possibilities.

V. Conclusion

The off-label use of medicinal products is a standard part of medical practice. If it meets certain criteria, it is not contradictory to the standard of care. According to one of these criteria, the off-label use of medicinal products requires scientific justification. The standard of scientific evidence required for justification can be lowered in a critical situation. That has also been the case in the COVID-19 pandemic, especially in its early months. Even preprints can be used for scientific justification if the results have not been relevantly scientifically questioned. The case of HCQ is a vivid illustration of scientific justification of the off-label use amid a pandemic, with the necessary reliance on very small studies and *in vitro* results at first, with the scientific and political turmoil, and the ultimate gain of broader knowledge and understanding from big international trials. Dexamethasone, on the other hand, has been very successfully used for preventing many COVID-19 deaths. By early 2021, the off-label use of several other drugs was tested. Its permissibility will depend on the evidence of their efficacy (while very small studies are no longer sufficient for scientific justification of off-label use) as well as the gravity of the pandemic and the development of potential specific COVID-19 treatments.

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