

**The Enhanced Danger of Physicians' Off-Label Prescribing
During a Public Health Emergency**

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ABSTRACT

The COVID-19 pandemic represents a major challenge to both technologically advanced and resource-poor countries. There are currently no effective treatments for severe disease other than supportive care and advanced life support measures, including the use of mechanical ventilators. With the urgency and necessity bred from desperation, there have been many calls to utilize unproven therapies, such as hydroxychloroquine, for which little evidence of efficacy exists. We have previously argued that such off-label use, while legal, is problematic (and even dangerous) and have suggested several regulatory remedies that could protect patients and advance their interests while preserving the reasonable authority of physicians to do what they and their patients think is the best course of action. In this essay we ask whether the special conditions existing in a public healthcare crisis, such as the current pandemic, would justify a relaxing of our argument and permit ongoing unregulated off-label use. We outline at least four areas of concern, all of which can be exacerbated by the widespread distress and despair amongst doctors, patients and other stakeholders. We contend that, if anything, these conditions warrant even more caution and scrutiny of this practice.

I. INTRODUCTION

On December 26, 2019, a 41-year-old man was admitted to a hospital in Wuhan City, China, with flu-like symptoms including fever, painful cough, fatigue, and generalized achiness that began about a week before he presented for medical care. A novel coronavirus was isolated from his respiratory secretions that was genetically related to the pathogenic coronaviruses that cause SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory distress syndrome).¹ This virus is the etiologic agent that causes the disease now known as COVID-19 that is sweeping the globe. It is highly contagious and transmissible with an R_0 estimated to be between 1.4-3.28.² To date there is no known effective anti-viral treatment or vaccine; current therapy for those most severely affected consists of supportive care. The overall case fatality rate is about 2.3%.³

Recent reports have suggested that the antimalarial and immunomodulatory drugs chloroquine and hydroxychloroquine have *in vitro* antiviral activity against COVID-19.⁴ Based on this data and the fact that they are commonly used as prophylaxis against some types of malaria, rheumatoid arthritis, and systemic lupus erythematosus, several small open-label (i.e., non-blinded) and non-randomized clinical trials of these drugs – sometimes used in conjunction with the antimicrobial azithromycin – have been reported to have therapeutic efficacy in patients with severe COVID-19 disease.⁵ There are also a number of controlled clinical trials being undertaken to study the safety and efficacy of these medications in COVID-19 disease, but their results will take a number of weeks to months to be known. In the interim, two recent studies, one a retrospective case series analysis and the other a prospective blinded, randomized trial,

¹ Fan Wu, et al., *A new coronavirus associated with human respiratory disease in China*, 579 NATURE (2020).

² Ying Liu, et al., *The reproductive number of COVID-19 is higher compared to SARS coronavirus*, 27 JOURNAL OF TRAVEL MEDICINE (2020). The term R_0 refers to the number of expected secondary cases of infection produced in non-immune, susceptible patients exposed to an infected, infectious individual. The higher the number, the more capable the infection (and its causative agent) is of being transmitted and causing infection in others (i.e., how contagious it is). Hence, if the R_0 is 2, then up to 2 uninfected individuals exposed to an infected individual could catch the disease and become infected. Lorenzo Pellis, et al., *Reproduction numbers for epidemic models with households and other social structures. I. Definition and calculation of R_0* , 235 MATHEMATICAL BIOSCIENCES (2012). As a comparison, the R_0 for measles is at least 18 (and likely higher). See Fiona M. Guerra, et al., *The basic reproduction number (R_0) of measles: a systematic review*, 17 THE LANCET INFECTIOUS DISEASES (2017). The R_0 of the H5N1 strain of influenza that caused the 2009-2010 pandemic was a bit more than 2. M. P. Ward, et al., *Estimation of the basic reproductive number (R_0) for epidemic, highly pathogenic avian influenza subtype H5N1 spread*, 137 EPIDEMIOLOGY AND INFECTION (2009).

³ Zunyou Wu & Jennifer M. McGoogan, *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention*, JAMA (2020). This seems to vary depending upon the population, the methods used to report deaths, and the amount of pre- and post-mortem testing for COVID-19 infection.

⁴ Manli Wang, et al., *Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro*, 30 CELL RESEARCH (2020).

⁵ Philippe Gautret, et al., *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial*, INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS (2020); Jianjun Gao, et al., *Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies*, 14 BIOSCIENCE TRENDS (2020).

have demonstrated either no therapeutic benefit or unacceptable cardiac side effects with high-dose treatment.⁶

Still, because chloroquine, hydroxychloroquine, and azithromycin have been FDA-approved for many years and are widely available with a physician's prescription, they are also being used off-label outside of the clinical trials setting. Indeed, *The New York Times* on March 24, 2020, reported on the finding by “pharmacy boards in states around the country” that “[d]octors are hoarding medications touted as possible coronavirus treatments by writing prescriptions for themselves and family members.”⁷ Numerous other accounts from around the country also documented this phenomenon, leading to reported shortages of all three medicines in pharmacies.⁸ While there is no substantive evidence that these drugs work in COVID-19 infections, that has not stopped some prominent people, including the President of the United States, from publicly endorsing their use.⁹

At least four negative consequences follow from this state of affairs: First, the shortages limit their availability for their FDA-approved uses, thus risking harm to patients who are dependent on them. Second, patients who may or may not be infected with COVID-19 are exposed to drugs whose safety profile is unknown in these patients; this is particularly concerning in this context where even on-label uses involve important side effects.¹⁰ Third, patients taking these drugs for an unapproved use with little evidence to substantiate either efficacy or safety are, in effect, participating in individual unregulated clinical trials without proper informed consent.¹¹ Fourth, if these drugs enter widespread use for proven and suspected COVID-19 infections, it

⁶ Both of these studies appeared on the website MedRxIV, a “preprint server for health sciences” and as of this writing, have not been published in a peer-reviewed scientific journal. See Joseph Magagnoli, et al., *Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19*, MEDRXIV (2020); Mayla Gabriela Silva Borba, et al., *Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study)*, MEDRXIV (2020).

⁷ E. Gabler, States say some doctors stockpile trial coronavirus drugs, for themselves, *The New York Times*, March 24, 2020, available at <https://www.nytimes.com/2020/03/24/business/doctors-buying-coronavirus-drugs.html>.

⁸ J. Evans, Physicians seek to reassure amid hydroxychloroquine shortage, *Medscape News*, March 27, 2020, available at <https://www.medscape.com/viewarticle/927668>.

⁹ C. Piller, “This is insane!” Many scientists lament Trump’s embrace of risky malaria drugs for coronavirus, *Science*, March 26, 2020, available at <https://www.sciencemag.org/news/2020/03/insane-many-scientists-lament-trump-s-embrace-risky-malaria-drugs-coronavirus>.

¹⁰ See infra notes 28 and 44 and accompanying text. See also Andre C. Kalil, *Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics*, JAMA (2020).

¹¹ In some contexts, these are sometimes referred to as “n-of-1” clinical trials, where “n” refers to the number of patients enrolled. While some authors have endorsed their utility, others have been more skeptical. Compare Weyinmi A. Demeyin, et al., *N of 1 trials and the optimal individualisation of drug treatments: a systematic review protocol*, 6 SYSTEMATIC REVIEWS (2017) with RD Mirza, et al., *The history and development of N-of-1 trials*, 110 JOURNAL OF THE ROYAL SOCIETY OF MEDICINE (2017). Whatever one’s view, they all suffer from inherent observer bias and the lack of a trustworthy control group and hence the inability to distinguish any placebo effects.

could be difficult to enroll patients in gold standard, randomized double-blinded clinical trials as they may be reluctant to be assigned to the control or “placebo” arm.¹²

In response to physician “hoarding” numerous state boards of pharmacy (those agencies charged with regulating both pharmacists and dispensing and compounding pharmacies)¹³ have stepped in and issued orders barring the prescribing of these drugs for non-FDA-approved uses.¹⁴ Where these restrictions are in place, physicians are barred from writing prescriptions for themselves—so-called “self-prescribing”; and they are required to include on their orders the clinical indication for which the drug is being prescribed. Only those written for approved indications will be filled. Some states have also limited the number of pills that can be dispensed at one time. No new or additional sanctions are included to deter physicians or others licensed to prescribe (such as physician assistants and nurse practitioners) from violating these restrictions. Specifically, state boards of medicine have not issued any guidance in this matter, thus maintaining their longstanding endorsement of the established tradition of allowing physicians full autonomy in their prescribing practices. If physicians wish to prescribe chloroquine or hydroxychloroquine for individual patients with proven or even suspected COVID-19 for whom they feel it could be of some benefit – the essence of the justification for permitting unregulated OLU – they remain free to do so. Whether pharmacies will dispense the drugs in the context of this national emergency is another matter.

Most recently, other events seem to have overtaken local concerns about OLU prescribing of chloroquine and hydroxychloroquine. The pharmaceutical giants Sandoz (a unit of Novartis) and Bayer, both major manufacturers of these drugs, have decided to donate millions of doses to the US Strategic National Stockpile. And in a press release, the Department of Health and Human

¹² We are obviously forecasting here, as we are writing in the midst of the pandemic and just as formal trials are being implemented. But we do so with the benefit of ample historical precedent. For example, one of the most notable of which is the experience with studying the efficacy of myeloablative chemotherapy with autologous stem cell rescue for advanced breast cancer. After initial small, uncontrolled trials in the 1980s established the feasibility of this procedure, its advocates also found reason to believe that it was also more effective than existing treatments, which were not very good. Their reports generated a lot of publicity and desperate women and their doctors flocked to the few institutions that offered this intensive, dangerous, and expensive therapy. After several years of glowing testimonials, including in the medical scientific literature, insurance companies began to balk at paying the costs associated with what was essentially unproven, experimental treatment. This resulted in a number of successful lawsuits against insurers – and terrible publicity asserting that denial of the procedure was killing women – followed by widespread introduction of the therapy into clinical practice. Eventually, a movement was generated formally to investigate if the claims about its benefits were actually true. Several clinical trials were initiated both in the US and in abroad. Those in the US had a great deal of difficulty enrolling patients due to patient fear that they might be randomized to the control arm and to physician and patient confidence that the treatment worked. Thus, the trials took much longer to complete than they should have. When the trial results were analyzed and published, it was demonstrated that the intensive therapy offered no benefit over standard treatment and was, if anything, more toxic. RICHARD A. RETTIG, et al., *FALSE HOPE. BONE MARROW TRANSPLANTATION FOR BREAST CANCER* (Oxford University Press. 2007).

¹³ See, e.g., North Carolina Pharmacy Practice Act, N.C. Gen. Stat. §§ 90-85.2 to 90-85.44 (2020) (establishing the Board of Pharmacy “to protect the public health, safety and welfare in pharmaceutical matters).

¹⁴ See, e.g., North Carolina Board of Pharmacy, COVID-19 Drug Preservation Rule, March 24, 2020, available at <http://www.ncbop.org/LawsRules/COVID19DrugPreservationRule21NCAC46.1819.pdf>. This order is similar to those that have been issued in many but not all states.

Services (HHS) announced: “Given the importance of understanding the efficacy of these medications for the treatment and prevention of COVID-19, federal agencies, such as the National Institutes of Health and ASPR’s [Assistant Secretary for Preparedness and Response] Biomedical Advanced Research and Development Authority (BARDA), are working together to plan clinical trials.”¹⁵

At the same time, the FDA issued an (EUA) to permit these compounds “to be distributed and prescribed by doctors to hospitalized teen and adult patients with COVID-19, as appropriate, when a clinical trial is not available or feasible.”¹⁶ The FDA’s statement acknowledged that the evidence supporting such OLU are only “[a]necdotal” and that the issuance of EUA are only permissible when they are necessary “to prepare for and respond to chemical, biological, radiological and nuclear threats” and when

the FDA determines that, among other criteria, the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product, and there are no adequate, approved, available alternatives. Emergency access to a medical product under an EUA is separate from use of a medical product under an investigational drug application.¹⁷

Almost 10 years ago we examined the clinical, legal and ethical landscape for off-label prescribing by physicians in the United States. We concluded that some regulation of OLU was called for to protect both society’s interests in the health and welfare of the community and patient safety and autonomy. But we did so assuming “baseline” conditions, not in the context of a healthcare crisis or public health emergency. In this essay we revisit our earlier arguments and view them through the lens of widespread disaster conditions. We ask whether our original arguments in favor of modest and targeted legal regulation of OLU can withstand scrutiny in a pandemic that necessitates altering standards of care and the urgency to develop new and additional treatment options.¹⁸ Part II summarizes our original analysis, reasoning, and conclusions. Part III evaluates their applicability to current conditions. We conclude that although individual autonomy interests remain strong, the need for regulation is enhanced rather than diminished where public health interests predominate.

¹⁵ HHS Press Release, HHS accepts donations of medicine to Strategic National Stockpile as possible treatments for COVID-19 patients, March 29, 2020, available at <https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html>.

¹⁶ Id.

¹⁷ Id.

¹⁸ P. M. Rosoff, *Should palliative care be a necessity or a luxury during an overwhelming health catastrophe?*, 21 J CLIN ETHICS (2010); Philip M. Rosoff, *Does Desperation Justify Departures From Ethical Standards? The Case of the Ebola Epidemic.*, CLINICAL RESEARCHER (2014); Philip M. Rosoff, *Caring for the Suffering: Meeting the Ebola Crisis Responsibly*, AMERICAN JOURNAL OF BIOETHICS (2015).

II. BACKGROUND

In our 2007 article *The Case for Legal Regulation of Physicians' Off-Label Prescribing*,¹⁹ we argued that off-label uses (OLUs) of pharmaceuticals and biologics that are not justified by high quality evidence should be legally regulated to protect society's interests in safe and effective treatment and individual patients' interest in health and autonomy. High quality evidence is characterized by the use of clinical investigation techniques analogous to those used for FDA approval.²⁰ Borrowing the classifications developed by other scholars, we described as "problematic OLU" those that are unjustified, justified by some but not high-quality evidence, or, justified by the need or desire to innovate.²¹ We explored the historical commitments and values inherent in the law's longstanding *laissez faire* approach to the physician-patient relationship, but concluded that, on balance, the arguments in favor of unregulated prescribing authority in particular were insufficient to override the concerns associated with that authority.²²

Physicians have always had the authority to prescribe drugs and biologics "off label", meaning in ways that are different from those for which they were formally approved. However OLU are justified, the fact that they are used off label means that their safety and/or efficacy were not evaluated or else not established during the FDA approval process for the illness and conditions in which they were studied. Drugs and biologics are described as being used "off label" when they are prescribed for conditions other than those for which they were approved, in higher or lower than indicated dosages, and for populations other than those in which they were tested during the FDA approval process.

That being said, many OLU are supported by high quality evidence and thus are not problematic by our definition.²³ For example, the antineoplastic drug etoposide is approved by the FDA for use in testicular cancer and small cell cancer of the lung.²⁴ However, excellent clinical studies

¹⁹ 86 Notre Dame L. Rev. 649 (2011).

²⁰ Deborah J. Cook, et al., *Systematic Reviews: Synthesis of Best Evidence for Clinical Decisions*, 126 ANNALS OF INTERNAL MEDICINE (1997); Amir Qaseem, et al., *The Development of Clinical Practice Guidelines and Guidance Statements of the American College of Physicians: Summary of Methods*, 153 ANN INTERN MED (2010).

²¹ Id. at 652, 656. See also A. P. Abernethy, et al., *Systematic review: reliability of compendia methods for off-label oncology indications*, 150 ANN INTERN MED (2009).

²² In this conclusion, we joined other scholars who have argued for some form of limitation of off label prescribing authority. See also, e.g., R. Dresser & J. Frader, *Off-label prescribing: a call for heightened professional and government oversight*, 37 J LAW MED ETHICS (2009); N. Ghinea, et al., *No evidence or no alternative? Taking responsibility for off-label prescribing*, 42 INTERNAL MEDICINE JOURNAL (2012); Tewodros Eguale, et al., *Association of Off-label Drug Use and Adverse Drug Events in an Adult Population*, 176 JAMA INTERNAL MEDICINE (2016); Aviv Ladanie, et al., *Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials*, 94 JOURNAL OF CLINICAL EPIDEMIOLOGY (2018).

²³ Aviv Ladanie, et al., *Off-label treatments were not consistently better or worse than approved drug treatments in randomized trials*, 94 JOURNAL OF CLINICAL EPIDEMIOLOGY (2018).

²⁴ See the FDA-approved "package insert" for etoposide, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020457s016lbl.pdf.

have demonstrated its efficacy in a variety of other diseases, such as Ewing's sarcoma, a form of bone cancer.²⁵

Many other off-label drug uses are supported by some but not high-quality evidence and may be reasonable (under certain conditions) to have in the physicians' armamentarium because no better treatment options for an individual or a disease or condition exist.²⁶ For example, physicians could use a drug in a similar chemical class or one that works in a manner that could plausibly attack the underlying biochemical pathology of a certain disorder. This is the way in which the drug imatinib, originally approved for use in chronic myeloid leukemia as one of the first small molecule targeted anti-cancer therapies, was used off label to treat gastrointestinal stromal tumor, a malignancy with a related (but distinct) mutation.²⁷

For similar reasons, the need to innovate sometimes supports OLUs even where they are not evidence-based, although this should be understood for what it is, as experimentation. As we argue below, the use of chloroquine and hydroxychloroquine for treating symptoms of COVID-19 are illustrative of OLU that fall in this category because of the lack of substantive data demonstrating any beneficial effects in any phase of the disease.

Finally, some OLU are affirmatively contraindicated, or else unjustified by any evidence of efficacy. Chloroquine and hydroxychloroquine may also fall into this category. Not only is there little data-driven justification for their off-label use (outside of a controlled clinical trial), but there are well-known side effects to these drugs that could make them very risky to use in many patients. For example in high doses these drugs (especially when used in conjunction with the antibiotic azithromycin) can produce prolongation of the QT interval, a dangerous antecedent to potentially fatal cardiac rhythm disturbances.²⁸

²⁵ Linda Granowetter, et al., *Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study*, 27 JOURNAL OF CLINICAL ONCOLOGY : OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (2009).

²⁶ It is, of course, understandable that patients who have run out of options may be interested in experimenting with unproven and even otherwise unsafe approaches before finally turning to palliative care; and that their physicians might be supportive. The Right to Try Act, which affords patients in these circumstances the option to seek access to pre-market experimental drugs, reflects policymakers' determination that such access is appropriate in carefully delineated circumstances. See [Public Law No: 115-176](https://www.congress.gov/115/plaws/publ176/PLAW-115publ176.htm), available at <https://www.congress.gov/115/plaws/publ176/PLAW-115publ176.htm> (21 U.S. Code § 360bbb) Thus, our point in characterizing OLU motivated by the need or desire to innovate is not that experiments of one are never appropriate, but rather that – as experiments – they should trigger relevant conditions. See also Alison Bateman-House & Christopher T. Robertson, *The Federal Right to Try Act of 2017—A Wrong Turn for Access to Investigational Drugs and the Path Forward*, 178 JAMA INTERNAL MEDICINE (2018) and Kelly Folkers, et al., *Federal Right to Try: Where Is It Going?*, 49 HASTINGS CENTER REPORT (2019); and *infra* note 56 (further discussing The Right to Try Act).

²⁷ Heikki Joensuu, et al., *Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor*, 344 NEW ENGLAND JOURNAL OF MEDICINE (2001).

²⁸ Mayla Gabriela Silva Borba, et al. *op cit.* Also see Nicholas J. Mercuro, et al., *Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19)*, JAMA CARDIOLOGY (2020). See also *infra* note 44 (further discussing the drug's side effects).

Regardless of why they are prescribed – and in what context - OLU are effectively unregulated.²⁹ With the exception of restrictions on advertising and promotion by drug companies and on the distribution of certain narcotics, the federal government only formally regulates drug trials (HHS) and drug approvals for on-label uses (FDA).³⁰ Otherwise, it leaves the regulation of the doctor-patient relationship to the states.³¹ The states do so only very lightly and in ways that do not have a material effect on physicians’ OLU prescribing practices. That is, the states require medical licensing boards only generally to supervise the competence of physicians practicing in the jurisdiction; and while state tort law does provide for liability, i.e., when their treatment choices violate the standard of care and cause injury to their patients, that standard has specifically been interpreted not to require doctors to disclose the OLU status of a drug or biologic to their patients, and OLU have not typically been a successful basis for injured patients’ theory of breach.³² Finally, the profession itself, through its medical organizations, only issues nonbinding recommendations to their members which often go unheeded.

This laissez faire approach to physicians’ treatment choices – and to the doctor-patient relationship more generally – is rationalized on the grounds that physician and patient autonomy together are most likely to result in decision-making in the patients’ best interests.³³ The medical profession is considered to be properly self-regulated to these ends both because training is strictly and uniformly governed, and because it is steeped in important fiduciary norms.³⁴ Patients benefit from their physicians’ fealty to those norms as well as from their freedom to exercise their best medical judgment in circumstances that are often highly individualized and personal. And assuming access is not a constraint, patients benefit from the freedom to choose or to refuse treatment options based on their own risk-benefit calculus and values. Indeed, access constraints are typically viewed by patients and doctors as both violations of individual liberty interests and as obstacles to best treatment decisions.³⁵

These considerations are legitimate and properly weighty, to the point that arguments in favor of regulating physicians’ off-label prescribing – a form of access constraint – have never gained traction.³⁶ Nevertheless, we made the case for such regulation on the grounds that it is likely the

²⁹ Rosoff and Coleman, *supra* note 19 at 660-676.

³⁰ *Id.* at 661-63.

³¹ *Id.* at 664-74.

³² *Id.* at 666-73.

³³ *Id.* at 678-79.

³⁴ *Id.* at 679.

³⁵ *Id.*; see also Jeffrey A. Singer, Doctors, Not Politicians, Ought to Decide Whether Off-Label Use of Hydroxychloroquine Is Appropriate for COVID-19 Patients, Reason, April 7, 2020, available at https://reason.com/2020/04/07/doctors-not-politicians-ought-to-decide-whether-off-label-drug-use-of-hydroxychloroquine-is-appropriate-for-covid-19-patients/?utm_medium=email.

³⁶ Rosoff and Coleman, *supra* note 19 at 678.

most effective means to ensure that patients and society are protected from the harms associated with problematic OLU because physicians are the direct link – or in legal terms the direct cause – of patients’ use of drugs and biologics off-label. Moreover, we argued that if done right, the regulation would enhance rather than detract from patient wellbeing.³⁷

Given the patient-centered rationales for unfettered prescribing authority, we identified the most important harms associated with problematic OLU as being that they may not be safe or effective for their intended use - physicians often don’t disclose this fact or the OLU status of the product – to their patients, who are then unable to take this into account as they decide whether they want to proceed with the suggested course of treatment. Depending on the nature and extent of the evidentiary basis for any particular prescription, the OLU could be viewed as, in effect, an unregulated experiment, again often conducted without the patient’s (subject’s) knowledge.³⁸

³⁷ Id. at 678-80.

³⁸ Id. at 653-55. Some scholars and physicians who favor maintaining the status quo of unregulated OLU argue that individual doctors must have the freedom to tailor their prescribing to individual patient needs as they both see fit, and to innovate their therapeutic choices, also with their patients’ best interests foremost. See, e.g., Colleen Conners, *Illuminating the off-Label Fable: How off-Label Promotion May Actually Help Patients* Student Comments, JOURNAL OF LAW, ECONOMICS & POLICY (2017); Eric von Hippel, et al., *Market failure in the diffusion of clinician-developed innovations: The case of off-label drug discoveries*, 44 SCIENCE AND PUBLIC POLICY (2016). At the ragged edges of this argument lies the ability of physicians (and patients) to discern the difference between clinical research and therapeutic innovation within the context of clinical practice. This difference has been notoriously difficult to pin down.

In Volume 1 of the Appendix to The Belmont Report, for example, Robert J. Levine conducted an exhaustive analysis of the boundary between the two, ultimately defining “innovative therapy” as

a term applied to a simple activity that is ordinarily conducted by the physician with either pure practice intent or varying degrees of mixed research and practice intent. It is distinguished from accepted and standard medical practice in that it has not been sufficiently tested to meet peer group or regulatory agency standards for acceptance or approval... In other cases, innovative therapy may be conducted with pure practice intent. Thus, a physician may decide to administer a drug to a patient who has a serious abnormality requiring treatment for which there is no alternative. It might be that there is no other drug or other form of treatment available for this condition. Alternatively, it might be the case that alternative therapeutic modalities have been tried and failed. Thus, the physician may proceed with pure practice intent. In some cases the physician might not perceive himself as an investigator.

Robert J. Levine, *The boundaries between biomedical or behavioral research and the accepted and routine practice of medicine* at 6, 14-15, in THE BELMONT REPORT (1975)). NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BETHESDA BEHAVIORAL RESEARCH, MD., THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (ERIC Clearinghouse. 1978). See also F.D. Moore, *Therapeutic Innovation: Ethical Boundaries in the Initial Clinical Trials of New Drugs and Surgical Procedures* 98 DAEDALUS (1969). In that same piece, Levine also considered the complexities and potential problems associated with using certain drugs (for example) in a patient when the therapy is poorly studied (or not studied at all) or may be counter to the “standard” approach. In doing so, he anticipated the regulatory vacuum in this area, writing that “for purposes of considering drugs as either accepted or not accepted there is the FDA which helps solve some boundary problems and which may contribute to the creation of some others. There are a variety of other types of therapeutic and diagnostic modalities for which we have no standard-setting agencies. For these, for the time being, one might consider developing mechanisms to devise guidelines which will help practitioners distinguish accepted from unaccepted.” Id. at 12. See also John Robertson, *Legal implications of the boundaries between biomedical research involving human subjects and the accepted or routine practice of medicine* in THE BELMONT REPORT (1975), Appendix II, Chapter 16) (arguing for some forms of regulation, although primarily located within the profession of medicine and affiliated institutions such as hospitals).

In addition to these individual harms, which involve both the patient's physical welfare and their autonomy interests, we noted that society also bears important costs, primarily in the form of increases in health care spending and delays in securing effective treatment.³⁹

Where unfettered autonomy risks these harms, we urged policymakers to consider narrowly tailored restrictions.⁴⁰ Specifically, we identified the following as necessary elements of a sound regulatory regime: First, restrictions would be on a sliding scale based on the OLU's evidentiary support, from none for OLU supported by high quality evidence to the requirement that OLU justified only by the need or desire to innovate be permitted only in circumstances where there was no safe and effective alternative. Second, in cases of problematic OLU, FDA status or the state of the evidence would be treated as medically material information. Third, real sanctions would be put into place for violations. Fourth, OLUs would be subject to reporting requirements in view of the development of a publicly available safety and efficacy database.⁴¹ We concluded with the reminder that although there is broad and deep support for the sanctity of the doctor-patient relationship, including for both doctor and patient autonomy, our political and constitutional scheme is one of ordered (not unfettered) liberty. The doctor-patient relationship is, like the parent-child or spousal relationship, both properly respected but also properly subject to public ordering to ensure consistency with public health requirements and contemporary ethical standards of evidence-based medicine and informed consent.

III. DO ALTERED STANDARDS OF CARE IN A PANDEMIC JUSTIFY UNRESTRICTED OLU?

The question we consider in this essay is whether our original analysis holds true in pandemic conditions. Specifically, in pandemic conditions where there is no known effective approach to prevention or treatment, does the *need* for unrestricted access to problematic OLU overcome standard objections to their use? Once again taking into account the nature of the OLU at issue, the regulatory landscape, and individual and public health considerations, we conclude that while individual considerations may predominate in baseline circumstances, public health considerations make regulation of OLU especially important in pandemic conditions like this one involving a novel disease.

Based on this methodology, the use of an approved drug in a novel way (such as hydroxychloroquine) with an individual patient would generally not be considered a formal research activity in the absence of a plan or with the intent to utilize information gained from this single experience to apply it to similar clinical situations. But as Levine's discussion suggests, the reality of clinical practice where these activities are not uncommon: innovation can readily morph into research as what is interpreted as a "success" is applied to the next patient with a comparable disease, and so on. Indeed, it is reasonable to assume that such is the genesis of many published retrospective case series. For example, see John A. Segreti, et al., *Daptomycin for the Treatment of Gram-Positive Bacteremia and Infective Endocarditis: A Retrospective Case Series of 31 Patients*, 26 PHARMACOTHERAPY: THE JOURNAL OF HUMAN PHARMACOLOGY AND DRUG THERAPY (2006); Swetha Kambhampati, et al., *Nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh class B cirrhosis: Safety and clinical outcomes in a retrospective case series*, 125 CANCER (2019). Notably, the Veterans Administration retrospective study of hydroxychloroquine cited above was also of this type. See *supra* note 6 (citing the Maganoli, et al. study).

³⁹ Rosoff and Coleman, *supra* note 19 at 655.

⁴⁰ *Id.* at 680-90.

⁴¹ *Id.* at 690-91.

It is precisely in such circumstances that unscrupulous salesmen are wont to peddle false or unproven hope,⁴² and that well-meaning practitioners may be motivated to try what one front-line physician has described as a “maybe-maybe-this-will-work cocktail”⁴³ for their desperately ill patients. Albeit differently motivated, both uses are unjustified in an evidentiary sense and thus risk harm to individual patients.⁴⁴ And, both compromise the ability of the public health system to develop a robust understanding of their safety and efficacy for this particular condition.

The OLU at issue here qualify as “problematic” according to our original rubric because they are primarily justified on the basis of a need or desire to innovate. To date, there is only anecdotal evidence of efficacy for the off-label use of chloroquine and hydroxychloroquine (with or without the addition of azithromycin) with Covid-19.⁴⁵ Regardless of how the state of the evidence is characterized, however, it is undoubtedly insufficient according to standard protocols

⁴² Kevin Roose and Matthew Rosenberg, Touting Virus Cure, ‘Simple Country Doctor’ Becomes a Right-Wing Star, *The New York Times*, April 2, 2020, available at <https://www.nytimes.com/2020/04/02/technology/doctor-zelenko-coronavirus-drugs.html>.

⁴³ S. Fink, ‘Code Blue’: A Brooklyn I.C.U. Fights for Each Life in a Coronavirus Surge, *The New York Times*, April 4, 2020, available at <https://www.nytimes.com/2020/04/04/nyregion/coronavirus-hospital-brooklyn.html> (Dr. Joshua Rosenberg describing the combination of hydroxychloroquine and azithromycin as a “maybe-maybe-this-will-work cocktail,” because only a couple of tiny studies supported its effectiveness against Covid-19” and as noting, “I don’t think the public realizes how often we don’t really know” whether something works”).

⁴⁴ The “maybe-maybe-this-will-work cocktail” described in note 43 resulted in an unexpected adverse cardiac event (unexpected in the sense that many people initially prescribing this drug who had never used it before may have been unfamiliar with this well-known adverse reaction; it is also possible that prolonged QTc with hydroxychloroquine may be more frequent in patients with proven COVID-19 or with the higher doses employed), see id. In that case, it was likely a prolonged QTc interval that can predispose susceptible patients to life-threatening cardiac arrhythmias, due to either – or both – azithromycin and hydroxychloroquine. See Rachael A. Lee, et al., *Evaluation of baseline corrected QT interval and azithromycin prescriptions in an academic medical center*, 11 *JOURNAL OF HOSPITAL MEDICINE* (2016); Nicholas J. White, *Cardiotoxicity of antimalarial drugs*, 7 *THE LANCET INFECTIOUS DISEASES* (2007). These drugs, while relatively safe to use for malaria and lupus erythematosus, are by no means harmless. In addition to effects on the population generally, they may also exacerbate existing disparities. For example, chloroquine and hydroxychloroquine tend to cause hemolysis (the destruction of red blood cells) in patients with glucose-6-phosphate dehydrogenase deficiency (G6PDD). This enzyme deficiency is the most common in the world, affecting an estimated 400 million people, almost all of them men due to it having an X-linked recessive inheritance pattern. There are hundreds of variants amongst various ethnic populations. It is most prevalent in regions historically (and currently) associated with a high prevalence of malaria. Episodes of acute hemolysis are generally initiated by exposure to naturally occurring compounds in certain foods (e.g., fava beans) or drugs, such as chloroquine and hydroxychloroquine. Depending upon the subtype a patient has, and the kind of chemical agent causing the episode, the hemolysis could be relatively mild or life-threatening. See Matthew S. Karafin, et al., *The clinical impact of glucose-6-phosphate dehydrogenase deficiency in patients with sickle cell disease*, 25 *CURRENT OPINION IN HEMATOLOGY* (2018).). In the United States, up to 10% of African-American men are affected, most with the “A-” form, which leads to mild or moderate hemolysis upon exposure. See Ernest Beutler, et al., *Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency in Sickle-Cell Disease*, 290 *NEW ENGLAND JOURNAL OF MEDICINE* (1974).). Nevertheless, it is likely that prolonged high doses of pro-hemolytic drugs could be catastrophic in a significant number of patients, especially if they are also sick with COVID-19.

⁴⁵ Notably, the published studies have been retrospective, non-randomized case series with relatively small number of patients. See supra note 6.

to justify the breadth of use that is currently being contemplated by some individual physicians and policymakers. The *laissez faire* tradition regarding OLU prescribing practices assumes baseline conditions in which experimentation outside of highly-regulated clinical trials is rare; and, the tradition is rationalized on the grounds that physician and patient autonomy carry greater weight than any public health concerns and most likely to yield decisions in the individual patient's best interests. As we argue below, these premises have been thrown out the window in the context of Covid-19.

Still, the regulatory landscape remains almost intact. The federal government has fast-tracked gold-standard clinical trials, but it has also provided that physicians can prescribe the drugs off-label and has even tacitly encouraged such as by adding to the nation's strategic stockpile to make that possible on a broad basis.⁴⁶ In other words, rather than imposing new restrictions on physicians' OLU because of the dearth of evidence pointing to their safety and efficacy and to support the integrity of the clinical trials, it has signaled that it will enable them on a grand scale. Most state governments to date have not acted in this area, although the associated liability issues that will eventually make their way into the state courts are being discussed.⁴⁷ The same is true of state medical boards, although state pharmacy boards have sought to restrict their professionals from dispensing based on certain physician orders, i.e., in circumstances where there is evidence of scarcity and hoarding.⁴⁸ This regulatory status quo is not justified in these circumstances. Neither individual concerns nor the public health situation support unfettered OLU of the drugs at issue.

It remains the case in these pandemic conditions, as it was in the baseline conditions we examined in our first OLU paper, that individual patients have a recognized, extremely important interest in their own health and welfare and certainly in their survival. They also continue to have a recognized, extremely important interest in their own and by extension their physicians' autonomy. But as we argued in that earlier paper, a patient's health and welfare is not enhanced by the use of an experimental drug (or a known drug in an experimental therapeutic setting) in circumstances where alternative approaches are available; it is only in "Hail Mary" settings where the individual risks are likely to be worth taking. Relatedly, patient autonomy would be enhanced not diminished by a regulatory determination that the off-label status or evidentiary basis for a prescription is medically material information that must be disclosed as part of the informed consent process. This is especially likely to be the case in circumstances like this one, involving OLU that are primarily justified by the need or desire to innovate and where – outside of some "Hail Mary" situations – it is not clear that the benefits of the prescription will override the risks. The latter include not only any negative side effects associated with the use that might

⁴⁶ See *supra* note 15 and accompanying text.

⁴⁷ News reports indicate that states are beginning to issue restrictions, however many or most of these are through state pharmacy boards and not from state governments. See Jared S. Hopkins, States Try Reducing Malaria Drug Hoarding Amid Unproven Coronavirus Benefit, *The Wall Street Journal*, April 5, 2020, available at <https://www.wsj.com/articles/states-try-reducing-malaria-drug-hoarding-amid-unproven-coronavirus-benefit-11586095200>.

⁴⁸ See *supra* notes 13-14 and accompanying text. It is reasonable to assume that the state pharmacy boards that have issued restrictive dispensing rules (not prescribing guidelines as that is not in their purview), will relax or eliminate them once these drugs become more plentiful and available.

be especially problematic in an already-compromised patient, but also the costs associated with foregoing alternative preventative or ameliorative approaches. Physicians should be restricted in their OLU prescribing outside of “Hail Mary” situations; and they should be required to disclose the OLU status of the drugs or their experimental nature to their patients or their patients’ proxies before a prescription is written.

These restrictions would benefit physicians along with their patients as they would operate to insulate them from – or to reduce the likelihood of – eventual malpractice liability. Such liability could arise on one of two standard tort theories. First, patients who suffered adverse outcomes in part from the drugs themselves could argue that it was malpractice to prescribe them in circumstances where the risk-benefit calculus was unknown and there were better understood alternatives. Second, patients could argue that the experimental nature of the prescription was medically material information which needed to be disclosed as part of the informed consent process. As to this second possibility, the current state of the caselaw is that a drug’s OLU status is not medically material information;⁴⁹ but unless the federal government or state legislatures act affirmatively to insulate physicians from liability in circumstances where they fail to disclose that information, a factfinder could – easily in our view – find that a reasonable patient would want to know that a prescription would render them an experiment of one but without the usual protections associated with human subjects research.

Beyond always-important individual interests is public health which is, by definition, of particular significance in pandemic conditions. Here, the unit of concern is the population as a whole, taking into account discrete subpopulations as classified by factors such as age, sex, ethnicity, and regional, political, and socioeconomic status. A focus on the individual in this context is only relevant insofar it benefits the collective. For example, public health authorities – in both developed and resource-poor countries (to the extent practicable) – spend a great deal of time and effort performing contact tracing for certain highly communicable diseases, such as tuberculosis, as well as ensuring that infected patients take their medication to reduce contagiousness.⁵⁰ In the case of a fast moving, highly deadly communicable disease like Ebola, public health authorities are authorized even further to restrict individual liberty to the point of mandatory quarantines.⁵¹

In pandemic conditions involving a novel disease like COVID-19, there is no public health justification for *unregulated* OLU motivated only or mainly by a need or desire to innovate. To the contrary, the absence of regulation in this context affirmatively harms the public interest. This harm results both from the misleading if not flat out erroneous signal to the population that

⁴⁹ Rosoff and Coleman, *supra* note 19 at 671-73.

⁵⁰ Christopher Craig, et al., *Contact tracing in pulmonary versus non-pulmonary tuberculosis- the impact of the 2016 NICE guidelines?*, 50 EUROPEAN RESPIRATORY JOURNAL (2017).

Kristen M. Little, et al., *Yield of household contact tracing for tuberculosis in rural South Africa*, 18 BMC INFECTIOUS DISEASES (2018).

⁵¹ Roger Detels, et al., *Oxford Textbook of Global Public Health at Section 3* (Oxford University Press 6th ed. 2015).

the drug or drugs have preventative or treatment effects, and from undermining the government's ability to develop high quality evidence of safety and efficacy. Thus, while chloroquine, hydroxychloroquine, and associated cocktails may be justified as a "Hail Mary" in individual cases, their *unregulated* use for COVID-19 regardless of the circumstances can result in irrational behavior, disease spread, and diminished opportunities for public health authorities not only to establish their real risk-utility calculus, but also that of different, better-justified approaches that are de-emphasized or foregone as a result of capricious investments in this one.

We conclude our analysis on this last point, which is ultimately most compelling. To safeguard the health and welfare of society, public health authorities need high quality evidence about the safety and efficacy of the drugs and biologics to which they would turn in pandemic conditions. It is abundantly well-understood that such evidence is best obtained through large, randomized clinical trials that are statistically powered to these ends; such trials are the gold standard for reliable and trustworthy evidence collection.⁵² Although this alternative is not preferred, it is also understood that in some cases, high quality evidence can also be obtained over time through the collection and analysis of trustworthy data from individual, isolated OLU. In our earlier paper, we described OLU justified by the latter category of evidence as non-problematic because by its quality and quantity, the data supporting their safety and efficacy approximate that which is collected in the formal trials process.

The regulatory status quo undermines this critical project because it disincentivizes participation in clinical trials and, because it doesn't impose any restrictions or data collection or reporting requirements on prescribing physicians, it fails even to provide the opportunity for the development of high-quality evidence outside of the gold standard. Why would a reasonable patient with COVID-19 sign up for a clinical trial if they can readily obtain the drugs they want without enrolling, thereby avoiding both the uncertainty of blinded randomization and the other, sometimes cumbersome, regulatory requirements associated with human subjects research? And, once the pandemic has passed, how will we know whether the many OLU of chloroquine, hydroxychloroquine, and associated cocktails worked or not; if they did, when they did; and the range, nature, and degree of their side effects so that, going forward, public health authorities will be operating on the basis of at least better if not the best information? By authorizing wide-scale, unregulated use of these drugs in this setting, we are effectively launching a national experiment without tending to the matter of how to collect its precious results.

Given this, the ideal would be for the federal government to consider using its emergency powers under the Defense Production Act of 1950⁵³ to commandeer supplies of hydroxychloroquine and chloroquine and to restrict prescriptions to either FDA-approved indications or to others for which good clinical evidence would support its use. The remaining stocks would be available only to those patients willing to enroll in clinical trials, not unlike the situation that exists for almost all investigational new drugs that are seeking FDA approval.

⁵² Olga Dumont Flecha, et al., *A commentary on randomized clinical trials: How to produce them with a good level of evidence*, 7 PERSPECTIVES IN CLINICAL RESEARCH (2016). Benjamin Djulbegovic & Gordon H. Guyatt, *Progress in evidence-based medicine: a quarter century on*, 390 THE LANCET (2017).

⁵³ 50 U.S.C. App. § 2061 et seq., available at https://www.fema.gov/media-library-data/20130726-1650-20490-5258/final_defense_production_act_091030.pdf.

In the alternative, we urge the federal government – or a consortium of state governments such as those that are forming for other COVID-related matters⁵⁴ – to develop a robust, centralized reporting requirement to gather data, similar to the post-FDA approval reporting.⁵⁵ The quality of evidence gathered by physicians and other prescribers and transmitted to the associated centralized database could be expected to be highly variable given that most clinicians are not trained in research protocols. However, carefully designed, guided reporting forms could focus their entries to maximize the utility of the data entered. The reporting requirements for investigational drugs obtained via the Right to Try Act of 2017 could be used as a model for this design.⁵⁶

⁵⁴ As we have detailed, to the extent that physicians' prescribing practices are already regulated, it is primarily by the states through tort law, and to a lesser extent through the requirements imposed on medical boards. Individual states could tighten the regulation of problematic OLU through either of these or different means. In other words, their longstanding laissez-faire approach is not based in a lack of authority, it's a policy choice. States exercising their police powers – their authority to regulate in the interests of society's health and welfare – could also form regional groups to develop a coordinated approach, i.e., multi-state compacts. The latter approach is most likely in circumstances where there are shared, cross-border concerns and the states can agree on solutions. Historical examples of multi-state consortia include, among others, coordinated water usage rights and crime fighting agreements. Like water and crime, infectious disease and the consequences that flow from disease aren't constrained by political boundaries, and so it is not surprising that we see the emergence of multi-state consortia in the context of the spread of the novel coronavirus. Where the federal government might sometimes be relied on to coordinate a national response that includes, e.g., the development of a database to which local reports might be sent, in other instances this role might be filled by sub-national, regional groups. See Colm Quinn, U.S. Governors Defy Trump by Forming Regional Alliances, *Foreign Policy*, April 14, 2020, available at <https://foreignpolicy.com/2020/04/14/us-governors-states-rights-defy-trump-by-forming-regional-alliances/>; Matt Dixon, Southern governors create a COVID-19 coalition and experts fear a 'perfect storm', *Politico*, April 21, 2020, available at <https://www.politico.com/states/florida/story/2020/04/21/southern-governors-create-a-covid-19-coalition-and-experts-fear-a-perfect-storm-1278753>; Greg Hinz, Midwest governors form COVID coalition, *Chicago Business*, April 16, 2020, available at <https://www.chicagobusiness.com/greg-hinz-politics/midwest-governors-form-covid-coalition>; See also Anastasia Kalinina, What the world can learn from regional responses to COVID-19, *Atlantic Council*, April 24, 2020, available at <https://atlanticcouncil.org/blogs/new-atlanticist/what-the-world-can-learn-from-regional-responses-to-covid-19/>.

⁵⁵ U.S. FDA, Postmarketing Surveillance Programs, April 2, 2020, available at <https://www.fda.gov/drugs/surveillance/postmarketing-surveillance-programs>. Our proposal contemplates that such reporting would be mandatory rather than optional, as is the case for post-approval reporting and under the Right to Try Act, which specifies a rigorous reporting requirement as a condition for gaining access to and receiving investigational drugs. See supra note 26.

⁵⁶ Id. The Act provides, inter alia, that

The manufacturer or sponsor of an eligible investigational drug shall submit to the Secretary an annual summary of any use of such drug under this section. The summary shall include the number of doses supplied, the number of patients treated, the uses for which the drug was made available, and any known serious adverse events. The Secretary shall specify by regulation...to require the submission of such annual summary in conjunction with the annual report for an applicable investigational new drug application for such drug...post an annual summary report of the use of this section on the internet website of the Food and Drug Administration, including the number of drugs for which clinical outcomes associated with the use of an eligible investigational drug.

Id. at §561b.

IV. CONCLUSION

In pandemic conditions, OLU that are justified only or mostly by a need or desire to innovate may be rationalized on the basis of individual autonomy interests, so long as the patient or their proxy is fully briefed on their experimental nature, and the uses don't risk important harm to the public health. Physicians who suggest that there is no requirement that they get their patients' informed consent before subjecting them to a de facto, unregulated clinical trial of chloroquine and hydroxychloroquine for the treatment of COVID-19 are acting outside of both professional norms and the law.⁵⁷ Indeed, such prescriptions are anachronistic to the point that they ignore decades of development of bioethics and informed consent rules that privilege not only the practice of evidence-based medicine, but also the exercise of physician autonomy only in circumstances where such exercise is in conjunction with patient autonomy in the patient's best medical interests. Desperation and even panic in pandemic conditions are foreseeable, but they call for cool heads to prevail, not the abandonment of principle.

Whether the prescriptions risk harm to the public health that preempts individual autonomy interests depends on the nature and scale of the prescribing. In this essay, we argue that unregulated experimental uses on a broad scale in circumstances involving a novel, highly-contagious disease like COVID-19 risk important harm to our effort to develop, through gold-standard clinical trials, robust information about the safety and efficacy of the government's arsenal of weapons that can be used to fight such disease. It is our view that the ability successfully to mitigate this risk on behalf of the population generally outweighs the interests of individuals in prescriptions that have not been proven to be effective to prevent or treat disease.

Thus, we join others who have called for the restriction of innovative OLU to permit established clinical trials to take their course.⁵⁸ We suggest a bifurcated approach to data collection that complements those trials with a supervised approach to those OLU that do take place. Innovative OLU would be restricted to individual cases involving hospitalized patients who are diagnosed with the disease in issue; and it would require their physicians to report relevant information to a centralized database that would support the evidence gathered through standard clinical trials. This bifurcated approach is not ideal but it balances individual and public interests in a way that is consistent with strongly held political norms.

We understand that our proposal is aspirational and that existing laissez faire norms are entrenched to the point that formal regulation of physicians' OLU prescribing practices remains unlikely. We say unlikely – although not impossible – because, of course, physicians' traditionally unfettered prescribing practices have already been submitted to some constraints in the modern period by some third party payers, including insurers and the federal government

⁵⁷ Vanessa Romo, COVID-19 Patients Given Unproven Drug In Texas Nursing Home In 'Disconcerting' Move, National Public Radio, April 10, 2020, available at https://www.npr.org/2020/04/10/830348837/covid-19-patients-given-unproven-drug-in-texas-nursing-home-garnering-criticism?utm_term=nprnews&utm_source=twitter.com&utm_campaign=npr&utm_medium=social.

⁵⁸ Michael Wilkes & Margaret Johns, *Informed Consent and Shared Decision-Making: A Requirement to Disclose to Patients Off-Label Prescriptions*, 5 PLOS MEDICINE (2008); R. Dresser & J. Frader, *Off-label prescribing: a call for heightened professional and government oversight*, 37 J LAW MED ETHICS (2009); N. Ghinea, et al., *No evidence or no alternative? Taking responsibility for off-label prescribing*, 42 INTERNAL MEDICINE JOURNAL (2012).

through its Medicare and Medicaid programs. While Medicare Part D only rarely refuses to pay for approved drugs, even when used off label,⁵⁹ private insurers are more reluctant to do so, especially for expensive medicines like biologics when prescribed in situations for which little evidence of efficacy exists.⁶⁰ Regardless, ongoing consideration of alternative approaches is certainly warranted. Among the most promising are developments in professional association codes and standards that go beyond general pronouncements specifically to the articulation of standards of care and medical errors that can be borrowed by law.⁶¹ Ultimately, our aspirations for the development of sound medical policy in the interests of individuals and the public at large are based in the same concerns about evidence-based medical practice that would guide those pronouncements.

BRIEF BIOGRAPHIES:

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⁵⁹ David Kwok, *Controlling Excessive Off-Label Medicare Drug Costs through the False Claims Act*, HEALTH MATRIX: JOURNAL OF LAW-MEDICINE (2017).

⁶⁰ See, e.g., Coverage of Drugs and Biologicals for Label and Off-Label Uses, United HealthCare, Aug. 14, 2019, available at <https://www.uhcprovider.com/content/dam/provider/docs/public/policies/medadv-guidelines/c/coverage-drugs-biologicals-label-off-label-uses.pdf>.

⁶¹ P. J. Pronovost, *Enhancing physicians' use of clinical guidelines*, 310 JAMA (2013).