Report Information from ProQuest

24 January 2024 00:50

DAFTAR ISI

The Boston Medical Center Immigrant Task Force: An Alternative to Teaching Immigration Law to Health Care Providers

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ABSTRAK (ENGLISH)

As healthcare providers engage in the politics of reforming and humanizing our immigration and asylum “system” it is critical that they are able to refer their patients whose health is directly impacted by our immigration laws and policies to experts who can help them navigate the system and obtain the healthcare they need.

TEKS LENGKAP

The landscape of immigration law and policy in the United States (US) has shifted through the decades and is set to shift again in a Biden administration. However, since January 2017, immigration policy has been starkly and steadily reshaped in a rapid-fire fashion, unprecedented by historical reference, and with indifference to the health and safety of immigrants and their families. The Trump administration has promulgated more than 400 executive actions on immigration, spanning everything from border and interior enforcement to refugee resettlement and the asylum system, Deferred Action for Childhood Arrivals (DACA) and the asylum courts, among many others.[1]

The COVID-19 pandemic has been used to further accelerate the administration’s restrictive and punitive immigration agenda, with the primary goal of deterring migrants from crossing our borders under the guise of public health. The net result of these policies on our immigrant communities is a toxic environment of fear, pain, and stress. With the Trump administration’s empowering of Immigration and Customs Enforcement (ICE), raids, arrests, and detentions have risen sharply. ICE director Thomas Homan, in a 2017 House Appropriations Committee meeting, said that “… if you’re in this country illegally, and you committed a crime by entering this country, you should be uncomfortable, you should look over your shoulder, and you need to be worried …”[2]

Several of the Trump administration immigration policies, including termination of Temporary Protected Status (TPS), the “Zero-Tolerance” Policy directing forced separation of children from their parents, the Migrant Protection Protocol (MPP), Third Country Agreements, Title 42, and Public Charge deserve comment, understanding that they represent only a few examples of the complex web of legal policies that undermine the health of migrants.[3]

The complexity of immigration law, and its relentless pursuit of immigrants under the Trump administration, has deterred many immigrants from seeking health care they need and are eligible to obtain.[4] Nonetheless, as La Charite and colleagues document, very few healthcare providers know enough about immigration law and enforcement to be a helpful source of information on this subject.[5] A few more examples of acts against the interests of immigrants suggests that health care providers cannot realistically take on this task. TPS is a humanitarian program that allows foreign nationals to remain in the US if conditions in their country pose a danger to personal safety due to ongoing armed conflict or humanitarian disaster. In November 2017, TPS was terminated for Haitians, in January 2018, it was terminated for El Salvadorans, and then for Nicaragua, Sudan, Honduras, and Nepal. Many families who came to the US under TPS have established roots and have US citizen children. They are now fearful of deportation and family separation. Hopefully the Biden administration will reverse these decisions.

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With the Trump administration's empowering of Immigration and Customs Enforcement (ICE), raids, arrests, and detentions have risen sharply. ICE director Thomas Homan, in a 2017 House Appropriations Committee meeting, said that "… if you're in this country illegally, and you committed a crime by entering this country, you should be uncomfortable, you should look over your shoulder, and you need to be worried …"
In May 2018, former Attorney General Sessions announced the "Zero Tolerance Policy" that prosecuted parents who crossed into the US illegally with children. Border agents forcibly separated children from their parents at the Mexican border to deter other parents from attempting to come to the US with their children. From October 2017 through May 2018, at least 2700 children were separated from their parents. Although the policy was ended after public outcry, reuniting families has been difficult. As of October 2020, it was reported that 545 migrant children have yet to be reunited with their parents, but the number is likely much larger. This policy has caused irreparable harm in the process. It has resulted in state-sponsored child abuse that can rise to the level of torture.[6]
In December 2018, the "Migrant Protection Protocols" (MPP) — often referred to as the "Remain in Mexico" program — was established. Under MPP, individuals who arrive at the southern border and request asylum are given notices to appear in immigration court and then are sent back to Mexico to wait for their court hearing. The decision to send a person or family back under MPP is discretionary and is made by individual CBP officers or Border Patrol agents and almost always puts the asylum-seeker at significant risk of harm. According to Human Rights First, through January 21, 2020, there were more than 816 publicly documented cases of rape, kidnapping, assault, and other crimes committed against individuals sent back under MPP.[7] Multiple people, including at least one child, have died. The conditions are inhuman: makeshift encampments, unsanitary conditions, scarce food and potable water, limited medical care, and exposure to the elements. Families have also been separated under this policy.
Asylum seeking has effectively been prohibited at the southern border. On July 16, 2019, the Trump administration announced a bar on seeking asylum for any individuals (including children) who enter the United States at the "southern land border" after transiting through another country after leaving their home and who fail to establish that they applied for and were denied a grant of asylum in a third country en route to the US. This severely impacts asylum seekers from the Northern Triangle, many of whom are torture survivors.
Title 42 is short-hand for the public health power given to the Surgeon General, to quarantine foreign nationals who pose a public health risk. This authority has been punitively invoked, and arbitrarily, under the guise of COVID-19, radically expanded to close the border to asylum seekers. According to US Customs and Border Protection, there have been almost 200,000 people expelled from the United States from March to September 2020 under Title 42. These expulsions were all without the customary asylum screenings that ensure the United States isn't violating domestic and international law. This order operates outside of the normal immigration process, eliminating refugee protection obligations, and has no public health or legal merit. Use of this authority to exclude unaccompanied minors from seeking asylum was struck down by a US District Court judge in mid-November.
Another policy that has directly impacted health care access to immigrants is expansion of the existing public charge rule, finalized in February 2020. Public charge is a US government designation for someone who is considered or is likely to become primarily dependent on government-funded benefits. Immigrants considered a "public charge" may be prevented from adjusting their legal status to lawful permanent resident or US citizen, and even denied admission into the US. Historically, non-cash benefits were excluded from the original determination; however, the new rule includes programs such as Medicaid, Supplemental Nutritional Assistance Program (SNAP), and public housing. Immigrant patients have reported avoiding necessary medical services or other critical social services for fear that it may prevent their ability to adjust their status.
La Charite and colleagues report that in their survey of healthcare professionals only about 25%, considered their workplace prepared to respond to an enforcement action.[8] Most respondents (70%) recommended staff training. We support staff training, but in this area, which as these examples illustrate, is extremely complex and rapidly changing, we have adopted a different approach in our Medical Center and recommend that other institutions consider it as well: the formation of an Immigrant Task Force which can act as a catalyst both to provide relevant

information to patients and providers, and develop institutional policies in areas directly affecting immigrants.

The BMC Immigrant Task Force

Immigration law and policies may have profound health consequences for our patients or their family members still living under the threat of persecution or harm, although we expect the Biden Administration to change most of them. It is not realistic to expect health professionals to keep up with the rapid pace of evolving immigration law, nor to understand how the nuanced laws and policies impact their individual patients. Health professionals are not trained as immigration attorneys or licensed to give legal advice, nor should they be. Immigration, however, is a social determinant of health and should be incorporated into health screeners, with clinicians being able to identify the need for referral to immigration services.

Boston Medical Center (BMC) is the largest safety net hospital in New England and serves a large immigrant population, which includes refugees and asylum seekers. BMC has numerous clinical programs which address the specific needs of immigrant and refugee patients across multiple departments, including Primary Care, Psychiatry, Ob-Gyn, and Pediatrics. We have recently created an Immigrant and Refugee Health Center to serve as an umbrella program to streamline BMC's existing hospital wide immigrant health services. The BMC Immigrant Task Force has approximately 100 volunteer members, from across many departments in the hospital and holds quarterly meetings. The Task Force was created in direct response to the harmful and cruel immigration policies implemented by the Trump administration.immediately after the initial "travel ban" (also known as the "Muslim ban") executive orders were issued in January 2017. We recognized that these policies could increase psychosocial stress and deter patients from accessing health care because of fears related to immigration, including fears of deportation and detention. In addition, patients could avoid participating in important state and federal programs such as Medicaid, CHIP, WIC, and SNAP, which has been demonstrated nationally. The mission of the Task Force is to identify and respond to challenges in the rapidly changing immigration policy landscape that impacted health delivery and well-being of our immigrant patient population. Specific objectives are contained in Box 1.**Box 1**

The Objectives of the Immigrant Task Force

- 1. Ensure that there are health care professionals who have the skills and knowledge to address the special needs of immigrant populations in each major unit/ department of the hospital.
- 2. Develop a hospital wide expertise addressing the psychosocial, legal, and ethical issues faced by employees as they care for immigrant patients. The Task Force will monitor for, and educate on, changing legal rules and regulations, so that BMC staff are providing health care with accordance with legal and regulatory mandates.
- 3. Develop a BMC wide intranet educational website which all employees can use as a source of important information about immigrant health, including lists of resources outside the hospital such as legal, financial, and psychological for referral services as appropriate.
- 4. Develop and implement educational programs for all employees on immigrant health.
- 5. Collaborate with other New England hospitals so to share best practices expertise and programming.
- 6. Collaborate with special community-based agencies which specialize in immigrant health such as MIRA (Massachusetts Immigrant and Refugee Advocacy Coalition), those in the religious community and legal advocacy and support.
- 7. Evaluate the impact of this Task Force with Quality Assurance methodology, using stories, clinical experiences and other data while maintaining patient confidentiality.
- 8. Develop subcommittees to address particular issues.

•9. Keep hospital administration up to date with progress of the Task Force.

•10. Develop patient materials and outreach plans to assure that immigrant patients are appraised of their ability to access services at Boston Medical Center.

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The Task Force had the strong backing of the hospital's CEO and recruited members from a wide variety of departments and services [(including Medical Departments (physicians, nurses, social workers, case managers, patient navigators, mental health specialists), Patient Financial Services, Patient Advocacy, Public Safety, Legal, Government Affairs, and Administration]. The Task Force serves as the central source for patient information, staff education, and data collection on the effects of immigration policy on the health and wellness of our immigrant population. The Task Force has developed educational materials, networked with community agencies and hospitals, and worked to ensure that the psychosocial needs of patients and staff were met. Our program has hosted "Know Your Rights" presentations for both patients and employees to provide tools for navigating specific situations, enhance empowerment, and relieve anxiety. For example, these trainings addressed questions such as "what do I do if an ICE officer approached me in a public area, or knocked on my door?"

The Task Force has developed guidelines and provided training for professionals on how to document relevant facts in the medical record without revealing a patient's immigration status, (in the remote possibility of broad subpoenas). We have worked with Public Safety to develop a protocol for employees on how to respond to ICE presence on hospital property or to a request for information about patients. Our pediatric colleagues have created and disseminated a comprehensive tool for families facing separation via deportation or detention. We created welcoming signage for the institution, reassuring patients that we will provide care no matter the immigration status. We informed and guided change of the patient identification policy so that a government issued photo ID is not required to receive care. The Task Force worked with Human Resources to create a benefit for immigrant employees to have the I-693 (green card medical exam) completed through the hospital by our civil surgeons, and an Immigration Resource Guide for BMC Employees was published.[8] Most recently, the Task Force recruited staff members to provide targeted messaging on the COVID-19 vaccine to immigrant communities.

Our General Internal Medicine clinic has embedded a legal navigator into clinical services. This was accomplished by hosting an AmeriCorps member whose role was to help patients navigate the complex immigration system through triage and referrals to community immigration legal programs, and by advocating for them during their interactions with the immigration legal process. Examples of types of assistance or information provided includes: asylum applications, public charge determinations, concerns about deportation and detention, family reunification, medical deferred action, medical reports for adjusting status (green card examinations), and disability waivers, among others. The navigator provides services to approximately 300 patients each year.[10]

Health care professionals caring for immigrant patients should recognize that immigration status is a critical social determinant of health. However, understanding the details of how evolving immigration policy impacts individual patients is beyond the scope of most health care professionals' expertise. The critical point is not that they understand how immigration law works, but that they are able to readily access someone at the health care facility who does and who can help them and their patient navigate the system. We recommend that hospitals and health care facilities create an infrastructure and services that will meet patients' immigration needs, such as imbedded legal services, and immigration resources for easy access by both patients and staff.

The end of the Trump administration and its antiimmigrant policies will not end the need to provide both accurate

legal information and health care to immigrants. It will be years, if ever, until all hurtful anti-immigrant and anti-healthcare programs are ended, and immigrants will continue to be fearful of ICE and deportation. During what we may call the Biden transition, a hospital entity like the BMC Immigrant Task Force will continue to be needed to support both immigrants and health care professionals.

Note

The authors have no conflicts of interest to declare.

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DETAIL

Subjek:	Immigration policy; Health care industry; Immigrants; Health services; Noncitizens; Political asylum; Teaching; COVID-19
Lokasi:	Mexico; United States--US
Orang:	Homan, Thomas
Perusahaan / organisasi:	Nama: Boston Medical Center; NAICS: 621111, 622110; Nama: US Immigration &Customs Enforcement; NAICS: 921130
Pengidentifikasi/kata kunci:	Immigrant Health; Asylum; Immigration law; Health care reform; Health policy; Immigration; Health professional; Immigration Law; Trump Immigration Policies
Judul:	The Boston Medical Center Immigrant Task Force: An Alternative to Teaching Immigration Law to Health Care Providers
Pengarang:	Crosby, Sondra S; Sonis, Lily; Annas, George J

Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	59-63
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles: Commentary
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Commentary
DOI:	https://doi.org/10.1017/jme.2021.10
ID dokumen ProQuest:	2730847325
URL Dokumen:	https://www.proquest.com/scholarly-journals/boston-medical-center-immigrant-task-force/docview/2730847325/se-2?accountid=211160
Hak cipta:	
Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

Employer Liability for “Take-Home” COVID-19

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ABSTRAK (ENGLISH)

Workplace exposure to SARS-CoV-2 has sickened workers and, subsequently, their family members. Family members might be able to recover from the employer in a negligence action using “take-home” liability theory.

TEKS LENGKAP

The coronavirus pandemic has exacted a devastating toll from Americans in death, illness, economic hardship, and intangible damage to our social fabric and quality of life. As with other aspects of contemporary life, however, suffering caused by the pandemic has not been distributed equally across society. People with preexisting health conditions, older people, members of racial and ethnic minorities, and those with hazardous jobs have borne a disproportionate share of the burden.

One broad class of employees, “essential workers,” includes those who work in emergency services, health care, meat and poultry processing, agriculture and food service, utilities, energy, and transportation. These employees are often low-paid, unable to work from home, inadequately protected against workplace hazards, and among the most devastated by the pandemic. For example, as of January 2021, more than 45,000 workers in meatpacking plants had tested positive for COVID-19, and at least 239 had died.[1] As of February 2021, 405,302 hospital and nursing home staff had been infected at work, with 1420 deaths.[2]

The highly transmissible nature of SARS-CoV-2, including the infectiousness of asymptomatic[3] and presymptomatic[4] individuals, means that family members of infected workers are also at risk. According to one estimate, between 56.7 and 74.3 million adults at an increased health risk for COVID-19 (based on CDC criteria) lived with or were themselves essential workers.[5] According to another estimate, between 7% and 9% of the first 200,000 deaths from COVID-19 resulted when an individual became infected on the job and then transmitted the virus to a family member.[6]

Workers who become infected in the course of their work are eligible for workers’ compensation benefits if they can establish the employment-based source of their illness and other key elements of a workers’ compensation claim. However, they are generally barred from recovery in personal injury cases because workers’ compensation laws in every state are the “exclusive remedy” of employees who become ill or injured on the job.[7] Family members later infected by workers are not eligible for workers’ compensation because they were not harmed in the course of employment, but they may not be barred from proceeding with a common law personal injury case. We are aware of only one pending case involving COVID-19 filed by a family member of a worker exposed on the job,[8] and there is no established legal precedent on whether recovery is possible in such a case. Nevertheless, infected family members of workers desperately needing income replacement for living and medical expenses during the pandemic are likely to seek compensation from the employers of their family members.[9]

Take-Home Liability

Lawsuits by family members who become ill after their family member is exposed on the job are known as “take-home” liability cases. The paradigmatic application of this theory is liability for take-home exposure to asbestos.[10] Employees who worked with asbestos in manufacturing, construction, shipbuilding, automotive, and other industries have worn their asbestos-contaminated clothing home where their spouses, children, and other family members were exposed during laundering of the clothing or in other ways, such as by wearing the contaminated clothing while playing with their children.[11] The take-home theory was developed to provide a remedy for the deaths and significant

illnesses caused by this secondary exposure to workplace asbestos.

Among the most important reasons for recognizing take-home liability for asbestos exposure are the following: (1) asbestos has been widely used in numerous workplaces, and it has resulted in hundreds of thousands of deaths;[12] (2) asbestosis and mesothe-lioma are serious respiratory diseases caused solely by asbestos exposure,[13] thereby making it easier to prove causation; (3) an OSHA standard in effect since 1972 explicitly recognizes the risk of take-home exposure and requires employers with certain asbestos exposures to provide protective clothing and change rooms to prevent employees from wearing home and laundering their asbestos-contaminated clothing;[14] and (4) asbestos is a product, which permits family members or their estates to sue using strict products liability law rather than having to prove the negligence of the employer.[15]

Personal injury litigation based on asbestos exposure has been ongoing for decades and take-home cases use a novel legal theory to provide a remedy for individuals otherwise unable to obtain compensation for their illness. Unsurprisingly, the states differ on whether to permit these actions. As of 2021, 16 states hold that a duty exists,[16] or potentially exists,[17] running from the employer to their employees' family members, thereby permitting a legal action based on negligence. In contrast, 13 states hold that no duty exists because the harm is not foreseeable[18] or there is no significant relationship between the exposed family member and the employer.[19] Two states have enacted legislation barring take-home actions,[20] and the remaining 19 states have not yet addressed the issue.[21]

Legal Theories for COVID-19 Liability

Unlike exposure to asbestos, products liability is not a viable legal theory for take-home exposure to SARS-CoV-2 because the coronavirus is not a "product." Nevertheless, personal injury actions based on strict liability or, more likely, negligence are possible for harms caused by take-home exposure.

Unlike exposure to asbestos, products liability is not a viable legal theory for take-home exposure to SARS-CoV-2 because the coronavirus is not a "product." Nevertheless, personal injury actions based on strict liability or, more likely, negligence are possible for harms caused by take-home exposure.

Strict Liability

Strict liability is imposed without regard to a defendant's negligence or intent to cause harm when the actions of the defendant cause physical harm to the plaintiff. Strict liability only applies to "abnormally dangerous activities" involving a foreseeable and highly significant risk of physical harm even when reasonable care is exercised, and the activity is not one of common usage.[22] Strict liability has been imposed for blasting, wild or abnormally dangerous animals, storage of hazardous waste, radioactive emissions, and similar dangerous activities.

Courts are unlikely to apply strict liability to COVID-19, even though it is a deadly and highly contagious disease. In the leading case of *Doe v. Johnson*,[23] the plaintiff alleged that the defendant wrongfully transmitted HIV to her through consensual sexual intercourse. The district court judge, applying Michigan law, held that there was no precedent for extending strict liability to this case. The court's opinion emphasized that Michigan cases limited strict liability to such hazards as blasting and storing inflammable liquids, the risks of a sexually transmitted infection could be reduced by the exercise of reasonable care, and sexual activity is not an inherently dangerous activity.[24]

Negligence

Plaintiffs bringing lawsuits for negligence are required to prove that the defendant breached a duty to the plaintiff, which caused the plaintiff to suffer damages. Each of these four traditional elements: duty, breach, causation, and damages, raises distinct issues in the context of take-home exposure cases against employers for COVID-19.

Duty. The essence of a personal injury lawsuit based on negligence is that the defendant breached a duty to the plaintiff by failing to exercise reasonable care under all the cir-cumstances.[25] In take-home exposure cases, the defendant-employer is alleged to have breached a duty to their employee's family member -- an individual without an employment relationship with the employer, in a setting beyond the workplace, and involving a person whose identity or even existence might not have been known to the defendant. Thus, the initial question is whether an employee's family member is a foreseeable plaintiff to whom the employer owed a legal duty.

In the leading case of *Kesner v. Superior Court*,[26] Johnny Blaine Kesner, Jr.'s uncle, George Kesner, an employee of Pneumo Abex, LLC, was exposed to high levels of asbestos in the course of his work. Johnny Kes-ner stayed at his

uncle's home about three days per week for six years and alleged that he was exposed to asbestos through dust on his uncle's clothing, and that this exposure caused him to contract peritoneal meso-thelioma, from which he died.[27] The Supreme Court of California held that employers have a duty to prevent the secondary exposure to asbestos of their employees' family members, and take-home exposure via the employees' bodies and clothing was foreseeable. In the context of COVID-19, the plaintiff would have to prove that inadequate protections in the workplace and the transmissibility of SARS-CoV-2 made it foreseeable that employees exposed on the job would infect their family members. Because SARS-CoV-2 could be spread to numerous other potential plaintiffs besides family members, defendants would likely raise the possibility of unlimited liability as a reason to reject any take-home liability. The court in *Kesner* specifically addressed this issue by holding that an employer's duty only extends to the members of a worker's household. "By drawing the line at members of a household, we limit potential plaintiffs to an identifiable category of persons who, as a class, are most likely to have suffered a legitimate, compensable harm."[28]

Breach. The next step is to determine whether the defendant breached the applicable standard of care. Testimonial and documentary evidence of OSHA violations established through enforcement or adjudication are inadmissible in a personal injury case as evidence of the employer's negligence,[29] but applicable OSHA standards are generally admissible as evidence of the standard of care.[30] OSHA standards may be admissible even where the plaintiff was not an employee, such as the driver of an automobile, a visitor touring the workplace, or a safety inspector.[31] Thus, OSHA standards, including those requiring employers to supply necessary personal protective equipment, would seem to be admissible in take-home liability cases to prove the duty owed to the employee and the employee's foreseeable family members. There are no cases on whether OSHA guidance documents are admissible, and this issue is important because during the Trump Administration there were no federal OSHA standards promulgated for COVID-19, only non-mandatory guidance documents.[32]

The admissibility of an OSHA standard in personal injury litigation depends on the state common law used in negligence cases. In 33 states, an employer's failure to comply with an applicable OSHA standard constitutes "some evidence" of negligence.[33] The evidentiary effect of "some evidence" of negligence within these jurisdictions varies. The evidence may give rise to an inference of negligence, establish prima facie negligence, or create a rebuttable presumption of negligence.[34] In 14 states and the District of Columbia, noncompliance with an applicable OSHA standard establishes negligence per se.[35] The effect of negligence per se is to establish a breach of the relevant duty, but a plaintiff is still required to prove causation and damages, and the defendant may assert any defenses.[36] OSHA standards are generally inadmissible in three states,[37] but they might be admissible under certain circumstances.[38]

Causation. For liability to be imposed, the negligent conduct of the defendant must be a factual cause of the harm sustained by the plaintiff.[39] With take-home exposure cases there are two parts to causation. First, the negligence of the employer must be a cause of the employee's infection. Because SARS-CoV-2 is so prevalent in the community it might be asserted that the employee could have been infected in other ways, such as in public places, on public transportation, or at public or private gatherings. Second, the family member's infection must have been caused by exposure to the infected employee. Here again, the family member also could have been infected by exposure to other individuals.

Causation is more problematic for take-home COVID-19 than asbestos disease because coronavirus exposures are more common, and in more settings, than asbestos exposures. Nevertheless, the law does not require the plaintiff to prove the exact sequence of the parties' exposures.[40] "And whether the defendant's negligence consists of the violation of some statutory safety regulation, or the breach of a plain common law duty of care, the court can scarcely overlook the fact that the injury which has in fact occurred is precisely the sort of thing that proper care on the part of the defendant would be intended to prevent, and accordingly allow a certain liberality to the jury in drawing its conclusion."[41] Public policy concerns, including "moral blame, preventing future harm, burden, and availability of insurance"[42] also might be considered in deciding whether causation will be satisfied.

Damages. The final element of a plaintiff's take-home exposure case is the least difficult conceptually. The plaintiff must prove that the defendant's negligence resulted in a legally recognized harm. In take-home asbestos cases

courts have applied traditional principles of tort damages, although many of the appellate cases have been decided on the issue of whether the jurisdiction recognizes the actionability of such claims rather than the permissible damages.[43] Take-home COVID-19 cases almost certainly would be brought by employees' family members who became seriously ill or their estates in the event of death. Successful plaintiffs should be able to recover a range of compensatory damages, including lost income, medical expenses, and pain and suffering. Punitive damages also might be recoverable under state common law if the employer's conduct was willful, wanton, or evidenced a reckless disregard for the rights of the employees or their family members.[44]

Policy Issues

In considering the viability of take-home exposure cases it is essential to consider the broader issues of OSHA enforcement efforts to prevent COVID-19, workers' compensation cases brought by infected workers, and legislation at the state or federal level to immunize employers from liability for COVID-19. On all three issues, workers —many of whom have been deemed essential —have been left to bear an outsized burden of illness and financial ruin caused by the pandemic.

OSHA Protections

By any measure, the federal Occupational Safety and Health Administration (OSHA) failed in its efforts to protect workers during the first year of the pandemic.[45] Six months into the pandemic, despite receiving nearly 10,000 complaints from employees,[46] OSHA had cited only 85 employers with a total of $1.2 million in penalties.[47] For example, OSHA assessed civil penalties of merely $15,615 to meatpackers JBS Foods, Inc., of Greeley, Colorado, and $13,494 to Smithfield Packaged Meats of Sioux Falls, South Dakota, after a total of 1,000 workers at those facilities contracted COVID-19, resulting in 94 hospitalizations and 10 deaths.[48] It is unlikely that these paltry penalties assessed by OSHA, which are being contested by the companies, will have a deterrent effect because both meatpackers are multi-billion dollar enterprises.[49]

Although the prompt issuance of an emergency OSHA standard prescribing employer duties to prevent exposure to SARS-CoV-2 likely would have reduced viral transmission,[50] during the Trump Administration, OSHA declined to promulgate such a standard.[51] The guidance documents for employers issued by OSHA[52] and the CDC[53] during this time were mere suggestions or recommendations. Among other things, employers were advised to "encourage" sick employees to stay home, "consider" conducting daily health checks, and "encourage" workers to wear a cloth face covering. There was no requirement that employers adopt these policies nor require their employees to follow them. Only OSHA has the regulatory authority to mandate compliance, and despite thousands of deaths from COVID-19 attributable to workplace exposures, OSHA failed to undertake emergency rulemaking or vigorous enforcement.[54]

Workers' Compensation

Employees who become ill from occupational exposures are usually entitled to workers' compensation pursuant to state law. If the illness is an "ordinary disease of life," however, then the employee must prove that the disease was caused by workplace exposures. In some jurisdictions, the courts are reluctant to award compensation for occupational illnesses, even though the general rule is that if employees develop diseases from a relatively sudden and unexpected exposure to germs, it is compensa-ble.[55] Some employers have contested the workers' compensation claims for COVID-19, thereby adding financial insult to serious illness for vulnerable workers and their families.[56]

To ease the burden of proof for employees sickened on the job by COVID-19, legislative enactments in eight states and executive orders and regulatory policies in nine others make it easier for workers to obtain compensation.[57] Although the state laws vary, they most commonly establish a rebuttable presumption that COVID-19 by a health care worker or first responder is the result of occupational exposure.

Immunity

Contrary to the laws making it easier for employees to obtain workers' compensation benefits for COVID-19, at least 13 states have enacted laws immunizing most or all businesses from personal injury liability for COVID-19 claims.[58] Similar proposals have been introduced in Congress, principally by Republicans in the United States Senate.[59] The reasoning behind the legislation is that many businesses have been so weakened financially by the pandemic that

they could not afford to remain open or reopen if they were subject to liability for COVID-19 or had to purchase expensive liability insurance.

The liability issue promises to be debated vigorously in Congress and state legislatures for the foreseeable future. One possibility for balancing the interests of employees and employers is for liability protection to be available for only small employers (defined by business volume or number of employees). Claims brought against small employers would be paid by a government financed insurance system, thereby permitting timely compensation for the victims of COVID-19 without threatening the solvency of small employers.[60]

Conclusion

Inadequately protected and underpaid essential workers and their families have suffered disproportionately in the pandemic. Their struggle to survive medically and financially often was overlooked by the public in the political wrangling over wearing masks and other public health measures versus asserted economic and personal liberty. CDC guidelines indicate that contact tracing, testing, and quarantine pending test results should be implemented for individuals with a total of 15 minutes exposure within six feet of all laboratory-confirmed or probable SARS-CoV-2-infected individuals.[61] Based on these guidelines, it is foreseeable that many family members of workers exposed to SARS-CoV-2 have been placed at a high risk of infection.

Justice demands fair compensation for the health effects and financial consequences sustained by the family members of exposed workers. Equally important is the deterrent effect of potential tort liability on employers whose obligations to their workers were in the recent past —and possibly in the future —minimized by lax OSHA enforcement and limited workers' compensation awards. If concerns about the possibility of damage awards for their workers' ill or deceased family members motivates some recalcitrant employers to improve working conditions, then take-home liability lawsuits will be responsible for saving lives.

Acknowledgement

John Tyler Stocking, J.D. 2020, Louis D. Brandeis School of Law, University of Louisville, provided excellent research assistance.

Note

The authors have no conflicts to disclose.

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26. 384 P.3d 283 (Cal. 2016).
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DETAIL

Subjek:	COVID-19; Employees; Employment; Employers' liability; Workplaces; Employers; Families &family life; Coronaviruses; Negligence; State court decisions
Ketentuan indeks bisnis:	Subjek: Employees Employment Employers
Lokasi:	United States--US; Michigan
Perusahaan / organisasi:	Nama: Occupational Safety &Health Administration--OSHA; NAICS: 926150
Pengidentifikasi/kata kunci:	COVID-19; Coronavirus; Employment; COVID-19; Vicarious liability; Severe acute respiratory syndrome coronavirus 2; Employer Liability; Negligence; OSHA; Workers' Compensation
Judul:	Employer Liability for "Take-Home" COVID-19
Pengarang:	Rothstein, Mark A; Irzyk, Julia
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Oppor tunities, and Challenges
Halaman:	126-131
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Columns: Currents in Contemporary Bioethics
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X

Operationalizing the Ethical Review of Global Health Policy and Systems Research: A Proposed Checklist

Rattani, Abbas; Hyder, Adnan A

ABSTRAK (ENGLISH)

There has been growing consensus to develop relevant guidance to improve the ethical review of global health policy and systems research (HPSR) and address the current absence of formal ethics guidance.

TEKS LENGKAP

Health policy and systems research (HPSR) is the investigation, evaluation, and/or implementation of healthcare strategies or issues at the institutional or systems-level. HPSR includes, but not limited to, questions of system strengthening, capacity building, policy or strategy implementation and evaluation — including operations, organizational structure, finance, governance, management, and improvement of health systems.[1] HPSR is characteristically different from clinical research in terms of methodology, analysis, approach, definition, and ethical issues.[2] Where clinical research is concerned with studying the efficacy or effectiveness of an intervention, HPSR may be concerned with studying how and why the intervention is delivered and accessed within a health system or at a regional level. HPSR often involves the study of collective effects on a group or sub-group of people — making consent challenging when compared to clinical research which prioritizes the individual. Thus, the uniqueness of HPSR stems from the type of question it aims to address as opposed to a particular methodology.

As a result, research ethics committees (RECs) (e.g., institutional review boards) and review mechanisms may

therefore be inappropriate for evaluating HPSR. RECs may overlook important ethical issues or create delays in review processes altogether. These barriers to appropriate and timely review are often related to a lack of experience in appraising HPSR, misclassifica-tion of HPSR as clinical research, or the application of imprecise or variable criteria.[3]

Previous studies have highlighted the paucity of HPSR guidance with the apt concern that RECs globally are reviewing this type of research without appropriate considerations.[4] An international HPSR ethics working group of nearly two dozen experts noted that RECs may not be applying appropriate ethical frameworks in the evaluation of HPSR. A scoping survey of several dozen RECs at major public health institutions worldwide also corroborated that RECs are not equipped to appropriately review HPSR.[5] As HPSR grows, especially in low- and middle-income countries (LMICs), addressing the unique ethical concerns of this type of research becomes more of an immediate priority for researchers and RECs alike.[6]

Recently, there has been growing consensus to address the current absence of formal ethics guidelines by developing relevant guidance to improve the ethical review of HPSR.[7] However, guideline development is an iterative and deliberative process that will require involvement from a multitude of stakeholders internationally — especially from LMICs.[8] In the meantime, it is arguably worthwhile to collate the current guidance and lessons in the form of an initial protocol that takes into account usability and practicality for immediate implementation by RECs while also serving as a starting point from which the iterative process can germinate.

Our group has been engaged in concerted efforts to operationalize the ethical review of HPSR through (1) a series of international workshops and surveys eliciting expert opinion, (2) scoping and systematic reviews, (3) numerous publications, and more recently as (4) contributors to a benchmark report published by the World Health Organization (**Box 1**). We aim to summarize the knowledge on HPSR ethics to date (with a focus on the most salient ethical issues of HPSR in LMICs) in the form of a practical checklist for use by researchers and RECs. In addition, we provide a summary of each component of this inaugural checklist and review it alongside a case study to better elucidate its application.

We aim to summarize the knowledge on HPSR ethics to date (with a focus on the most salient ethical issues of HPSR in LMICs) in the form of a practical checklist for use by researchers and RECs. In addition, we provide a summary of each component of this inaugural checklist and review it alongside a case study to better elucidate its application.

A Proposed Checklist

We employed a mixed-methodological approach by incorporating a scoping review of the literature, expert opinion in the form of an international REC survey, content analysis of the literature, WHO HPSR ethics report, and relevant workshops (**Box 1**). The checklist aims to address the challenges faced by review committees by incorporating the key features expected of an HPSR guidance tool as outlined by Pratt et al.[9] and Luyckx et al.[10] The proposed checklist is divided into ten categories (**Table 1**) and designed to facilitate discussions between investigators and RECs.[11] Therefore, we propose the checklist be completed by both the REC and investigator independently. Areas of disagreement between the REC and investigator should serve as an opportunity for clarification, revision, and establishment of strong ethical practice. The fixed items (Yes/No/Not Applicable (NA)) should be routinely audited and additional information should be requested at the discretion of reviewers. Each category and respective item is discussed below in brief detail.

Table 1 Proposed Checklist for Ethical Review of Health Policy and Systems Research

HPSR Features and Ethical Principles

In the design of HPSR studies, who will receive the intervention and who will be observed (Category I) should be established early as these units are often different in HPSR and can impact the validity of a study.[12] Next, who will be studied (individuals versus groups) (Category II) and whether they reflect a fair sample of the population — including vulnerable communities (Category III) — are additionally important HPSR features for consideration. The subsequent two features of HPSR — nature of the intervention and features of comparison groups — are combined into one category (Category IV) and should be considered alongside Category I to assess study validity. While

community engagement is listed as Category V, it is an important aspect of HPSR and should also be established early in the study design process. Concerted community engagement efforts can help inform other checklist categories related to acceptability of benefits and risks, informed consent mechanisms, respect for persons/communities, responsiveness, and post-study features.[13] Where appropriate, community engagement can inform study validity concerns as well.**Box 1**

Sources for Proposed Checklist

- 1. Seminal scoping and systematic reviews of the literature aimed at capturing relevant references to ethical issues in HPSR.67
- a. Including Pratt et al.'s expansive review, which queried both indexed medical/scientific and gray literature databases until 2015.68
- 2. Our own search via PubMed/MEDLINE for HPSR literature published between January 1, 2015 and April 1, 2019. Articles were included if HPSR ethical issues were discussed in general or specific to methodology or study design, REC evaluation, challenges encountered by RECs or researchers, or application of legal or ethical frameworks.
- 3. Discussions at a two-day international workshop convened in Baltimore, Maryland (USA) in June 2013 to specifically discuss and analyze ethical issues pertinent to health systems research, especially in LMICs.69
- a. This was published in the December 2016 special issue of the journal *Developing World Bioethics*.70
- 4. An international survey sent to public health institutions and associated institutional ethics and scientific regulatory review boards.71
- 5. The World Health Organization's "Ethical Considerations for Health Policy and Systems Research" report published in 2019.72

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Benefits and risks (Categories VI and VII) can take on special forms in HPSR which are articulated in more detail under their respective sub-sections. The social value or responsiveness of a study is an important part of the global justice commitment of HPSR (Category VIII).[14] Appropriate responsiveness follows from transformative community engagement that aims to understand and respond to the needs of the community and provide meaningful social value.[15] Finally, what is owed to the host community both immediately and over time are important post-study considerations that should be outlined and discussed before the start of the study and after its completion. These items are respectively captured in Categories IX and X.[16]

We contextualize each checklist category below in terms of the larger ethical principles and HPSR features. Because of the nuances and complexity, some categories are informed by more than one principle which is then expounded upon in detail. In brief, each category can be traced back to the larger ethical principles of autonomy, beneficence, non-maleficence, and justice.[17] The ethical principle of autonomy, which is often understood as respect for the dignity and decision-making capacity of individual persons, is expanded to include a respect for groups, communities, and populations. This respect informs the checklist items on defining types of subjects, informed consent, fair subject selection, community engagement, and dissemination. The principle of beneficence in turn informs the checklist items pertaining to benefits assessment, responsiveness, dissemination, and research translation and sustainability. The concept of reducing harm or non-maleficence serves as the basis for the checklist

items pertaining to informed consent, fair subject selection, standard of care, and risk assessment. Finally, justice as fairness is understood in terms of global justice — which demands that global health research promote health equity and improve the well-being of the worst-off.[18] All HPSR should aim to decolonize global health and alleviate existing health inequities. Global justice informs the basis of the checklist categories on defining types of subjects, fair subject selection, standard of care, community engagement, responsiveness, dissemination, research translation and sustainability.

Checklist Categories

I. Types of Subjects

In contrast to clinical research where the target of an intervention is often an individual person, HPSR oftentimes involve groups or clusters of individuals. The unit of intervention may also be different from the unit(s) of observation or data collection — a departure from clinical research where the unit of intervention and observation are identical.[19] As such, defining who is the subject has proven to be challenging.[20] For example, in attempting to study student outcomes following a workshop for instructors, the unit of intervention may be teachers while the unit of data collection is student performance. Defining the appropriate unit is not only an important consideration for study validity and analysis, but it determines the consent process and associated downstream ethical requirements for each unit.

Apart from the consent issues the differences in units pose (e.g. who should be consented?), further consideration is required in differentiating direct and indirect research subjects. Direct subjects are defined as those either receiving the intervention or those from whom data is to be collected. These units are directly impacted by the research and follow from the objective of the study. The Ottawa Statement offers guidance in helping researchers identify who constitutes as an individual human subject in research:

A research participant can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that is, an individual (1) who is the intended recipient of an experimental (or control) intervention; or (2) who is the direct target of an experimental (or control) manipulation of his/her environment; or (3) with whom an investigator interacts for the purpose of collecting data about that individual; or (4) about whom an investigator obtains identifiable private information for the purpose of collecting data about that individual. Unless one or more of these criteria is met, an individual is not a research participant.[21]

If the final point of delivery is a single subject, investigators are required to follow human subjects protections guidelines as outlined by the Ottawa Statement.

Indirect subjects, on the other hand, are those affected as consequence of the research. These are subjects who may exist on the periphery of the study. They can include a vast diversity of entities and as a result are more challenging to identify. It is important for researchers to consider the ways in which their study may extend beyond direct subjects and may have implications or render consequences beyond those who are immediately identifiable.

II. Informed Consent

Issues related to informed consent and respect for persons are quintessential to all ethical considerations. In HPSR study designs, consenting individuals may not be feasible. For example, in a program designed to study a new trauma triaging system involving patients, first responders, hospital staff, etc. — consent requirements are less clear. As such, individual representatives of a community may serve as a proxy for consent. The principles of respecting the dignity and autonomy of human beings must still be upheld even if it is extended to a respect for groups. To this end, our checklist asks researchers to further define the unit of intervention being tested — individual versus group/population. By “tested,” we specifically mean both the units of intervention and data collection. It is possible for the unit of intervention to be individuals while the unit of data collection to be population-level or vice versa. In such

scenarios where the units differ in terms of individual and group, the researcher should aim to answer questions 2 and 3 in this section respectively.

The second series of questions take established clinical research ethics principles and extend their application to groups/populations. In studies where individual consent is to be waived, all the outlined conditions in Item 2a must be met. However, consent may be meaningless in situations where it is difficult to avoid exposure to a study arm. In these circumstances a waiver of consent may still necessitate that the research population be informed of research being conducted along with details about the protocol and waiver of consent justification must also be provided in relevant situations.[22] As we discuss below, respect for persons must extend to those most vulnerable and marginalized; study information must penetrate to these groups as well. Given literacy or education concerns, mechanisms to inform and opportunities to opt-out must be thoughtfully considered.

In consent situations where gatekeepers are to serve as a proxy for individual community members, one should also be aware of the nature of the gatekeeper in relationship to their authenticity, legitimacy, conflicts of interest, and their degree of connectedness or separation to the study population(s) (e.g., government official, community leader, head of household, hospital administrator). An awareness of power dynamics, dependency, undue influence, or coercion at various gatekeeping levels are necessary for cultivating protections to individual community members. The role of the gatekeeper is also important in community engagement efforts as briefly discussed in Category V.

Given the recent literature on solidarity and global justice in HPSR, it is incumbent on researchers to (1) be aware of sensitive or controversial interventions where great potential for harm is possible and (2) take extra measures to mitigate and minimize this poten-tial.[23] Researchers and review committees should have protocols in place for potential issues of misunderstanding or mistranslations in the consent process.

Assuming the criteria to waive consent is not met, individual consent is often required for anyone directly participating in research and may also be required for indirect participants who may be affected by the outcomes of the study. Acknowledging the potential for complexity in HPSR study designs, consent may need to be tailored for each component where relevant. Finally, as stressed above and in sections below, the voluntariness of the consent process needs to be ensured for vulnerable and marginalized populations given their increased risk for exclusion, exploitation, coercion, or undue influence.

Beyond the scope of this checklist are standard research ethics requirements which must be adhered to for what consent covers and for how long consent is applicable.

III. Fair Subject Selection

Implicit in the title of this category is ensuring fairness in who is recruited because this reflects a commitment to the global justice framework of HPSR.[24] HPSR in LMICs present special considerations when defining vulnerable, disadvantaged, and marginalized populations. Poverty and illiteracy often compound vulnerability, especially when it involves previously defined vulnerable communities (e.g., disabled, prisoners, children, etc.).[25] Through community engagement efforts (Category V), researchers can gain a better understanding of who are worst-off and how best to surmount challenges to inclusion and recruitment with guidance form community leaders.[26] In defining how these barriers to recruitment are to be addressed, special precautions to limit harm and risk should also be included.

IV. Standard of Care

Standard of care considerations are born out of a commitment to avoiding or reducing harm, especially in LMICs where great variability of care may exist within various levels of a health system. Standard of care concerns are primarily salient in interventional studies wherein populations may be subjected to receive care outside the status quo.

The nature of an intervention can be examined as two non-exclusive conditions: (1) deploying a novel intervention,

and (2) creating demand for existing services. Novel interventions pose challenges in constrained-resource settings where a greater responsibility is placed on researchers to justify the intervention's need in an already resource-constrained setting due to the possibility of further burdening the current health system. A novel intervention can also consist of increasing demand for existing services which in turn can exacerbate pre-existing fault lines within a health system. In developing new intervention methods, some have raised the issue of limited human resources and whether it is ethical to employ community health workers when this may further weaken existing healthcare systems.[27] Therefore, Item 1 of the checklist asks researchers to define comparators and corresponding interventions to identify what care looks like at various levels of data collection. Depending on the standard of care participants are subjected to, RECs may modify the extent of justification required from researchers to explain the rationale behind the care being received.

When considering new interventions and the conditions for equipoise, researchers should aim to contextualize their proposed study with a concerted effort to identify similar studies and their outcomes. By doing so, this will help elucidate whether clear uncertainty is apparent in achieving equipoise and whether exacerbations to existing health systems are justified.

Attention should be given to comparison groups affected by a restructuring of the local health system. Groups may be impacted differently based on varying levels of care at various health system levels or locations (e.g., urban versus rural). Thus, a referral mechanism that directs participants to appropriate levels of care must be articulated by researchers. If the intervention arm proves efficacious, what is owed to the control group by researchers versus local ministries of health must also be considered. In more complex study designs, it is possible that one group may be set to receive less than the local de facto standard of care. Clearly, these types of situations place a greater requirement for ethical deliberation to justify providing less then the standard while remaining committed to the larger goals of global justice to improve the health welfare of the worst-off.[28]

Equipoise, as defined here, is true uncertainty between the efficacy or benefit of competing interventions — justifying randomization of groups to either a control (current standard of care) and an experimental group. Defining equipoise can be difficult in situations where standards of care may differ between the national and local level or between two neighboring local communities. Establishing equipoise may be more evident in certain parts of a health system and ambiguous in others.[29] For example, if equipoise exists in terms of delivery method, but not in the quality of health services being offered — to what extent can the nature of the intervention and corresponding conditions of equipoise be evaluated?[30]

When considering new interventions and the conditions for equipoise, researchers should aim to contex-tualize their proposed study with a concerted effort to identify similar studies and their outcomes. By doing so, this will help elucidate whether clear uncertainty is apparent in achieving equipoise and whether exacerbations to existing health systems are justified.

V. Community Engagement

Community engagement in HPSR is based on an important commitment to relationship-building with host communities and nations that stems from a concerted effort to understand and respond to their health needs.[31] Through thoughtful community engagement efforts, researchers can begin the process of identifying the religious, cultural, socioeconomic, environmental, and political factors at various and phases of research that may be at stake during a systems-wide undertaking. Traditional figures of wisdom, traditional healers, community gatekeepers (see Category II), and authority figures should be respected and appropriately engaged with when HPSR is conducted. Sensitivity and deference should be shown to populations where HPSR may be relatively new or unfamiliar. Given the litany of cultural considerations, the onus of responsibility is placed on researchers to highlight that they have

fully considered and offered solutions to potential problems.[32]

Partnerships can occur at multiple-levels (national, district, local) depending on the nature and design of the study with varying health needs and concerns requiring response. Moreover, different phases of research may require involvement from different communities, gatekeepers, or stakeholders. Researchers must be aware of what may be lost by only engaging partners at a national versus local level or at the stage of study topic selection versus data collection or dissemination, for example.

Equality in the distribution of power to make decisions, object, or modify various aspects of the study must be established between researchers and communities. An absolute requirement of ethical HPSR is the empowering of local researchers and the facilitation of capacity building or strengthening. One suggestion is requiring a local researcher of the host nation to serve as the first or last author of any published work. This suggestion is meant to go beyond a gesture or formality, but to establish the role of the local research in a given project. Researchers should outline expectations and engagement processes toward the development of an agreeable set of principles that empowers host communities and ensures their participation (i.e., memoranda of understanding).

In addition to who is involved in community engagement and who is being represented by stakeholders — especially in efforts to include the voices of vulnerable and marginalized populations — it is important for researchers to outline processes by which dissent or alternative/competing community leaders are incor-porated.[33] Moreover, channels of communication must remain transparent and accessible even after the study has been concluded so host countries can raise issues and obtain relevant management assistance.[34]

VI. Benefits Assessment

Given the nature of HPSR, benefit assessments (like risks) should include immediate benefits to be seen during the study, as well as post-study benefits as part of global justice goals of what is owed to host communities and nations. This also stems from the larger transformative goal of HPSR—i.e., to improve the health situation of those worst-off.[35] Therefore, our checklist requires researchers to articulate the benefits to the individual (if applicable), group, and system both during and after the study period.[36] Our checklist also provides a list of study benefits that represent the key aspirations of HPSR to actively contribute and ensure the future healthcare and scientific success in LMICs.[37]

VII. Risk Assessment

Risk assessment stems from the principle of non maleficence with the primary objective being harm reduction. The protection of vulnerable and marginalized populations is especially prioritized in this category. Researchers need to be aware of how the risks of their study are compounded across domains (i.e., medical, social, economic, psychological, and political) and levels (i.e., individuals, groups, and systems). The compounding of risks is especially increased among vulnerable populations. Researchers are required to ensure their safety, wellbeing, and livelihood by interfacing with communities to identify all possible consequences or implications of their study. For example, one foreseeable unintended consequence that researchers should be aware of is the double role of providers or medical assistants as researchers, which may result in confusion among participants between research and health care. This is particularly salient in LMIC contexts where the research enterprise is not as established or widely familiar as an integrated component of a health system.

In addition to an awareness or understanding of risks, researchers must be prepared to provide clear, and preferably validated, strategies to mitigate and address those risks as they emerge.[38] Longitudinal monitoring mechanisms are equally important in capturing and terminating risks as they emerge in a study's cycle. Monitoring harms should be an important component of HPSR and RECs are best positioned to request regular reports on how risks are monitored, measured, and minimized.

Researchers should further aim to adhere to the principle of proportionality wherein the intended benefits and study

goals are commensurate with the anticipated risks.[39] The anticipated risks should be directly associated with the benefits that stand to be gained and not as a by-product or peripheral aspect of the study. The clinical research ethics concept of maximizing benefits and minimizing harms serves as a reminder to researchers that they must concretely assess risk and actively design practical strategies toward risk reduction.[40]

HPSR often involves the use of incentives to promote behaviors of interest. However, the use of incentives creates a unique risk for harm especially in LMICs where the socioeconomic effects of poverty may inappropriately influence participation.[41] Removing incentives may also lead to negative consequences if participant behaviors are reliant on these incentives.[42] Some have also argued whether incentives are autonomy-promoting versus autonomy-reducing, the former refers to incentives that expand a participant's range of opportunities and the latter refers to incentives that entice participants to undergo risks they would not otherwise.[43] Concern arises when participants are unclear or indifferent towards an incentivized activity. Thus, the nature of incentives should be considered in parallel with their appropriateness in the study design. Our checklist includes points for consideration around incentive use, and where applicable, researchers should provide clear examples and strategies to minimize these risks.

VIII. Responsiveness

A central principle of global justice in HPSR is for studies to improve the lives of the worst-off/most vulnerable, which is arguably achieved by understanding and responding to the needs of the host population.[44] Our checklist incorporates this principle by asking researchers at what levels of society does their study respond to: the national, regional, district, and/or local health system(s). It is important for researchers to recognize that local needs, for example, can differ or even contradict national needs. In cases where local or district needs are forgone in favor of national priorities, researchers should provide justification for why both needs could not be addressed, why higher level needs were pursued, and at what cost to the local community. If a study is designed to create demand for existing services, it is important for interventions to address barriers to accessing services and whether supply is adequate to meet the new demand.[45]

IX. Dissemination

In the same line of reasoning of defining what is owed to host nations, dissemination of findings to improve systems remains an important post-study consid-eration.[46] While dissemination is a post-study consideration, it should be anticipated and planned for in advance as part of the study protocol. Researchers must consider a dissemination strategy at various levels to ensure results are communicated to all LMIC stakeholders, gatekeepers, and policymakers in a timely manner. This is important in continuing the commitment to "knowledge translation and exchange" in regions where HPSR takes place.[47] Dissemination represents questions around data ownership, application of research findings, engagement with policymakers and stakeholders toward implementing these findings, and the responsiveness to the research needs of LMICs.[48]

X. Research Translation and Sustainability

Considerations for application, translation, and sustainability are important goals of HPSR and is a deliberative process that should begin at the study development stage. To ensure the long-term benefits to host nation health systems, timely engagement with partners, stakeholders, and policymakers is necessary.[49] Outlining such strategies early in the research process is important to ensuring post-study success and implementation of sustainability efforts. These four items are necessary in ensuring that HPSR is imple-mentable if proven efficacious. However, we recognize the variability in HPSR studies and have included an opportunity for researchers to explain why their post-study implementation plan may not meet these requirements.

Case Study

To better contextualize the application of the checklist, an HPSR case study on conditional cash transfers has been

adapted for this purpose (**Box 2** and **Appendix 1**).[50] The case study highlights the value of the checklist in identifying important ethical considerations. A sample checklist to this study (**Appendix 2**) is included as a reference aid for researchers and RECs. The briefness of the example checklist is for deliberative purposes and used herein to represent initiated answers that invites further detail upon interrogation by RECs (as represented either by “etc.” or ellipses).

Briefly, the case study represents a cash transfer in the form of vouchers that is awarded once certain conditions are met. The study exhibits one of the classic features of HPSR, i.e., the unit of intervention differing form the unit of observation (Category I). Namely, pregnant women, nursing mothers, and children in beneficiary households are the units receiving the intervention, but data is being collected from local health services. Those receiving the intervention clearly meet the conditions of the Ottawa Statement and thus are consent appropriate. However, the unit of data collection, i.e., the use of health and educational services, represents a larger entity of comparison. The ambiguity around “who” or “what” is the unit of data collection may also hint at the difficulties in identifying the indirect subjects that may be impacted by the study. These indirect subjects may include, but not limited to, those providing the health services or those standing to benefit from the allotment of resources to health teams.

While the units of intervention may be required to give consent, it is likely that the unit of data collection may qualify for a waiver. In which case, Category II will need to be completed for both the unit of intervention and the unit of data collection. As is noted in item 3d, each of the four study arms will require a detailed consent process and assurance that the units of intervention and data collection either meet waiver criteria or require consent. This study also focused on municipalities with the highest prevalence of malnutrition and substantial illiteracy, and thus it is assumed the researchers were cognizant about including vulnerable and marginalized populations (Category III). As such, RECs may request more information about the barriers to recruitment and an explanation for addressing these barriers in addition to what was provided as an example in the sample checklist. Additional questions about risk and harms related to the inclusion of pregnant women and children from multiple municipalities should be detailed in Category VII along with the ways in which minimal administrative autonomy, inferior infrastructure, and high illiteracy rates may compound risk.

This design is similar to a case-control study, but with several comparison groups and one control representing the local de facto standard of care (Category IV). It is assumed that the cash transfers are to incen-tivize the use of the Honduran de jure health services. RECs may require further justification if less than de jure services are to be rendered. Moreover, the study must have social value and be responsive to local priorities (as will be further explored in Category VIII). In responding to the needs of a community, researchers must highlight how their current study is based on precedent and/or expands upon previous work. In this example, RECs will need to further interrogate the uncertainty in this study to establish clear grounds for equipoise for this study to proceed. Given that this case study is an expansion of a previously conducted study, the details of the first study may need to be provided at the discretion of the REC.

In this case study we have assumed that the researchers employed rigorous community engagement efforts rooted in solidarity (Category V).[51] At a minimum, researchers must have engaged with Honduran health officials both at the municipality and national level to execute this study. The interests of the funders or international partners must not supersede that of the host community. RECs must also ensure that the women heads of household are engaged in the process — with gatekeepers possessing the power to interrogate each phase of research as appropriate. RECs may wish to request more information for any of the items to learn how researchers plan to execute each fixed item (Yes/No/NA). The absence of secondary questions soliciting explanation does not preclude RECs from further requesting additional explanation. This point is applicable across all items within the checklist.**Box 2**

Brief Summary of an HPSR Case Study on Conditional Transfers (see Appendix 1 for additional detail)

Background

- Direct payments have been used in some poor households in LMICs to promote demand for maternal and child health interventions or services.
- In one such case, the Honduran government created a program requiring pregnant women, nursing mothers, and children in beneficiary households to make regular visits to health centers in exchange for freely exchangeable monetary vouchers for cash or health care services.
- The program expanded to increase the household incentive by making its receipt contingent upon beneficiary mothers using more health services.
- Several entities from high-income countries decided to formally compare which form of resource transfer resulted in higher use of health services: maternal-child vouchers or allotting service resources to local health teams.

Methods &Study Design

- Municipalities with the highest prevalence of malnutrition (1/3 of whom were illiterate) were enrolled and randomly assigned to one of four groups: (I) household-level package alone, (2) service-level package alone, (3) both packages, and (4) standard services (control group).
- Beneficiaries of the household-level vouchers were informed that their payments would be suspended if they did not keep updated with routine antenatal and well-child preventive health care, or if children did not attend school regularly. Adherence to these requirements was not strongly enforced.
- The service-level package was aimed at strengthening peripheral health services.
- Evaluation surveys asking about use of health services (primary outcome) and convergence of interventions (secondary outcome) were undertaken at baseline and 2 years later in a representative sample of all households in each municipality.
- Reports were supplemented with data from children's health cards and government service utilization data.
- Analysis: mixed effects regression accounting for municipality-level randomization.

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Given the uniqueness of this case study, benefits to both individuals and groups should be accounted for as the example matrix highlights (Category VI). The aim of this study is to increase the use of important services, and thus it is reasonable that this study does not improve research capacity for individuals or strengthen the health system. The latter benefit is arguable, but in our review of this case, it appears that the study is primarily focused on health services and may not be positioned to improve the health system in its entirety. Regardless, RECs may decide to question researchers on their decision-making for determining what is owed to the population as part of the actualized benefits.

A few examples of possible risks across multiple domains and levels have been provided in the sample risk assessment matrix. Items 2 through 6 in Category VII are assumed to be true as they would be important requirements for ethical research. The unique feature of this study that RECs may be interested in auditing further is

the use of incentives in a low resource setting, where the potential for harms is increased if these incentives are not autonomy-promoting as aforementioned. The use of vouchers as incentive for utilizing services carries the potential for serious harms on an already vulnerable population. However, the potential for harm does not preclude the study from being conducted. Rather, it requires researchers to be honest in their risk assessment and forthright about minimizing these risks. Similarly, the risks outlined in the matrix may require further explanation by RECs if harm minimization strategies are unclear. We recommend engaging with communities and stakeholders at every level to solicit additional risks and discuss ways to respond to these anticipated risks in total.

It appears that the researchers aimed to respond to the need of improving health and educational services among this population (Category VIII). The important global justice principle behind responsiveness is to improve the health situation of the worst-off and the generation of new knowledge should be directly responsive to this goal. The objectives of this study arguably incorporate these important global justice principles by focusing on a specific vulnerable population. Continuing with the goals of HPSR, dissemination of knowledge at various levels are thus vital for the collective improvement of communities (Category IX). The types of dissemination strategies are assumed here and not articulated in the study itself, and will need to be articulated before the commencement of the study. Finally, the partnership between researcher and host country need to continue beyond the study to ensure appropriate translation of findings, policy guidance, and sustainability long after the study has concluded (Category X). The dissemination, translation, and sustainability efforts are expectations of ethical HPSR and are assumed in this study.

While this case study is an example of one type of HPSR, we have reviewed it in the context of the proposed checklist as a means of informing researchers and reviewers alike of the checklist's application. We have only provided sample answers as a means of initiating additional conversation on how the proposed checklist would have helped had this study been reviewed against HPSR ethics principles.

Discussion

In this paper we respond to calls for the creation of a checklist for the ethical review of health policy and systems research.[52] This work represents an initial proposal for a practical, "living" checklist aimed to reflect and incorporate important HPSR ethics scholarship to date and serve as a tool to facilitate conversation between researchers and RECs. Given the depth of HPSR scholarship and lack of standardization in the REC review processes of non-clinical stud-ies,[53] this checklist can offer supplement guidance to the review process. We want to reiterate that RECs should frequently solicit additional information from researchers for any checklist item as appropriate. We subsequently agree with other scholars on establishing a deliberative feedback process.[54] We call on HPSR researchers and review bodies to implement and test the checklist and develop a volume of experience to further refine and improve the review of HPSR.

RECs should consider this checklist in the broader context of the challenges for RECs outlined by our group,[55] the WHO,[56] and Luyckx et al.[57] in improving the sophistication by which HPSR is reviewed. Given the complexity and uniqueness of HPSR, the onus of responsibility to design ethically mindful studies should not only fall on researchers alone. The nature of HPSR requires RECs to engage with these issues internally and help educate researchers who may be struggling with the more ethically ambiguous aspects of their study.[58] By having both the investigator and REC compare completed checklists, areas of disagreement become points of ethical discussion. RECs should frequently interrogate and modify the fixed items (Yes/No/NA) as appropriate to obtain additional clarity from investigators.

As noted, this checklist represents a "living document" requiring subsequent iterations as HPSR ethics continues to grow and develop as a field and as committees and researchers alike encounter their respective challenges.[59] For

example, the importance of gender analysis and intersectionality is an important consideration in HPSR review given disparities in literacy and representation in LMICs.[60] Other debated issues include whether generalizability is possible — or even a necessary component — given the unique context in which some HPSR may be conducted.[61] As the study of the ethics of HPSR evolves, we anticipate that this checklist will be updated accordingly.

We hope to also encourage a more reflexive and deliberative process at the level of both researchers and stakeholders with the goal of fostering a more thoughtful approach to study design prior to REC submission.[62] RECs may find it beneficial to explore these topics at greater length by reviewing the WHO's recent report on the ethics of HPSR,[63] which was largely inspired by important work on which our checklist is based.[64] Furthermore, we recognize that ethical issues can also emerge while studies are in progress.[65] The secondary utility of a checklist is to solicit strategies or reasoning behind certain processes and better prepare researchers to address ethical issues as they arise.

It is important to reduce the variability in the review of HPSR across ethics committees and move toward a more standardized process. In addition to encouraging the presence of health systems researchers on RECs committees, [66] this checklist should be seen as part of the effort to establish a guidance tool for meaningful review.

Acknowledgements

We would like to thank Bridgett Pratt, Ph.D. for her comments and suggestions on an earlier version of this manuscript. Meghan Werbick assisted in the formatting of this manuscript. Rena Miu provided additional copyediting assistance.

Appendix 1 Detailed Summary of an HPSR Case Study on Conditional Transfers

Although effective maternal and child health interventions exist, they do not reach all those who need them. Scalingup effective preventive interventions in child and maternal health is hindered in many developing countries by various constraints including a lack of demand. In Latin America, some governments have been trying to increase demand for maternal and child health interventions by making direct payments to poor households contingent on them keeping up-to-date with such health services.

The Honduran government's programa de asignación familiar (family allowance programme), for example, was created in 1990 to mitigate the social effects of structural adjustment on the poor in Honduras. Its principal mode of action consists of the periodic distribution of monetary vouchers that are freely exchangeable for cash or certain goods to a variety of vulnerable groups. As part of the initial stage of this program, maternal and child vouchers were distributed to poor households with the requirement that pregnant women, nursing mothers, and children in beneficiary households make regular visits to health centers. Households could either use the vouchers to directly pay for health care at health centers or take the vouchers to a bank to exchange them for cash. The aim of introducing this household-level package (i.e. maternal and child voucher) was to increase use of antenatal and postnatal services by pregnant women and new mothers and to increase the numbers of children accessing health services.

At the end of 1998, the Inter-American Development Bank approved a $45 million USD loan to the family allowance program to implement a second-phase. The design of the second phase increased the value of the household-level package and made receiving it contingent upon mothers in beneficiary households making five pre-natal visits during their pregnancy and attending a post-partum check-up. Children were required to attend nutritional and health check-ups. The Inter-American Development Bank loan also set aside a substantial budget for evaluation of the family allowance program, which, it was specified, would include both a baseline assessment and subsequent evaluation after two years.

To perform the evaluation of the maternal and child voucher component, a research team from the London School of

Hygiene and Tropical Medicine, Emory University (USA), and the Food Consumption and Nutrition Division, International Food Policy Research Institute (USA) undertook a program effectiveness trial (randomized at the municipality level) in Honduras to assess this approach (i.e. the household-level package), contrasting it with a direct transfer of resources to local health teams (i.e. a service-level package). The researchers hypothesized that the conditional payments to households would increase use of maternal and child health-care services by these groups by wholly compensating any cost to the user (since the value of the health vouchers was, by design, equal to the market rate for a day's agricultural labor during the coffee harvest).

The second phase of the maternal and child voucher program was implemented and evaluated in 70 municipalities in the west of Honduras, with a total population of 660,000. These municipalities were selected because they had the highest prevalence of malnutrition in the country.They are mountainous and rural, with limited road and health infrastructure, minimal administrative autonomy, and an average land area of about 166 km.2 In mid-2000, there were just 159 health centers in the area, most of them staffed by a sole auxiliary nurse. Nearly a third of the population aged older than 12 years was unable to read and write. The 70 program municipalities were randomly assigned to one of four groups: (1) household-level package alone, (2) service-level package alone, (3) both packages, and (4) standard services (the control group).

The household-level package consisted of monetary vouchers paid to women in households. Each beneficiary household received vouchers worth 55 Lempiras ($3.71 USD according to currency conversion rate in late 2001) per month for each pregnant woman or child younger than 3 years of age in the household, up to a maximum of two. In addition, all households with children between 6 and 12 years of age enrolled in primary school in grades 1—4 received, for each child up to a maximum of three, vouchers worth 80 Lempiras ($5.40 USD) per month, for 10 months of the year. Thus, the total monthly entitlement for a household with at least one young child or pregnant woman could vary from 55 to 350 Lempiras. By way of reference, the monthly value of staple foods (maize and beans) consumed by an average household in the region was 301 Lempiras in the second half of 2000. The vouchers were distributed on three occasions between the baseline and post-intervention surveys. A fourth round of voucher distribution partly coincided with the post-intervention survey. Beneficiaries of the 55 Lempira vouchers were informed that their payments would be suspended if they did not keep up-to-date with routine antenatal and well-child preventive health care, or if children did not attend school regularly. From late 2001, beneficiaries had to deposit a certified, bar-coded attendance slip in an urn on every visit to their local health center to demonstrate they were meeting the requirements for receiving the household package. However, adherence to the requirements was not strongly enforced. No beneficiary was actually suspended for non-compliance.

The service-level package was aimed at strengthening peripheral health services. Quality improvement teams set up at each health center in municipalities allocated to this intervention, and with a wide representation from the local community, were given basic training in quality assurance methods. They produced an annual work plan with a budget ceiling dictated by the program. The median value was 70,733 Lempiras ($4,773 USD) per year. Work plans could include minor structural repairs, as well as the purchase of equipment, materials, and essential drugs, and money to pay lay assistants. The package also included the introduction of a community-based nutrition program for children younger than 2 years in two villages per health center. This intervention, previously implemented and documented in other parts of Honduras, involved the training of lay nutrition promoters. The promoters held monthly meetings in their community at which all young children (younger than 2 years) were weighed and their mothers were individually counselled.

Evaluation surveys of about 5,600 households were undertaken at baseline and roughly 2 years later in a representative sample of all households in each municipality. In each household, pregnant women and mothers of

children younger than 3 years old were asked about their use of health services (primary outcome) and coverage of interventions such as immunization and growth monitoring (secondary outcome). Interviews were done in respondents' homes by specially trained fieldworkers employed by an independent data collection company. The same team undertook both surveys. Reports were supplemented with data from children's health cards and government service utilization data. Analysis was by mixed effects regression, accounting for the municipality-level randomization.

Adapted from: S.S. Morris, R. Flores, P. Olinto, J. M. Medina, "Monetary Incentives in Primary Health Care and Effects on Use and Coverage of Preventive Health Care Interventions in Rural Honduras: Cluster Randomised Trial," *Lancet* 364 (2004): 2030-2037.

Appendix 2: Sample Checklist for Case Study on Conditional Transfers

Note

The authors have no conflicts of interest to declare.

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DETAIL

Subjek:	Ethics; Review boards; Research; Public health; Principles; Validity; Informed consent; Workshops; Health care policy; Medical ethics
Ketentuan indeks bisnis:	Subjek: Workshops
Perusahaan / organisasi:	Nama: World Health Organization; NAICS: 923120
Pengidentifikasi/kata kunci:	Health Systems Research; Systems theory; Global Health; Health policy; Review; Global Health; Health Policy; Ethical Review; Checklist
Judul:	Operationalizing the Ethical Review of Global Health Policy and Systems Research: A Proposed Checklist
Pengarang:	Rattani, Abbas; Hyder, Adnan A
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	92-122
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article

A Survey of Overlapping Surgery Policies at U.S. Hospitals

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ABSTRAK (ENGLISH)

The authors surveyed hospitals across the country on their policies regarding overlapping surgery, and found large variation between hospitals in how this practice is regulated. Specifically, institutions chose to define “critical portions” in a variety of ways, ultimately affecting not only surgical efficiency but also the autonomy of surgical trainees and patient experiences at these different hospitals.

TEKS LENGKAP

Background

The Boston Globe Spotlight report on concurrent and overlapping surgery in October 2015 spurred a national debate on this practice and examination of existing policies.[1] While some argued that leaving a patient in the hands of a trainee while the attending surgeon operated in another room was an unacceptable risk to patient safety,[2] others argued that with appropriate precautions, overlapping surgery (OS) provided greater patient access to care and enhanced training without jeopardizing surgical outcomes.[3] The only existing public regulations at that time were based on billing rules: the Centers for Medicare and Medicaid Services (CMS) permitted some overlap of surgical procedures as long as the teaching (billing) physician was “physically present” for the “critical portions” of the procedure. In these rules, the definition of critical portions is determined by the surgeon (“that part [or parts] of a service that the teaching physician determines is (are) a critical or key portion”).[4]

After this story broke in the national media, the American College of Surgeons (ACS) updated a section of their Statement on Principles to guide surgeons more precisely through the intricacies of OS.[5] This section defined concurrent and overlapping surgery and clearly indicated that “concurrent surgery,” when critical portions of two procedures overlap, was “inappropriate.” This update also provided potentially acceptable OS scenarios, elaborated on key terms used in CMS billing language (e.g., “critical portions,” “immediately available,” “backup surgeon,” “physically present”), and stated the need for patient-surgeon transparency about overlapping cases.

Since this report was released, there has been no assessment of whether and how hospitals have implemented these recommendations from the SFC. In order to assess the national response to both this report and the attention of the national media, we contacted hospitals across the country and evaluated their OS policies and informed consent documents. The purpose of our study was to examine the presence of policies, determine what aspects of the SFC recommendations were implemented, and assess variations in these policies.

Given the concern of patient safety and questions of inappropriate reimbursement, the U.S. Senate Finance Committee (SFC) investigated this issue in 2016. The Committee asked 20 unidentified teaching hospitals to create and share their policies surrounding OS.[6] After evaluating these policies in comparison with the ACS recommendations and definitions, the committee urged all hospitals to make policies specifically prohibiting concurrent surgery, regulating OS, and increasing transparency with patients **(Table 1).** Regarding critical portions, the report indicated that while many hospitals used the ACS definition ("…those stages when essential technical expertise and surgical judgment are necessary to achieve an optimal patient outcome"),[7] a substantial number "have developed, or expect to develop, lists of procedures, generally by surgical department, of the critical components, most of which also identify the procedures and patient conditions where overlapping surgical procedures are not appropriate,"[8] and recommended that all hospitals follow the latter pathway.

Table 1

2016 Senate Finance Committee Report on Concurrent and Overlapping Surgery Patient Safety Recommendations [16]

2016 Senate Finance Committee Report on Concurrent and Overlapping Surgery Patient Safety Recommendations[17]
1. Develop a concurrent and overlapping surgical policy that clearly prohibits the former and regulates the practice of the latter consistent with ACS guidance.
2. Formally identify the critical portions of particular procedures, to the extent practicable, as well as those portions unsuitable for overlap.
3. Develop processes to ensure that patient consent discussions result in a complete understanding by the patient that his/her surgery will overlap with another patient's; develop materials such as frequently asked questions; and educate their patients ahead of their surgeries, giving them enough time to review materials and fully consider their options.
4. Prospectively identify the backup surgeon when overlapping surgeries are scheduled.
5. Develop mechanisms to enforce the established concurrent and overlapping surgical policies and monitor and enforce their outcomes.

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Methods

We generated a list of hospitals based on the U.S. News and World Report (USNWR) "Top Hospitals" rankings as of

April 2018[9]: we included all top 20 hospitals as well as the top hospital in each state if not already in the top 20. Because hospitals receiving coverage in the national media might have a unique perspective on this issue, we additionally conducted a media search for articles on concurrent/overlapping surgery between October 2015 and April 2018 and included any hospitals receiving media attention that were not already on our list. We used online information and/or telephone calls to hospital departments to identify the Chair of Surgery, Director of Perioperative Services, and Chief Compliance Officer for each hospital, and contacted these individuals via email and/or phone call between April and August 2018 and requested a 10-minute phone call regarding OS policies with them or a designee. Non-responders were re-contacted up to three times. Hospital representatives were given the option of sharing policy documents via secure file transfer, or if they refused this, discussing the details of their policies in a structured phone interview with study personnel. All hospitals were assured that data collected would remain confidential and results would only be published in aggregate. For hospitals that did not respond, study personnel searched for policies or consent forms published online and included these in the study data. Data were abstracted from documents or interviews and entered into a secure REDcap electronic data collection form (www.projectredcap.org).[10]

We defined a “concurrent or overlapping surgery policy” as a document or part of a document that included regulations for situations in which an attending surgeon is responsible for two overlapping procedures. For each hospital, we assessed the following:

•1. Adoption of the five recommendations from SFC Report **[Table 1]**

•2. Definitions of the key terms “immediately available” and “backup surgeon” and “physically present”

•3. Descriptions of specific medical or surgical conditions (e.g., comorbidities) that would preclude overlap (a concept introduced by the SFC Report)

•4. Explicit discussion of permissibility of surgeon’s moving back and forth between overlapping cases

Regarding the latter, it is theoretically possible that two cases could have multiple, staggered overlapping portions between them or that during an intervening non-critical portion between two critical portions of a longer case, a teaching surgeon might leave the room to complete a small procedure in another room (e.g., biopsy) before returning to the prior room for the next critical portion to begin **[Figure 1].**[11] However, the language of CMS seems to imply that critical portions occur only centrally within a surgical procedure (“In the case of surgery, the teaching physician’s presence is not required during opening and closing of the surgical field”).[12] This is echoed by the two scenarios described by the ACS, neither of which include returning to the prior operating room:

“The first and most common [overlapping surgery] scenario is when the key or critical elements of the first operation have been completed, and there is *no reasonable expectation that the primary attending surgeon will need to return to that operation*… The second and less common scenario is when the key or critical elements of the first operation *have been completed* and the primary attending surgeon is performing key or critical portions of a second operation in another room.” (emphasis added) [13]

In the latter example, a “backup attending” would need to be identified. It is theoretically possible that this backup attending system could be used to allow a surgeon to complete staggered critical portions in two rooms with more substantial overlap, such as in Figure 1, scenarios D or E. This might still be in the spirit of CMS regulations if the procedures in question included periods of obvious non-criticality (e.g., awaiting intraoperative pathology or transitioning between distinct procedures in a multi-part operation). These latter scenarios would make the most efficient use of surgeon time, and for that reason we investigated whether they would be permissible at hospitals.

Figure 1 Diagrams of example overlapping surgery scenariosBlack bars represent the “critical portions” of

procedures, during which the attending surgeon must be present, whereas the white areas represent the “non-critical portions” that may be handled by a trainee without attending presence in appropriate circumstances. Scenario A shows two rooms with no overlap (“staggered”). Scenarios B and C represent the two overlapping scenarios described by the ACS (see text); scenario C requires a “backup attending” because some of the non-critical portion of the case in room 1 overlaps with the critical portion of the case in room 2. The greater degree of overlap allows the second room to end incrementally earlier through scenarios A-C. Scenarios D and E represent hypothetical scenarios not described by the ACS where one attending moves back and forth between two cases, but is always present for the intermittent, critical portions of each. These scenarios involve substantial overlap and therefore increase efficiency of surgeon time, but would require a backup attending and careful planning to ensure primary attending presence for critical portions of each case. Scenario D would require some flexibility as to when the second, small case (e.g., a biopsy) was started to ensure that timing would be appropriate; scenario E would be the most difficult to avoid inadvertent overlap of critical portions (and therefore becoming “concurrent surgery”).

We provided participating hospitals with an advance copy of our results prior to publication, and all policies sent to us were destroyed upon publication. The Vanderbilt University Medical Center IRB approved this research.

Results

In total, we identified and contacted 61 hospitals (58 from the USNWR rankings and 3 additional from media reports; **Figure 2).** Of these 61, 33 responded (54%), and 25 agreed to discuss their policies with us, although two of these 25 agreed only to disclose the presence of a policy and declined to provide any further details. Online search identified policies from two additional hospitals and an informational handout discussing policy for one additional hospital, for a total of 28 hospitals with policy information. These 28 hospitals were located in 22 states and ranged from smaller private institutions to large public hospitals **(Figure 2).**

Figure 2 Flowchart of hospital participantsGrayed boxes indicate the 28 hospitals that served as a data source for this paper. Bold outline boxes indicate the data sources for policy detail analysis (19 of these 21 had policy details and permitted some overlapping surgery; see text and table).

Presence of a Policy

Twenty-four of the 28 responding hospitals (86%) had overlapping or concurrent surgery policies. For one hospital, we were able to review only an educational handout describing its policy of concurrent surgery prohibition. Two other hospitals completely prohibited both concurrent and overlapping surgery, and two refused to discuss anything other than the existence of a policy, leaving 19 hospitals that permitted OS and provided policy details. These 19 hospitals included only 1 identified via media search. The variations of these policies and their adoption of SFC recommendations are summarized in **Figure 3** and reported below. Of note, 13 of the 19 policies (68%) explicitly prohibited concurrent surgery.

Figure 3 Policy adoption of SFC recommendations*An additional hospital had an educational handout which indicated concurrent surgery was prohibited at that institution.**Data from these two hospitals that prohibited overlapping surgery is not included elsewhere in this figure as it does not apply.***Because some hospitals had multiple compliance ensuring measures, the total data here will exceed19.

Attending Regulation

Of the policies we reviewed from the hospitals permitting OS, most (16/19, 84%) policies defined “immediately available,” with all but two giving specific geographic markers as to where the surgeon must be (e.g., in a hospital building or on a specific campus). Four required that the surgeon must be able to return to the operating room within a specific time interval between 5 to 10 minutes. By providing specific locations or time intervals, these hospitals avoid the pitfall noted in the SFC report — an imprecise requirement for a surgeon to be “on campus” can result in a

delay in return to the operating room at institutions with large or disconnected campuses.

Most (16/19, 84%) policies defined either “backup attending” or “qualified practitioner,” referring to the surgeon designated to take over the surgical case should the primary surgeon become unavailable. These terms were used interchangeably within policies. Of these sixteen, 9 (56%) provided definitions similar to the definition of “qualified practitioner” under the ACS guidance, requiring this surgeon to be licensed, have operating privileges, and be able to conduct a portion of a procedure without supervision. One hospital specifically prohibited all fellows from fulfilling this back up attending role.

Five of the 19 (26%) defined “physically present” within their policies. All five defined this term as within the operating room of the patient, with one further specifying that if the room was partitioned by curtains, the surgeon must be within the curtains within the patient’s partitioned area. No policies required that the attending surgeon be scrubbed into the case in order to be “physically present.”

Seven of nineteen hospitals (37%) specified explicitly that an attending could not return to a surgery after scrubbing into another procedure, thus prohibiting surgeons from going back and forth between rooms.

Critical Portions

Sixty-three percent (12/19) defined “critical portions” within the policy, and of these 12, half (n=6) were either identical to or very similar to the ACS definition (7). Two hospitals defined “critical portions” more broadly as “skin incision to skin closure.” Three hospitals (16%) defined this term on a departmental level and had predetermined lists of “critical portions” for certain procedures (a fourth hospital was in the process of creating such lists). No hospital reported having specific comorbidities or surgical conditions for which OS was unsuitable.

Surgeon-Patient Transparency

Fourteen (74%) of the 19 policies required the primary attending to tell the patient his or her surgery will (n=12) or may (n=2) be overlapping. The other 5 policies had no such requirement of disclosure. No hospitals had a minimum time period before surgery that a patient must know his or her procedure will or may be overlapping. One hospital’s policy noted that a patient has the right to ask the attending surgeon to be present for the entirety of the case. All 19 hospitals were willing to share their consent document details with us, and of these, 14 (74%) included language describing OS. Three of these 14 (21%) required patients to initial specifically next to the section with this language as well as at the end of the document.

Back up Attending Designation

Of these 19 hospitals, 12 (63%) required that a backup attending be chosen in advance of the surgical procedure for any planned overlapping case. One of these twelve required this backup be designated at the time of scheduling (thus in elective cases before the day of surgery). The other hospitals’ policies either did not specify when a backup attending was to be designated (n=6) or indicated a backup was only to be designated if the need arose (n=1). About half of the policies (10/19, 53%) specified explicitly that this backup attending could not be in another procedure.

Compliance and Tracking

Less than half (7/19, 37%) of policies identified measures to ensure compliance within the policy itself. Some of these hospitals (4/19, 21%) reported during phone calls that they had departmental or perioperative monitoring of overlapping surgeries not mentioned within the policy document. Compliance measures included review by surgery department, perioperative services, or a compliance or corporate integrity department, as well as penalties if the policy was violated.

One hospital developed a data management system that analyzes in/out times and other data to both identify surgeries with potential overlap as well as stratify them by risk. At another hospital, in order to book an OS, the

scheduling system requires a manual override by an anesthesiologist who must have conferred with the attending surgeon, ensuring all policy requirements are met before booking a surgery. A third hospital reported a special approval process by a department chair in order for a surgeon to be allowed to schedule OS.

When asked about OS oversight, 13 of the 19 hospitals (68%) responded that these surgeries were tracked. Representatives from one hospital remarked this was tracked in several different statistical measurements, like incision-to-closure ("skin-to-skin") overlap, or the time both patients were in rooms or under anesthesia. None of the four hospitals without policies tracked whether surgeries done at their institution had overlapping components.

Creation or Revision of Policy

All of these 19 policies reviewed had been created de novo (n=4) or revised (n=15) since March of 2016.

Discussion

Overlapping surgery and the roles of attending surgeons, trainees, and assistants in surgery is an area of increasing scrutiny by lawmakers and the public. The SFC report, while not law, is evidence of interest in this topic at the highest levels of government and a potential portent of intervention. In light of this, we reached out to 61 leading hospitals to see how they responded to the recommendations of the SFC, the revisions of the ACS Statement on Principles, and national media attention. Despite multiple contacts, many hospitals did not respond or refused to share data, suggesting that this is a particularly sensitive topic for hospitals. For those that did respond, we found substantial variability in the policies, with none meeting all the concerns of the SFC. However, public scrutiny did appear to have a motivating effect on hospitals, with all responding hospitals that allowed OS having updated their policies since March 2016.

Most hospitals' policies included the key definitions of "immediately available" and "backup attending." The ACS provided clear guidance on how to define these terms, and, importantly, these definitions seem particularly suited to specification by individual hospitals, as they are affected by each hospital's characteristics (campus geography and staffing structure). In contrast, what constituted "critical portions" was less commonly defined within policies, and, when defined, showed great variation: about a third (6/19) of hospitals defined the term broadly as at the surgeon's discretion, a third (6/19) explicitly defined "critical portions" for each procedure, on the one hand, or used a blanket statement like "skin incision to skin closure," on the other, and a third (7/19) had no definition.

This diversity of this aspect of the policies likely reflects the controversial nature of critical portions and an unresolved debate about the relative merits of strict regulation versus surgeon judgment, and how patient safety, trainee education, and system efficiency will be influenced by strategies governing OS. For example, if all but the most minor portions of a case (e.g., closing skin) are considered critical, then this places a significant limitation on opportunities for trainees to develop independence during residency; essential autonomy would have to occur after training, without the availability of a more experienced attending as backup. Conversely, policies that offer no standards for definition and rely solely on attending surgeon judgement carry a degree of moral hazard — while the attending surgeon might be expected (and intend) to make delegation decisions that are neutral or favor the patient's care over other considerations, competing priorities (e.g., desires to care for more patients, better training opportunities, or a shorter work day) can influence these decisions, and may do so unequally for some patients versus others. Further analysis of potential regulatory strategies regarding critical portions and their impact on patient care *and* surgeon training is warranted. As the SFC Report states, guidelines should, "identify the critical components of particular procedures while accounting for the individualized clinical judgment the surgeon must bring to each case."[14]

Patient comorbidities that would limit overlap was notably absent in any hospital policies we examined; while this was only mentioned in the SFC report and not part of their listed recommendations, it seems logical that certain

patient conditions would make a patient a poor candidate for overlapping surgery. Standards for this might include surgical problems of high complexity and unpredictability, or comorbidities for which prolonged anesthesia is dangerous.[15]

Standards for what *metrics* ought to be tracked (and potentially subject to audit) should also be considered **(Table 2)**, as we identified substantial diversity in hospitals' compliance and tracking protocols. Differences in perioperative informatics systems and staffing structures aside, hospitals and regulators ultimately must speak the same "language" when considering expectations and the effects of policies.

Table 2

Potential Operational Metrics in Overlapping Surgery

Potential Operational Metrics in Overlapping Surgery	
Operative metrics	Skin incision to skin closure time[18]
Skin incision to operation end[19]	Skin incision to start of closing[20]
Operative start to end time[21]	Time to exposure[22]
Exposure complete to start of closing time[23]	Anesthetic metrics
Anesthesia start to end time[24]	Other metrics
Attending surgeon sign-in time to sign-out time[25]	Patient room-in to patient room-out time[26]

As a final consideration, we found that 74% of the participating hospitals had policies for patient disclosure, but it remains unclear how the disclosure happens in practice. While beyond the scope of the present study, further work is needed to examine the language in consent documents and how surgeons actually discuss OS (and trainee participation) with patients.

While these SFC recommendations may eventually become requirements in whole or in part, either through changes to CMS rules or through other mechanisms such as revision of the Joint commission guidelines, it may be that some hospitals are waiting to find out which, if any, of the recommendations will be included in future regulations before adopting policies on this controversial topic. Further research should consider the rationale for a given hospital's policy, whether the SFC recommendations are optimally formulated, and whether other mechanisms, such as national practice guidelines, should be generated to guide OS. The lack of transparency and level of variation in policies among prominent US hospitals is clear evidence that more work needs to be done regarding OS.

The results reported herein may not represent the full spectrum of hospital policies nor the frequency of particular components due to the selection bias of hospitals willing to participate. We might suspect that hospitals that did not participate also had incomplete policies, but they may also have had comprehensive or even innovative policies but were reluctant to become involved in a study on such a nationally controversial topic. Furthermore, some of the hospitals that participated only read us their policy and did not share documents; despite our structured and specific interview questions we may have lost nuances in verbal transmission.

Our sample may have included hospitals that were also represented in the SFC report (their sample was unidentified), but the hospitals that participated in our study were not instructed to develop policies prior to participation; the substantial number of hospitals that did not specifically include the SFC recommendations in their policies may therefore be more representative of current practices. Our criteria for including hospitals was based on a national ranking that employs quality metrics and reputational scores and may not represent less prominent hospitals. Our media search may have missed hospitals that should have been included based on our criteria. However, even with this circumscribed sample, the diversity in adoption of SFC recommendations was substantial enough to uncover potential limitations in current regulatory strategy.

Conclusion

There remains substantial diversity in institutional policies regulating overlapping surgery, especially regarding “critical portions” definitions and compliance tracking. Hospitals may not yet be adopting current recommendations due to ongoing controversy about the optimal balance between individual surgeon judgment and standardization of care, and this is worthy of further study. Standardized metrics should be developed for compliance and tracking to enable ongoing assessment of the success of oversight of overlapping surgeries.

Funding Sources

This work was funded by a grant from the Greenwall Foundation.

Note

The authors have no conflict of interests to disclose.

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DETAIL

Subjek:	Surgery; Patient safety; Surgical outcomes; Hospitals; Consent; Congressional committees; Informed consent
Ketentuan indeks bisnis:	Subjek: Hospitals
Lokasi:	United States--US
Perusahaan / organisasi:	Nama: Senate-Finance, Committee on; NAICS: 921120

Pengidentifikasi/kata kunci:	Overlapping Surgery; Survey; United States; Policy; Surgery; Hospital; Concurrent Surgery; Critical Portions; Immediately Available; Informed Consent
Judul:	A Survey of Overlapping Surgery Policies at U.S. Hospitals
Pengarang:	Mitchell, Margaret B; Hammack-Aviran, Catherine M; Clayton, Ellen W; Langerman, Alexander
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	64-73
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Art icles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.11
ID dokumen ProQuest:	2730847016
URL Dokumen:	https://www.proquest.com/scholarly-journals/survey-overlapping-surgery-policies-at-u-s/docview/2730847016/se-2?accountid=211160
Hak cipta:	

Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

A Non-Profit Approach to Address Foreign Dependence of Generic Drugs

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ABSTRAK (ENGLISH)

The COVID-19 pandemic has revealed the vulnerability of the US generic drug supply chain to foreign production. Many policies have been proposed to mitigate this vulnerability. In this article, we argue that nonprofit drug manufacturers have the potential to make important contributions.

TEKS LENGKAP

A Non-profit Approach to Address Foreign Dependence of Generic Drug

The COVID-19 pandemic has exposed US dependence on foreign countries for generic drugs.[1] Although such reliance can lead to lower manufacturing or procurement costs, it increases supply chain vulnerability of US medical products and poses substantial national security risks, especially during global crises.[2] For example, amid the pandemic, production disruptions and local medical needs in China, a dominant supplier of generic drugs and active pharmaceutical ingredients, reportedly caused shortages of generic antibiotics needed to treat COVID-19-related secondary bacterial infections, such as azithromycin, ciprofloxacin, and piperacillin/taobactam.[3] In March 2020, China's official news agency threatened a ban on exports of these and other medical products to United States.[4]

In 2001, China joined the World Trade Organization and gained access to global markets. Since then, generic drug companies have shifted much of their manufacturing from the United States to China, motivated by China's low costs.[5] Today, China produces 9% of all generic drugs in the US market, while India, which produces 25% of all generic drugs in the US market, relies heavily on China for pharmaceutical ingredients.[6] Approximately 90% of pharmaceutical ingredients used for essential generic drugs treating serious Coronavirus infections in United States are made in China.[7]

In the wake of COVID-19, several bills have been introduced in Congress to address this foreign dependence (Table). Overall, they have three main objectives: (1) to provide funding to encourage domestic production of generic drugs, (2) to improve the transparency of the generic drug supply chain information and assess its vulnerability, and (3) to require that critical drugs purchased by Strategic National Stockpile be "Made in America." The Trump Administration has also invoked the Defense Production Act to fund some companies' effort to establish domestic manufacturing facilities for generic drugs and active pharmaceutical ingredients, and mandated that essential generic drugs purchased by the federal government be produced domestically.[8] These initiatives aim to diminish the cost differential between domestic and overseas production and reflect an opportunity to transform the US supply chain.

Amid the pandemic, production disruptions and local medical needs in China, a dominant supplier of generic drugs and active pharmaceutical ingredients, reportedly caused shortages of generic antibiotics needed to treat COVID-

19-related secondary bacterial infections, such as azithromycin, ciprofloxacin, and piperacillin/taobactam. In March 2020, China's official news agency threatened a ban on exports of these and other medical products to the Uniteds States.

While public attention has been focused on responses from for-profit companies, non-profit manufacturers may actually be better positioned to play an important role in bringing production back to the US. Manufacturing drugs requires considerable upfront capital investment and has a large fixed overhead cost, leading to high operating risks. When demand is low, manufacturers are likely to generate significant losses. Even with healthy demand, the profit margin for generic manufacturing is often thin, since the price needs to be competitive to the prices of overseas suppliers. However, for-profit entities must generate sufficient profits to reward investors, who would otherwise seek alternative investment options. For-profit entities, therefore, have a relatively high cost of capital and are often not likely to find the combination of a high operating risk and a thin profit margin attractive.

By contrast, non-profit entities have no equity investors; their initial capital usually comes from philanthropy; and they face no pressure to earn profits for the purpose of attracting and retaining investors.[9] They may directly contract with health systems, insurance companies, and pharmacies —independent of pharmacy benefit managers or group purchasing organizations. Non-profit entities can also accommodate fully transparent cost-plus pricing model and multi-year purchasing, which ensures demand and reduces revenue volatility and operating risks. Except in highly regulated environments such as defense and public utilities, such a model is generally unattractive to for-profit drug manufacturers due to its revenue-restricting nature.

The market for non-profits can be substantial if the federal, state, and local governments decide to purchase generic drugs that are "Made in America." Potential purchasers include government strategic stockpiles, the Department of Defense, the Veterans Administration, the Bureau of Indian Affairs, federally qualified health centers, government employees, Medicare and Medicaid, and prisons.On September 28, 2020, California Governor Gavin Newsom signed SB 852 into law, which requires the California Health and Human Services Agency to establish partnerships with drug manufacturers to produce or distribute more affordable generic prescription drugs, including at least one form of insulin.[10] Some other states are considering a similar approach or have expressed interest in purchasing drugs produced or distributed under this law from California.

These public programs would offer a continuous and stable demand for generic drugs. Multi-year contracting would ensure a large scale of production and allow the manufacturer to obtain a low fixed cost for each drug unit, making it possible to achieve the lowest possible price that is competitive with the prices of international suppliers and attractive to health systems, insurance companies, and pharmacies. The initial multi-million capital investment necessary could come from philanthropies, government grants, and/or loans. In addition to improving the supply chain resiliency and national health security, the establishment of domestic drug production would also create jobs and skilled human capital.

Table

Recently Introduced Legislation to Address Drug Supply Chain Vulnerability

Introduced Legislation	Co-Sponsors	Summary
House of Representatives		
Commission on America's Medical Security Act	David Roe [R-TN]	The Department of Health and Human Services (HHS) would report on the security of the medical product supply chain.

Paul Ruiz [D-CA]	Lauren Underwood [D-IL]	Medical Supplies for Pandemics Act
Susan Brooks [R-IN]	HHS would incentivize manufacture s to increase emergency stocks and diversity geographic production. HHS would also buy, lease, or enter into joint venture to produce medical supplies and work with distributors to refresh and replenish medical supplies.	Debbie Dingell [D-MI]
Eliot Engel [D-NY]	Sheila Jackson Lee [D-TX]	David McKinley [R-WV]
Eleanor Norton [D-DC]	Pete Olson [R-TX]	Elissa Slotkin [D-MI]
Fred Upton [R-MI]	Jefferson Van Drew [R-NJ]	Jackie Walorski [R-IN]

Strengthening America's Strategic National Stockpile Act	Susan Brooks [R-IN]	The annual authorized funding for the Strategic National Stockpile would increase from $610 million to $705 million from fiscal years 2020 through 2023. The Strategic National Stockpile would partner with manufactures to build domestic production capacity and sell items to other federal agencies. HHS would ensure the effective functioning of the stockpile contents, improve financial security, report on requests and the response, and establish transparent process for distribution. A $500 million pilot program would be established to support state efforts to expand and maintain their own stockpile.
Michael Burgess [R-TX]	G. K. Butterfield [D-NC]	Earl Carter [R-GA]
Gilbert Cisneros [D-CA]	Diana DeGette [D-CO]	Debbie Dingell [D-MI]
Anna Eshoo [D-CA]	Brian Fitzpatrick [R-PA]	Greg Gianforte [R-MT]
Richard Hudson [R-NC]	Ben Lujan [D-NM]	Tom Malinowski [D-NJ]
David McKinley [R-WV]	Joe Neguse [D-CO]	Kim Schrier [D-WA]
Elissa Slotkin [D-MI]	Darren Soto [D-FL]	Fred Upton [R-MI]
Jefferson Van Drew [R-NJ]	Jackie Walorski [R-IN]	**Senate**
Pharmaceutical Accountability, Responsibility, and Transparency Act	Gary Peters [D-MI]	Reporting requirement would be expanded for critical manufacturing data.
Help Onshore Manufacturing Efficiencies for Drugs and Devices Act	Gary Peters [D-MI]	HHS would establish a new agency to facilitate the investment to create domestic manufacturing capacity.

United States Pharmaceutical Supply Chain Review Act	Marco Rubio [R-FL]	The Federal Trade Commission would report on foreign investment in the U.S pharmaceutical industry.
Elizabeth Warren [D-MA]	Pharmaceutical Supply Chain Defense and Enhancement Act	Marco Rubio [R-FL]

Introduced Legislation	Co-Sponsors	Summary
House of Representatives		
Commission on America's Medical Security Act	David Roe [R-TN] Paul Ruiz [D-CA] Lauren Underwood [D-IL]	The Department of Health and Human Services (HHS) would report on the security of the medical product supply chain.
Medical Supplies for Pandemics Act	Susan Brooks [R-IN] Debbie Dingell [D-MI] Eliot Engel [D-NY] Sheila Jackson Lee [D-TX] David McKinley [R-WV] Eleanor Norton [D-DC] Pete Olson [R-TX] Elissa Slotkin [D-MI] Fred Upton [R-MI] Jefferson Van Drew [R-NJ] Jackie Walorski [R-IN]	HHS would incentivize manufactures to increase emergency stocks and diversity geographic production. HHS would also buy, lease, or enter into joint venture to produce medical supplies and work with distributors to refresh and replenish medical supplies.
Strengthening America's Strategic National Stockpile Act	Susan Brooks [R-IN] Michael Burgess [R-TX] G. K. Butterfield [D-NC] Earl Carter [R-GA] Gilbert Cisneros [D-CA] Diana DeGette [D-CO] Debbie Dingell [D-MI] Anna Eshoo [D-CA] Brian Fitzpatrick [R-PA] Greg Gianforte [R-MT] Richard Hudson [R-NC] Ben Lujan [D-NM] Tom Malinowski [D-NJ] David McKinley [R-WV] Joe Neguse [D-CO] Kim Schrier [D-WA] Elissa Slotkin [D-MI] Darren Soto [D-FL] Fred Upton [R-MI] Jefferson Van Drew [R-NJ] Jackie Walorski [R-IN]	The annual authorized funding for the Strategic National Stockpile would increase from $610 million to $705 million from fiscal years 2020 through 2023. The Strategic National Stockpile would partner with manufactures to build domestic production capacity and sell items to other federal agencies. HHS would ensure the effective functioning of the stockpile contents, improve financial security, report on requests and the response, and establish transparent process for distribution. A $500 million pilot program would be established to support state efforts to expand and maintain their own stockpile.
Senate		
Pharmaceutical Accountability, Responsibility, and Transparency Act	Gary Peters [D-MI]	Reporting requirement would be expanded for critical manufacturing data.
Help Onshore Manufacturing Efficiencies for Drugs and Devices Act	Gary Peters [D-MI]	HHS would establish a new agency to facilitate the investment to create domestic manufacturing capacity.
United States Pharmaceutical Supply Chain Review Act	Marco Rubio [R-FL] Elizabeth Warren [D-MA]	The Federal Trade Commission would report on foreign investment in the U.S pharmaceutical industry.
Pharmaceutical Supply Chain Defense and Enhancement Act	Marco Rubio [R-FL] Elizabeth Warren [D-MA]	$1 billion a year for 5 years would be provided to update domestic manufacturing capacity of critical drugs. DoD, VA, HHS, and Bureau of Prisons would purchase domestically made drugs.

Perbesar gambar ini.

This business approach —featuring a low cost of capital, a competitive and transparent cost-plus pricing model, and a multi-year purchase agreement —is based on the successful entry of a non-profit manufacturer in the generic drug

market recently. Civica Rx was established in 2018 by large health systems and philanthropies to address the lack of affordability and access to generic drugs in the U.S. market.[11] Since July 2020, Civica Rx has been providing more than 40 generic drugs to its institutional partners (health systems, insurance companies, and pharmacies), constituting approximately one-third of the U.S. inpatient generic drug market. Civica Rx has also formed an outpatient generic drug subsidiary —in partnership with insurance companies —that will provide affordable medications to more than 100 million beneficiaries.

The purpose of establishing Civica Rx was to address the market failures for generic drugs by promoting competition with for-profit companies. Its initial performance suggests that non-profit generic manufacturers can offer competitive pricing and generate value for their institutional partners and the patients they serve. Non-profits are also well positioned to address the supply chain vulnerability of generic drugs. With strong and transparent governance structure to ensure the alignment between business operations and their charitable mission, non-profit drug manufacturers have the potential to compete with for-profit entities to improve domestic production, reduce foreign dependency, and enhance national health security.

Note

Mr. Liljenquist is Senior Vice President and Chief Strategy Officer of Intermountain Healthcare and the Chairman of Civica Rx, a non-profit drug manufacturer; Dr. Anderson reports grants from Arnold Ventures during the conduct of the study; Dr. Sarpatwari reports grants from Arnold Ventures and the Open Society Foundations during the writing of the work, and personal fees from West Health outside the submitted work. Dr. Bai received funding from Arnold Ventures and consulting fee from Council for Informed Drug Spending Analysis.

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2. See, for example, Alexander G.C. and Qato D. M., “Ensuring Access to Medications in the US during the COVID-19 Pandemic ”, JAMA 324, no. 1 (2020): 31–32; T. Dai, G. Bai, and G.F. Anderson, “PPE Supply Chain Needs Data Transparency and Stress Testing”, Journal of General Internal Medicine 35, no. 9 (2020): 2748-2749.

3. See, for example, Yap C., “Pandemic Lays Bare U.S. Reliance on China for Drugs”, The Wall Street Journal, August 5, 2020, available at <https://www.wsj.com/articles/how-the-u-s-ceded-control-of-drug-supplies-to-china-11596634936 >(last visited September 25, 2020); K. Thomas, “First Drug Shortage Caused by Coronavirus, F.D.A. Says. But It Won’t Disclose What Drug or Where It’s Made”, The New York Times, February 28, 2020, available at <https://www.nytimes.com/2020/02/28/health/drug-coronavirus-shortage.html >(last visited September 25, 2020); S. Lupkin, “How Cora-onavirus Is Affecting the U.S. Pharmaceutical Supply”, NPR, March 12, 2020, available at <https://www.npr.org/sections/health-shots/2020/03/12/814623335/how-coronavirus-is-affecting-the-u-s-

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5. Yap C., supra note 1.
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DETAIL

Subjek:	COVID-19; Generic drugs; Purchasing; Pandemics; Generic products; Bacterial infections; Drug stores; Drugs; Manufacturing; Medical supplies; Coronaviruses; Suppliers; Nonprofit organizations; Competition
Ketentuan indeks bisnis:	Subjek: Drug stores Manufacturing Suppliers
Lokasi:	United States--US; China; California
Orang:	Slotkin, Elissa; Upton, Frederick S; Warren, Elizabeth; Dingell, De bbie; Walorski, Jackie; Rubio, Marco
Perusahaan / organisasi:	Nama: Department of Health &Human Services; NAICS: 923120
Pengidentifikasi/kata kunci:	Generic Drug; Drug; Generic drug; Nonprofit organization; COVID-19; Generic; Supply chain; Prescription Drug Manufacturing; Foreign Dependence; Non-profit; Drug Supply Chain
Judul:	A Non-Profit Approach to Address Foreign Dependence of Generic Drugs
Pengarang:	Liljenquist, Dan; Bai, Ge; Sarpatwari, Ameet; Anderson, Gerard F
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges

Halaman:	30-33
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.6
ID dokumen ProQuest:	2730847002
URL Dokumen:	https://www.proquest.com/scholarly-journals/non-profit-approach-address-foreign-dependence/docview/2730847002/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

Opportunities and Challenges in Translational Research: The Development of Photodynamic Therapy and Anti-Vascular Endothelial Growth Factor Drugs

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ABSTRAK (ENGLISH)

The development of photodynamic therapy and anti-vascular endothelial growth factor agents have revolutionized the treatment of retinal diseases, transforming the retina subspecialty by ushering in an age of pharmacological treatments for a wide range of diseases, including age-related macular degeneration (AMD).

TEKS LENGKAP

The entry of pharmacologic treatments for retinal diseases has transformed the field of ophthalmology, improving vision outcomes and quality of life for millions of people around the world. When I finished my vitreoretinal fellowship training in 1991, the retinal field was primarily surgical. Previous surgical advances had made it possible to repair retinal detachments, to operate on eyes with blinding complications of diabetes mellitus, and to repair other retinal conditions such as epiretinal membranes. However, the treatment for many other retinal conditions was limited. Laser photocoagulation, tested in National Eye Institute funded clinical trials,[1] was the only treatment for neovascular age-related macular degeneration (nvAMD). However, the therapy is less than ideal, as it is destructive to the neural retina and results in immediate loss of vision if applied to subfoveal choroidal neovascularization (CNV). Approval of verteporfin photodynamic therapy (Visudyne) for nvAMD in 2000 began a revolution in the treatment of retinal diseases, moving from surgical to pharmacological approaches and opened the way for the development of many novel agents, in particular, anti-vascular endothelial growth factor (anti-VEGF) drugs to slow and limit vision loss. The entry into a pharmacologic era was one of the most important translational research achievements in ophthalmology, revolutionizing the treatment of nvAMD, diabetic macular edema, macular edema following retinal vein occlusion, proliferative diabetic retinopathy, and retinopathy of prematurity.

Research and Development of Photodynamic Therapy for AMD

While PDT had a long history as a potential treatment for cancer, there were no approved drugs in the 1990s. By combining a light-activated photosensitizer delivered to target tissue with activation from a light source at a specific wavelength, PDT has a direct toxicity to tumor cells. Since PDT also causes vascular injury, a number of investigators pursued various photosensi-tizers and PDT in animal models of subfoveal choroi-dal neovascularization.

During my first year as a faculty member at Mass Eye and Ear, PDT using verteporfin, a liposomal formulation of benzoporphyrin derivative, was in clinical trial for skin metastases. If verteporfin PDT could safely treat experimental CNV, there would be a shorter, potential path for clinical application in nvAMD. To investigate this, I began conducting experiments using a non-human primate laser injury model in the macula, recapitulating many of the features of human CNV. For PDT, we needed a laser that could provide visualization and deliver laser light to the macula at the back of the eye with the right power and spot size. The optical bench laser used at Massachusetts General Hospital to treat experimental ocular tumors produced too large a spot size and had no ability to focus on the macula. We required a laser with slit lamp delivery typical of ophthalmic lasers, but able to produce a larger spot size and lower power. The group at Coherent, including David Dewey and George Marcelino, worked with me to build the first device, and they built early and improved prototype lasers with the necessary specifications that were used in our early studies. Once we moved to clinical trials, Coherent was joined by Zeiss to develop lasers for clinical use. QLT Phototherapeutics provided the photosensitizer, benzoporphyrin derivative, although in a form that had to be dissolved in dimethyl sulfox-ide rather than the liposomal form verteporfin, being used in dermatologic clinical trials.

The first experiments were performed using an irradiance of 150 mW/cm^2 —the same irradiance that was used in

the skin cancer clinical trials and in experimental choroidal melanoma. With this irradiance, treatment times were very long at 16 minutes, and it was difficult to focus using the low luminance setting of the slit lamp and the dim aiming beam. While these parameters worked experimentally, such a long treatment time for PDT with the difficulties in maintaining focus and localization, was not going to be practical for clinicians treating patients. Knowing that the choroid is a heat sink that could ameliorate any increased temperatures, we decided to try higher irradiance —all the way up to 1800 mW/cm^2. The experiments were a success, with no complications, and we were still able to achieve CNV closure as determined by fluorescein angiography and histopathology.[2] Importantly, we found that when treating normal retina, we could use the same parameters and avoid significant damage to the outer retina. From these experiments, we selected 600 mW/cm^2 for the clinical application, and this was the irradiance that was used in the nvAMD and pathological myopia clinical trials, and approved for clinical use.[3] The clinical trials proceeded from 1995 to 2000 and ultimately led to FDA approval for verteporfin, the first pharmacologic treatment for nvAMD.[4]

Research and Development of Anti-VEGF Therapy

During the same time period that we were developing PDT, we were also investigating the molecular drivers of neovascularization in CNV and ischemic retinopathies. The search for “Factor X” began with Michael-son’s observations in the 1940s that there must be a secreted factor released from ischemic retina to drive neovascularization of the retina, optic nerve, and iris.[5] In the 1970s, Judah Folkman’s laboratory identified tumor angiogenesis factor,[6] and Dr. Folkman published his seminal theory of tumor angiogenesis: that angiogenesis, or the recruitment and growth of new blood vessels, was required for tumor growth.[7] While Dr. Folkman’s theory was initially met with skepticism, he is now recognized for pioneering the concept of tumor angiogenesis, successfully elucidating tumor biology, and developing new cancer treatments.[8]

Napoleone Ferrara at Genentech was also initially seeking new treatments for cancer and cloned, sequenced, and characterized vascular endothelial growth factor (VEGF), recognizing its role in angiogenesis.[9] VEGF turned out to be the same molecule as vascular permeability factor, a very potent soluble permeability factor —50,000 times more potent than histamine[10] —that was previously identified and described by Harold Dvorak at Harvard Medical School.[11] As VEGF was a secreted endothelial cell mitogen and an angiogenesis factor that was regulated by hypoxia, a condition known to stimulate neovascu-larization in certain retinopathies, it met the characteristics of the elusive Factor X. Our two Boston groups —composed of ophthalmology clinician scientists and vision scientists —set out to explore the role of VEGF in ocular disease.

Anthony Adamis, Patricia D’Amore, David Shima, Evan Gragoudas, and our team demonstrated that VEGF protein levels correlated with neovascularization in vivo.[12] Lloyd Paul Aiello, George King, and their team showed that elevated VEGF protein levels also correlated with active retinal neovascularization in patients.[13] Next, we demonstrated that VEGF inhibition with an anti-VEGF antibody —the precursor of bevacizumab (Avastin) —provided by Napoleon Fer-rara at Genentech, prevented neovascularization in non-human primates.[14] Finally, we were able to show that injection of VEGF into normal monkey eyes led to iris neovascularization and neovascular glaucoma, recapitulating the pathology seen clinically with retinal ischemia.[15] VEGF was both sufficient and necessary for intraocular neovascularization —we had solved for Factor X.

Yet, despite the success of our VEGF studies, we struggled to obtain funding for our work. Genentech funded the VEGF discovery work of Napoleon Ferrara, while the National Institutes of Health (NIH) funded grants to support some of the initial studies, such as those performed in laboratories of Harold Dvorak, Patricia D’Amore, and George King. Additionally, while some of the more basic science studies in Drs. D’Amore’s and King’s laboratories were funded by NIH grants, the majority of our translational work was funded by small foundational grants and philanthropic funds. We applied multiple times for NIH funding for our nonhuman primate studies but were unsuccessful, primarily because of the use of nonhuman primates, even though they were the best available model and very predictive of human drug and light dose parameters for both efficacy and safety. Additionally, given the translational nature of these studies, it was generally felt that they should be industry supported.

Although the two groups had collectively demonstrated the key role of VEGF in ocular disease, and Genentech clearly had the best potential therapeutic, progress to clinical application foundered. Genentech remained primarily

focused on developing a treatment for cancer. Genentech may also have been negatively influenced by their part owner Roche (Basel, Switzerland), who had supported unsuccessful clinical trials in nvAMD using α-interferon.[16] Genentech considered licensing the intellectual property to another sponsor or trying to develop an ophthalmology program internally.

Two former Genentech employees, Marty Glick and John McLaughlin, saw the potential for anti-VEGF development in ophthalmology and left Genentech to pursue this path. Joined by three ophthalmologists —David Guyer, Samir Patel, and Anthony Adamis —they formed Eyetech Pharmaceuticals, licensing anti-VEGF aptamer technology from Gilead Sciences. Eyetech developed pegaptanib (Macugen) for AMD, and entered into clinical trials, progressing to Phase III trials with data demonstrating efficacy in slowing vision loss in all forms of nvAMD.[17] This was groundbreaking as the first demonstration of efficacy of an antiangiogenic therapy in ophthalmology. The vision outcomes with pegaptanib were similar to those achieved with verteporfin,[18] but achieved across a broader range of nvAMD subtypes.

The development and early promise of pegaptanib spurred interest at Genentech to enter the development path for their anti-VEGF agent ranibizumab (Lucentis), a recombinant, humanized monoclonal antibody fragment designed for intraocular use. Phase III results using ranibizumab for nvAMD were dramatic. Results from the 1-year MARINA trial[19] presented publicly in 2005, showed for the first time, that sustained vision improvement was possible in patients given intravitreal injections with anti-VEGF therapy (0.3 mg or 0.5 mg ranibizumab). Similar results were obtained at 2 years and after 1 year of treatment in the ANCHOR study,[20] comparing ranibizumab to verteporfin.

In addition to ranibizumab, Genentech had also developed bevicizumab, a full-length monoclonal antibody administered intravenously to treat cancer. In 2004, the US Food and Drug Administration (FDA) approved bevicizumab for the systemic treatment of metastatic colon cancer. Ranibizumab was created from the same parent mouse antibody as bev-acizumab and designed specifically for injection in the eye to block blood vessel growth in AMD. Since ranibizumab was going to be administered locally in the eye via intravitreal injection, we recommended that it be smaller in size than a full-length antibody, as we were concerned that a full-length antibody would not be able to cross the blood-retinal barrier. The same year that the ranibizumab results were presented (in fact, at the same meeting), Philip Rosenfeld presented a single case of a patient with nvAMD treated with intravitreal bevacizumab showing improvement in optical coherence tomography findings.[21] This was dramatic and unexpected, suggesting that the full-length antibody could penetrate the retina and be effective. This finding, combined with the extremely positive data from the large Phase III trials presented at the same meeting, provided a strong basis for anti-VEGF antibodies for AMD, and led to widespread off-label use of bevacizumab for nvAMD both before and after ranibizumab was approved by regulatory agencies. Genentech was placed in an awkward position, as ophthalmologists were keen to try bevacizumab, but Genentech was prohibited from promoting an off-label product. Moreover, Genentech had concerns about systemic safety of the full-length antibody based on their experience with systemic delivery —and, of course, Genentech had invested heavily in the development of ranibizumab for AMD.

With support from the National Eye Institute, Daniel Martin organized and led a multicenter trial called the Comparison of AMD Treatments Trials (CATT) to compare ranibizumab and bevacizuamb for the treatment of nvAMD. The CATT 1-year data showed that ranibizumab and bevacizumab had nearly identical effects on visual acuity, and that as-needed dosing did not lessen these effects.[22] The CATT 2-year results confirmed that ranibizumab and bevacizumab had similar vision outcomes over the 2-year period, although most of the vision change occurred in year 1.[23] Importantly, CATT (both 1-year and 2-year data) also showed similar rates in cardiac serious adverse events between the 2 drugs, which had been more of a concern for bevacizumab.[24] Similar findings comparing the safety and efficacy of ranibizumab and bevacizumab intravitreal injections to treat nvAMD were reported in the IVAN 1-year and 2-year studies.[25]

As for the government, its role should be to provide support for research at the basic and translational level. Federal funding is a somewhat limited resource —directing it towards later stage research and development limits the number of basic and translational projects that can be funded. As these studies are vital in feeding the research pipeline, it makes sense to focus federal resources here and then establish partnerships with the pharmaceutical

industry to drive large-scale clinical trials and product distribution.

We now have four FDA-approved anti-VEGF agents —brolucizumab (Beovu), aflibercept (Eylea), ranibizumab (Lucentis), and pegaptanib (Macugen), with additional agents in development. Bevacizumab is approved by for the treatment of colorectal and other cancers, and continues to be used off-label as a therapy for nvAMD and other conditions. These anti-VEGF therapies have revolutionized care for patients with AMD and other neovascular ocular conditions, and are administered millions of people worldwide.

Contributions of Industry, Academia, Nonprofits, and Government in Translational R&D for AMD

Partnership between the pharmaceutical industry and academia is essential for the development of approval-level clinical trials and deployment of new therapies to patients. Expertise on both ends —research and patient care —is important for proper study design and a critical factor in patient selection, dosage, and route of administration in early phase clinical trials. In the case of anti-VEGF therapy, the method of drug delivery was initially uncertain. Intravenous administration was considered, but experience with the Roche clinical trials of α-interferon for macular degeneration made our Boston group skeptical about systemic treatments for patients with AMD. The a-interferon doses studied in the clinical trials for AMD were similar to those used with acceptable side effects for HIV-infected patients. However, AMD patients are a much older population, and systemic side effects were a major problem in the interferon clinical trials for AMD. Local administration, or an intravitreal injection directly into the eye, seemed to be a better approach than systemic drug delivery. While there was considerable skepticism among retina specialists about this route of administration, specifically regarding obtaining an adequate dose into the eye and the practicality of repeated intravitreal injections, clinical trials were designed using monthly intravitreal injections. As described above, these trials were dramatically successful —accepted by clinicians, and importantly, by patients fearful of blindness without treatment.

In addition to the partnership between industry and academia, another important aspect in research and development is the role of clinician scientists, as they are able to bridge the gap between research and patient care. In our PDT work, as a clinician scientist, I was able to understand the practical requirements for an effective treatment. Long treatment times at a low irradiance (150 mW/cm^2) worked at an experimental level, but not as a practical treatment for patients. Recognizing this, we were able to modify our approach and use a higher irradiance (600 mW/cm^2) to lessen treatment times and still obtain CNV closure without damage to the outer retina. Ultimately, this higher irradiance was used in AMD clinical trials and approved for clinical use.[26]

It is also essential to recognize and value the contributions of different individuals and groups early in the process, especially in regards to intellectual property for development of technologies or therapies. Communicating with collaborators and making arrangements regarding invention disclosures, licensing, authorship, and other important details will help reduce the number of disagreements among interested parties. In the case of verteporfin, a lack of reasonable agreements at the outset led to more than a decade-long legal battle between Mass Eye and Ear and QLT/Novartis. Litigation and appeals over PDT ultimately resulted in a $126 million judgment for Mass Eye and Ear, and an ongoing royalty of about 3% of all sales worldwide as long as the drug is used.[27]

While the academic setting is supportive for transla-tional research, obtaining funding for these studies is difficult. Funding from federal sources, such as NIH, is often directed at earlier stage basic science studies or later stage clinical trials, leaving translational work underfunded. Our group was never able to obtain NIH funding for our PDT work and only obtained federal funding for our VEGF work at the basic science level. Moreover, even when researchers and clinician scientists have potential therapeutic treatments and approaches with good pre-clinical data, the pharmaceutical industry is hesitant to invest, asking for additional proof-of-concept studies in patient populations. Unfortunately, this space is difficult for academic researchers and clinician scientists to navigate, and those who do tend to seek out support from start-up companies and individual investors. The end result of this approach is that a number of promising therapeutic approaches end up “dying on the vine” or are studied in an incomplete and haphazard manner, never reaching clinical trial. Thus, there are likely many opportunities and potential treatments on which we are missing out.

However, once established positive proof-of-concept studies in patients have been obtained for a potential therapy,

the pharmaceutical industry is necessary for conducing large clinical trials, and if successful, product distribution. Successful Phase I and II studies often partner the pharmaceutical industry and academia, as clinician scientists are a valuable resource for helping to guide study design as mentioned above. However, on reaching Phase III trials, the pharmaceutical companies now routinely conduct these studies in community-based practices as they benefit from the more streamlined processes offered there. Exceptions for this would be in the case of gene-based therapies for inherited retinal disorders, as these are more complex, require a unique patient population, and specialized instrumentation that tends to be housed within academic medical centers.

As for the government, its role should be to provide support for research at the basic and translational level. Federal funding is a somewhat limited resource —directing it towards later stage research and development limits the number of basic and translational projects that can be funded. As these studies are vital in feeding the research pipeline, it makes sense to focus federal resources here and then establish partnerships with the pharmaceutical industry to drive large-scale clinical trials and product distribution. In 2008, the UK government boosted translational research when the National Institute for Health Research (NIHR) announced 12 new hospital-based biomedical research units, funding them with up to £1 million per year.[28] To further transform health research, the UK also aligned two previously separate funding entities —the Medical Research Council (MRC) and the NIHR —to coordinate basic discovery and clinical evaluation. As part of this initiative, the MRC is working to expand partnership opportunities with industry, while the NIHR is setting up large networks for clinical trials.[29]

Despite supporting initial research and development of potential therapeutics, the government should not try to keep an “equity” position in these inventions or therapies. Their role should be to support research than can end debilitating and/or lethal conditions. Instead, the U.S. government, could work at the other end of the pipeline, and negotiate drug prices as other countries do. This may help avoid a problematic debate on which disease areas are the most important and deserve funding and research effort. Additionally, adoption of a “one size fits all” approach is unnecessary, as there will be some therapeutic areas, such as antibiotics, where government mission-oriented investing may make sense.[30]

Conclusion

The development of pharmacologic treatments for retinal diseases has completely revolutionized the field of ophthalmology, improving vision outcomes and quality of life for millions of people. PDT and anti-VEGF drugs are among the most important translational research achievements in ophthalmology, yet this work was primarily funded by small foundational grants and philanthropic funds, as attempts to obtain federal funding for these projects were unsuccessful. To maximize the full potential of translational research and development, it is essential to establish a partnership between the pharmaceutical industry and academia, utilize and develop clinician scientists, recognize and value the contributions of different individuals and groups early in the process, and establish stable funding sources for these studies. The government should provide support for research at the basic and translational level and facilitate industry-academic collaboration, rather than increase regulatory burden.

Note

Presented by Dr. Miller as part of a Radcliffe Institute for Advanced Study Academic Ventures Exploratory Seminar entitled “US Government’s Contribution to Transformative Drug Development” held on December 10-11, 2018, in Cambridge, MA. The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of their affiliated institutions.

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DETAIL

Subjek:	Laboratories; Ophthalmology; Diabetes; Vascular endothelial growth factor; Macular degeneration; FDA approval; Lasers; Diabetic retinopathy; Experiments; Retina; Cancer therapies; Permeability; Skin cancer; Edema; Clinical trials; Disease; Medical treatment; Photodynamic therapy; Research &development--R &D; Angiogenesis
Ketentuan indeks bisnis:	Subjek: FDA approval
Perusahaan / organisasi:	Nama: Genentech Inc; NAICS: 325414, 541714
Pengidentifikasi/kata kunci:	Ophthalmology; Macular degeneration; Photodynamic therapy; Retina; Translational research; Macular Degeneration; AMD; VEGF; PDT; Industry; academia
Judul:	Opportunities and Challenges in Translational Research: The Development of Photodynamic Therapy and Anti-Vascular Endothelial Growth Factor Drugs
Pengarang:	Christina Kaiser Marko; Miller, Joan W

Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	19-24
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.4
ID dokumen ProQuest:	2730846993
URL Dokumen:	https://www.proquest.com/scholarly-journals/opportunities-challenges-translational-research/docview/2730846993/se-2?accountid=211160
Hak cipta:	
Terakhir diperbarui:	2023-11-28
Basis data:	Public Health Database

The Future of the Pharmaceutical Industry: Beyond Government-Granted Monopolies

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ABSTRAK (ENGLISH)

Just as tariffs lead to economic distortions and provide incentives for corruption, so do patent monopolies on prescription drugs, except the impact is often an order of magnitude larger.

TEKS LENGKAP

Introduction

We all know the story of why tariffs are bad. By raising the price of a product 10 or 25 percent (the typical range for tariffs among wealthy countries), in addition to raising the costs to consumers, the tariff also leads to bad outcomes in the form of corruption and wasted resources. For example, the tariffs that the Trump administration imposed on imported steel led to major battles over exemptions from these tariffs by various steel users.[1] There is always the risk that these exemptions will be decided based on political, rather than objective economic, criteria.

In public debates the distortions associated with patent monopolies are rarely seen as comparable to the distortions resulting from tariffs, but they are nonetheless of the same type. Patents typically raise the price of a protected drug thirty or forty-fold above the free market price and, in some cases by more than 100-fold. For example, when the Hepatitis C drug sofosbuvir was selling for almost $50,000 in the United States, a generic version was available in India for less than $400.[2] This is equivalent to tariffs of several thousand percent or even more than 10,000 percent. Just as businesses take steps to avoid trade tariffs, drug manufacturers take steps to abuse patents. The large gap between the patent monopoly price and the free market price encourages a wide range of rentseeking behavior, which has substantial economic costs as well as public health consequences.

The most troubling form of rent-seeking behavior in the pharmaceutical industry is misrepresenting the safety and effectiveness of drugs in order to maximize monopoly profits. Since drug companies have access to their data, and no one else does, they are often able to get away with these sorts of misrepresentations. They are helped by the fact that they can use a portion of their monopoly rents to pay for and promote statements of researchers and doctors touting the benefits of their drugs. The most notorious case of misrepresentations to promote drugs is with the new generation of opioids, where several major manufacturers were alleged to have deliberately downplayed their addictiveness in order to promote sales.

The drug companies also try to maximize their monopoly profits by using lobbying expenditures and campaign contributions to enlist the support of politicians, who can then support favored treatment for drugs in public programs like Medicare and Medic-aid.[3] They may also put in place laws or rules which require private insurers to pay excessive prices for drugs of little value.

Drug companies further utilize strategies to forestall generic competition.[4] They also often file patents of dubious validity. In these battles with generic manufacturers there is a fundamental asymmetry.[5] The brand manufacturer is fighting to be able to sell the drug at the monopoly price whereas the generic company is looking to sell the drug at the free market price. In this context, the brand manufacturer has an enormous advantage since they have so much more at stake.

These are well-known reasons for why patent monopolies have negative consequences in the prescription drug market. However, precisely because patent monopolies give so much power to the pharmaceutical industry, it is

difficult to envision a direct attack at the federal level on the patent-financed development of drugs. As an alternative, there are steps that can be taken at the state or local level, or by private non-profits, to try to undermine the system.
Patent monopolies also distort the research process itself. Drug companies will often spend large amounts of money developing drugs that essentially duplicate existing drugs, with the hope of getting a portion of the patent rents. While it is generally of some benefit to have multiple treatments available for a condition (some people may react poorly to a specific drug), in general, research money would be better spent on developing drugs for conditions where there is no effective treatment. There is also relatively little money devoted to developing treatments for conditions that primarily affect lower income people both in the rich countries and the developing world.
These are well-known reasons for why patent monopolies have negative consequences in the prescription drug market. However, precisely because patent monopolies give so much power to the pharmaceutical industry, it is difficult to envision a direct attack at the federal level on the patent-financed development of drugs. As an alternative, there are steps that can be taken at the state or local level, or by private non-profits, to try to undermine the system.

Working Around U.S. Patent Monopolies

Since the United States is the only wealthy country in the world that gives drug companies virtually unchecked patent monopolies, this means drug prices are considerably higher than in any other country.[6] This creates enormous opportunities for savings by getting around U.S. monopolies and allowing patients to get drugs at lower prices elsewhere. This means either bringing lower cost foreign drugs into the United States or having patients in the United States go overseas to take advantage of lower cost drugs.
Importing drugs into the country is the more efficient route, since it is much cheaper to transport drugs than people. However, large-scale importation is blocked by federal law, and even importation for personal use is illegal.[7] (The Health and Human Services Secretary does have the authority to allow importation from Canada). As a practical matter, the Food and Drug Administration has generally opted not to take enforcement measures against patients who import modest quantities of drugs (less than a three-month supply) for personal use.[8]
While state and local governments may run into legal obstacles if they were to directly promote importation, for example by keeping a list of high-quality mail-order pharmacies in other countries, they could take more modest measures which would almost certainly be within the law. For example, they could publish price lists showing the relative cost of drugs in the United States and a range of other countries. This would simply be providing information that allows people in the United States see how much more money they pay for drugs as a result of unchecked patent monopolies.
This is in fact the sort of action that could be undertaken by any organization and promoted by state and local governments who want to better inform their citizens on why drug prices are high. Specifically, if there were one website that catalogued prices for various drugs in countries around the world, any state or local government would be able to have this information posted on their own website to broaden public awareness of the price differences. If, based on this information, people decided to seek out lower cost drugs from other countries, that would be entirely their own choice.
The other route, of sending people to other countries to take advantage of lower drug prices, is considerably more costly, but may still make sense in the context of the large price differences for many important drugs. With the cost of many drugs in the United States 100 times or more above the cost of generic versions in other countries, it may be possible to pay for a patient's travel, including a family member, and still save money on the cost of treatment. The simple arithmetic suggests that such situations may not be rare. For example, the list price for the Hepatitis C drug Solvaldi was originally $84,000. High quality generic versions were available in India for less than $1,000.[9] If two round-trip airfares cost $6,000 and accommodations could be arranged for $100 per night for a 3-month course of treatment, this would mean total travel expenses of $15,000. With savings from buying the drug in India of $80,000, this would allow for net after-travel savings of more than $65,000. This could be split by a state government health insurance program (Medicaid, SCHIP, or public employee insurance) and the patient.
States could also structure their insurance regulations and liability rules to facilitate this practice among private insurers. This would mean setting up guidelines, presumably with some list of approved providers in other countries,

with whom insurers could arrange care. It could also adjust rules on malpractice to ensure that patients had clear recourse if something goes wrong with their treatment.

This not simply a hypothetical scenario. Utah, one of the most Republican states in the country, has put in place a system where it will pay patients, who are insured through its public employee health insurance program, to fly to San Diego and cross into Tijuana and buy drugs there. The state insurance plan will cover the transportation cost and give the patient $500 for their troubles.[10] This is not being done to make a political point, this is being done to save the state money. In 2019, 20 patients took advantage of the program for a savings to the system of $500,000. Both patients and the system's managers were very satisfied with the program.[11]

If this option proves popular with patients, it is likely that the state will look to expand it and that other states will also follow this path. In addition to saving money, allowing people the option to travel to countries where drugs are much cheaper is also a way to drive home the point that drugs don't have to be expensive. This realization is likely to be increasingly important as more people find themselves in a situation where they or a family member need a drug with an extremely high price in the United States.

While the industry has raised safety issues, regulatory agencies in many countries are at least as stringent as the Food and Drug Administration in ensuring quality. Using designated pharmacies should ensure that patients traveling abroad will be getting drugs that are safe and effective.

Towards Patent-Free Drugs

It would be a huge step forward if drug companies had more difficulty charging high patent-protected prices for their drugs. But this is only part of the long-term story for cleaning up the prescription drug market. While the industry exaggerates the costs associated with developing drugs, it is costly to bring a drug through the development process, clinical testing, and the FDA approval process. If drug companies are not allowed to charge some premium over a free market price, they will be unable to recoup these costs. If we are going to continue to develop new drugs, but not have drug companies don't rely on patent monopolies to finance their research, we will need some alternative source of research funding.

In the long-run the federal government would ideally pick up the cost, either through a system of direct funding that could look like an expanded National Institutes of Health or a patent buyout system under which the government would buy up drug patents and place them in the public domain so new drugs could be sold as generics.[12] However this sort of transformation of funding mechanisms is not likely to happen any time soon, since the pharmaceutical industry would likely use its full power to block the transformation of a system that is hugely profitable for it. In the meantime, there are possibilities for incremental progress either through the actions of state governments or private philanthropies.

In the case of state governments, a large amount of research at public universities is already directly or indirectly supported by state governments. States could look to increase this funding with the idea that the drugs developed would be available to the states' residents at generic prices. This would mean that any manufacturer could produce the drug to sell to the state's residents. The state could make this a condition for research at state supported universities. In order to allow it to recoup the costs of the research, the research could still be patented with the drugs developed selling at patent protected prices elsewhere. (Existing pharmaceutical companies could be contracted to market the drug outside of the state.)

Having low prices in one state, or a consortium of states, if several states agreed to act collectively, will naturally lead people to come to these states to take advantage of the low prices. That has the disadvantage of reducing the potential profits from selling the drug at the patent protected price in other states and countries. At the same time, it does help to both make the new drug available to a larger group of people at a low price, and it also helps to drive home the point that government intervention in the form of patent monopolies is the reason drug prices are high. In short, the outcome of people flocking to a state that pays for research to take advantage of its low drug prices should not be viewed as something to be feared.

There also is the advantage of a state paying for research that it can be a model for disclosure of results. This is especially important for clinical trials. While there have been efforts to increase disclosure of information on clinical

trials in recent years, the fact is most drug companies only make available the most minimal information about their outcomes. At present, they only disclose summary results of their trials.

Ideally, there should be a full breakdown of the results for each patient, subject to the limits required to ensure anonymity, that would allow any researcher to independently analyze the results of the trial. This would allow researchers to determine not only the effectiveness of the drug in aggregate, but also to assess differences by sex, age, prior health conditions, and other factors. This is actually now being done with the YODA project, which does provide detailed data to researchers on the outcomes of clinical trials.[13] One major manufacturer, Johnson and Johnson, is now providing its data through this channel.

There is no legitimate reason that this information should be kept secret. The fact that it is generally not public is a serious impediment to doctors trying to determine the best treatment for their patients. If universities used public funds to carry through clinical trials, they could be required to have full disclosure. This would be a benefit for those seeking a full analysis of these trials, but also provide a benchmark that could be used to demand more disclosure from industry funded trials.

The other potential source for funding the development of new drugs is philanthropic organizations. In this case, there is the advantage that there is no need to show a direct return for the money spent. In principle, an organization devoted to public health would be advancing its goals by directly funding research that led to the availability of important new drugs at a low cost.

There is already precedent for this sort of philanthropic support with the Drugs for Neglected Diseases Initiative.[14] DNDI has developed a number of effective new drugs and treatments on a budget that is less than has been estimated as the cost for developing a single drug in the United States. These treatments have benefited tens of millions of people in the developing world. It would be a small, but tremendously important step, to rely on philanthropic contributions to develop drugs that would be produced as generics in the wealthy countries.[16]

It is worth mentioning that most of DNDI's work has been devoted towards developing new uses of existing drugs or modifications of existing drugs, as opposed to developing altogether new drugs. However, this fact does not undermine the importance of its example.

First, if we can achieve substantial health benefits from exploring new uses of existing drugs, then we absolutely should want research in this direction. The fact that companies may not be able to get a patent for new uses discourages such research under the current system. The other point is that DNDI researchers have been able to innovate without the motivation of patent monopolies. This should help undermine further the rather odd notion that pharmaceutical research can only be properly motivated with the lure of patent monopolies.

If even a small number of successful drugs could be developed with philanthropic support, it could provide an incredibly powerful example. It would be a blunt reminder that drugs are cheap to produce, it is only patent monopolies and related protections that make them expensive. Also, as with state supported research, in the case of drugs developed with philanthropic support, all results could be put in the public domain, including the raw data from clinical trials.

Conclusion: The Waste and Corruption from Patent Monopolies in Prescription Drugs Offers Opportunities

In spite of its corruption and inefficiency, it would be difficult politically to directly challenge the patent system for financing prescription drug research at the federal level. However, the fact that drug prices in the United States are so far above their free market price offers enormous opportunities for smaller scale attacks on the system.

These attacks can take two main forms. The first involves facilitating the purchase of drugs outside the United States. Since patent protected drugs in the United States can typically be purchased at far lower prices in other countries, there are large potential gains from either bringing foreign drugs into the United States or sending patients overseas to take advantage of lower priced drugs.

The other form of attack is directly supporting the development of new drugs that can then be sold at generic prices from the day they are approved by the FDA. This can be done either by state governments, which already fund a substantial amount of research through their university systems, or by a private philanthropy. In the former case, it should be possible to design mechanisms that would allow the state to recover its additional spending through lower

prices to its residents, as well as a share of patent rents for drugs sold elsewhere.

In both cases, the example of new drugs being developed outside the patent system, and then sold at generic prices, should be an important model for an alternative system for supporting drug development. The fact that the current system does such a poor job of meeting health needs provides a large amount of room for improvement.

Note

The author has no conflicts of interest to declare.

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DETAIL

Subjek:	Patients; Drug prices; Market prices; Profits; Tariffs; Campaign contributions; Pharmaceutical industry; Prescription drugs; Cost control; Monopolies; Free markets; Corruption; Hepatitis; Health insurance
Ketentuan indeks bisnis:	Subjek: Drug prices Market prices Profits Tariffs Pharmaceutical industry Cost control Monopolies Free markets Health insurance
Lokasi:	United States--US; India
Pengidentifikasi/kata kunci:	Patents; Monopoly; Patent; Pharmaceutical industry; Clinical Trials; Open-Source; Drug Prices; Drug Development
Judul:	The Future of the Pharmaceutical Industry: Beyond Government-Granted Monopolies
Pengarang:	Baker, Dean
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	25-29
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles

Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	ht tps://doi.org/10.1017/jme.2021.5
ID dokumen ProQuest:	2730846990
URL Dokumen:	https://www.proquest.com/scholarly-journals/future-pharmaceutical-industry-beyond-government/docview/2730846990/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

Characteristics of Clinical Trials Launched Early in the COVID-19 Pandemic in the US and in France

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Link dokumen ProQuest

ABSTRAK (ENGLISH)

Based on hierarchical classification and logistic regression of early US and French COVID-19 clinical trials we show that despite the registration of a large number of trials, only a minority had characteristics usually associated with providing robust and relevant evidence.

TEKS LENGKAP

The SARS-Cov-2 pandemic has challenged world health care systems by causing a novel COVID-19 disease with no known treatments. In response, investigators around the world launched clinical trials to evaluate the efficacy and safety of various products hypothesized to alleviate the symptoms associated with the disease and reduce the mortality rate.[1]

The ecosystem of biomedical research involves multiple stakeholders with diverse interests involved in the design, conduct, and funding of clinical trials.[2] The characteristics of the trials organized in response to the pandemic strongly influence the nature of the evidence that can guide clinical and regulatory decision-making. The best evidence emerges from clinical trials that adhere to high levels of rigor. For example, blinded and randomized trials are considered the gold standard for trial design because they are most likely to minimize bias.[3] However, other trial characteristics also influence the relevance of the evidence and the trials to support decision-making, such as the primary outcome, comparator (e.g., active vs. placebo), population studied, or source of funding.[4]

Some reports have evaluated the nature of the clinical trials that emerged in the wake of the recognition of the SARS-CoV-2 pandemic. One included 244 studies available worldwide by early April 2020, described interventions (treatment arms and preventive or curative objective), size, randomization and blindness, status of recruitment, and country, with a description of the trials per therapeutic class.[7] A second by authors affiliated with the European Medicines Agency on the trials registered in the European database of clinical trials,[6] presenting however only limited details to support the comments of the authors. The third one reviews trials registered to test hydroxychloroquine only.[7] The fourth one includes 201 trials registered in the WHO's International Clinical Trials Registry Platform by the end of March 2020.[8]

However, none of these studies evaluates the rigor of the design of the trials being organized. To understand how well the international scientific community employed the principles of trial rigor in its initial response to the SARS-Cov-2 pandemic, we reviewed the characteristics of the clinical trials organized in France and the US. Analyzing the landscape of clinical trials can help judge how the clinical research community responded to the early outbreak and can help policymakers alter the response to the ongoing pandemic.

MethodsDatabase and Extraction

ClinicalTrials.gov,[9] a US-based clinical trials registry, was searched on May 8, 2020 to identify trials related to COVID-19, using the search tag provided by the registry. We used the registry ClinicalTrials.gov as the data source for several reasons, including the requirement by the FDA to register clinical trials in the database before the enrollment of patients in the US, and the real-time visibility of the registered trials in this primary database. The clinical trials organized in France and the US were selected as these countries were two of the hardest-hit with the virus and the two in the world registering the most clinical trials linked to the management of COVID-19 in ClinicalTrials.gov at the time of the study. We included only trials classified as "interventional (clinical trial)" originating from the US and France using the map display provided by the database. We excluded trials of procedures, blood sample collections, medical devices, diagnosis tests, and behavioral.

From qualifying trials, we extracted the following variables that were available in the database: status, results, interventions, outcome measure, phases, enrollment, funding source, study design, and primary completion date.

Figure 1

Data were extracted from the database, coded, analyzed, and organized using Microsoft Excel (Microsoft, Redmond, WA). The coding rules were discussed and defined by the four authors. A quality check was performed to ensure the correct classification of the observations.

Definition of the Variables

We assigned the variables extracted from the database to the following mutually exclusive categories:

•country in 3 categories (France, US, both countries),

•interventions in 3 categories (drug, product of human origin, other),

•status in 4 categories (recruiting, not yet recruiting, enrolling by invitation, active, not recruiting),

•enrollment in 2 categories (below or above the median),

•funding source in 3 categories (industry, mixed, other), with “industry” standing for the industry appearing as the sole funding source, “other” standing for no industry appearing among the funding sources and “mixed” standing for the industry appearing among other funding sources,

•primary purpose of the intervention in 3 categories (prevention, treatment, other),

•primary outcome of the trial in 3 categories (feasibility, safety, efficacy), in which any study including at least one efficacy outcome among the primary outcomes was classified as efficacy,

•design quality in 3 categories prone to discriminate the strength of evidence (low [non-comparative or not randomized], medium [randomized and open-label or single-blind], or high [randomized and either double, triple, or quadruple blind]),

•primary predicted completion date in 4 years (2020, 2021, 2022, 2023).

We developed three dichotomous variables related to the drug being tested:
•the drug under evaluation includes hydroxychloroquine/chloroquine (yes/no),

•the trial includes an arm with an active comparator (yes/no), in which placebo, standard of care and a different dosage of the similar drug are not considered active comparators,

•the trial includes at least one drug that was not approved on the market before the pandemic (yes/no).

For trials measuring the efficacy of the treatment for COVID-19, we classified the nature of the outcome in 4 categories related to the direct or indirect effect of the treatment on the clinical outcome (mortality, other clinical outcome, time to clinical evolution, surrogate), in which other clinical outcome includes any other clinical endpoint than mortality, including an ordinal scale of severity of COVID-19, or a type of care that is directly related to clinical status (e.g. admission to hospital or intensive care unit) or a surrogate endpoint that defines a clinical status (e.g. O_2 saturation above or below 93%). Time to clinical evolution includes the outcomes defined as the number of days without ventilation. Surrogates include viral load measure and O_2 levels without reference to a clinically meaningful threshold.

Descriptive Analysis

We presented data relative to all trials, with a focus on studies prone to guide clinical practice or regulatory approval by aiming to show efficacy in the treatment or prevention of COVID-19. We conducted a sub-analysis focused on trials likely to provide the highest level of evidence on efficacy defined as combining a “high” design, more than 200 patients enrolled, recruiting or enrolling by invitation and, for the trials evaluating the efficacy of treatment, a primary outcome of either mortality or another clinical endpoint.

Statistical Analysis

The exploratory analysis combined a Factor Analysis of Mixed Data (FAMD)[10] and a Hierarchical Classification on the Principal Components (HCPC),[11] first to select a set of variables (dimension and sub-dimensions) that characterized the clinical trials and second to cluster clinical trials based on commonalities and differences relative to these dimensions.[12] The FAMD and HCPC were implemented using FactoMineR packages from R software and

R software[13] (see Supplemental Digital Content 1, that details the FAMD and the HCPC).

A logistic regression was performed to estimate if variables used in the descriptive analysis and different clusters of clinical trials identified in the HCPC had differential correlations with the design of highest rigor. The logistic regression was performed using R software (see Supplemental Digital Content 2 for details of the logistic regression).

This study was not submitted for institutional review board review as it was based on publicly available data and involved no health records (45 Code of Federal Regulations [CFR] 46.102).

Results

There were 1,324 entries in the original search, of which 200 trials met our cohort entry criteria: 151 in the US, 44 in France, and 5 in both, with more trials including drugs or related in the US compared to France (Figure 1). French trials were less often classified as having high rigor compared to the US (30% vs. 47%), much more often classified with a medium rigor (64% vs. 26%), slightly more often funded outside industry (86% vs. 74%), and much more often had a primary completion date in 2020 (89% vs. 53%). The industry funded alone 2% of the trials in France vs. 15% in the US, and all 5 binational trials.

Characteristics of New vs. Repurposed Drug Trials

As seen in Table 1, most studies (73%) evaluated the repurposing of drugs that were already on the market and were funded without the participation of industry (75%). About one-third (34%) were registered but not yet described as recruiting. Slightly more studies registered as recruiting were funded outside industry compared to the whole set of studies (71% vs. 75%) and studied a drug non-approved for any indication (32% vs. 28%).

Table 1

Number of trials	France	US	US-FR[a]	Total
All trials	44 (100%)	151(100%)	5	200 (100%)
Intervention				
Drug	39 (89%)	127 (84%)	5	171 (86%)
Product of human origin	4 (9%)	20 (13%)	-	24 (12%)
Other intervention [b]	1 (2%)	4 (3%)	-	5 (3%)
Status				
Recruiting	22 (50%)	93 (62%)	5	120 (60%)
Not yet recruiting	20 (45%)	45 (30%)	-	65 (33%)
Enrolling by invitation	-	12 (8%)	-	12 (6%)

Active, not recruiting	2 (5%)	1 (0%)	-	3 (2%)
The trial includes at least one experimental (unapproved) drug				
Yes	6 (14%)	47 (31%)	2	55 (28%)
No	38 (86%)	104 (69%)	3	145 (73%)
Funding source [c]				
Industry	1 (2%)	23 (15%)	5	29 (15%)
Mixed	5 (11%)	17 (11%)	-	22 (11%)
Other	38 (86%)	111 (74%)	-	149 (75%)
Primary purpose of the intervention *outcome of the study* [d]				
Prevention	3 (7°%)	23 (15%)		26 (13%)
efficacy	3	18		21
feasibility		1		1
safety		4		4
Treatment	41 (93%)	126 (83%)	5	172 (86%)
efficacy	41	110	5	156
feasibility		4		4
safety		12		12
Other purpose [e]		2		2
Trials evaluating the efficacy of prevention	**3 (7%)**	**18 (12%)**	-	**21 (11%)**
Nature of the drug	Drug	3	16	19
Product of human origin		2		2
Status				
Enrolling by invitation		3		3

Not yet recruiting	1	6		7
Recruiting	2	9		11
Trial includes at least one experimental (unapproved) drug				
No	3	15		18
Yes		3		3
Funding source[c]				
Industry		2		2
Mixed	1	2		3
Other	2	14		16
Most frequent drug under evaluation [f]				
chloroquine/hydroxychloroquine	2	11		13
Design [g]				
High	2	11		13
Medium	1	2		3
Low		5		5
Trial includes an active comparator [h]				
Yes	1			1
No	2	18		20
Primary completion date				
2020	3	12		15
2021		6		6
Enrollment				
1-199		3		3

200+	3	15		18
Trials evaluating the efficacy of treatment	**41 (93%)**	**110 (73%)**	**5**	**156(78%)**
Nature of the drug				
Drug	36	95	5	136
Product of human origin	4	14		18
Discontinuation of a drug therapy	1	1		2
Status				
Active, not recruiting	2	1		3
Enrolling by invitation		6		6
Not yet recruiting	19	33		52
Recruiting	20	70	5	95
The trial includes at least one experimental (unapproved) drug				
No	35	78	3	116
Yes	6	32	2	40
Funding source [c]				
Industry	1	19	5	25
Mixed	4	12		16
Other	36	79		115
Most common drugs under evaluation [i]				
chloroquine/hydroxychloroquine	11	30	1	42
azithromycin	8	16		24
tocilizumab	2	5	1	8
remdesivir	1	3	2	6

lopinavir/ritonavir	2	3		5
interferon	1	4		5
Design [g]				
High	11	55	2	68
Medium	27	36	3	66
Low	3	19		22
The trial includes an active comparator [h]				
Yes	9	18		27
No	32	92	5	129
Primary completion date				
2020	36	56	5	97
2021	3	47		50
2022	1	5		6
2023	1	2		3
Enrollment				
0-199	21	55		76
200+	20	55	5	80
Primary outcome [j]				
Mortality	7	16		23
Other clinical outcome	17	55	4	76
Time to clinical evolution	9	20		29
Surrogate endpoint	8	19	1	28

Among the trials including a non-approved drug (n=55), 21 were funded by industry (19 in the US, 2 in both countries), 9 had a mixed funding source (2 in France, 7 in the US), and 25 were funded outside the industry (4 in France, 21 in the US). Among trials with efficacy as trial outcome (vs. safety or feasibility) (n=43), 19 were funded by the industry (17 in the US, 2 in both countries), 7 had a mixed funding source (2 in France, 5 in the US) and 17 were funded outside the industry (4 in France, 13 in the US).

Characteristics of Treatment vs. Prevention Trials

Among the 178 trials for which efficacy was the primary outcome, the primary purpose of the intervention under evaluation was treatment in 156 trials, prevention in 21 trials, and supportive care in 1 trial.

Among the 21 trials focusing on evaluating the efficacy of preventive strategies, we found no trials of vaccines, which were only in early phases evaluating safety; 18 were repurposing already-approved drugs, including chloroquine/hydroxychloroquine in 13 trials.

Among the 156 trials evaluating treatments for active COVID-19, 55 (35%) were not yet recruiting, 115 (74%) were funded without any support from the industry and 116 (74%) repurposed already-approved drugs. French trials are more likely to have mortality as a primary endpoint compared to the US (17% vs. 15%) less likely to have another clinical endpoint (41% vs. 51%), and more likely to compare several active treatment (22% vs. 16%). The countries are similar in the proportion of trials including hydroxychloroquine/chlo-roquine (73%).

Characteristics of Trials Based on Number of Patients Enrolled

The characteristics of the clinical trials vary when considering the number of individuals included in the trials instead of the number of trials, with a higher share of patients included in trials funded outside the industry, including hydroxychloroquine as a drug under investigation or in prevention trials (See Supplemental Digital Content 3, that mirrors Table 1, according to enrollment). However, this result was mainly driven by one large prevention trial aiming at enrolling 55,000 individuals.

Sub-Analysis

Thirty-one trials that evaluated the efficacy of a drug were classified as having a high-quality design, planned to enroll at least 200 individuals, were registered as either recruiting or enrolling by invitation, and for treatment trials, had either mortality or another clinical endpoint as primary outcome (See Supplemental Digital Content 4, the flow-chart of the selection of the sub-analysis). The subset of trials represents 9% of the trials in France and 17% of the trials in the US. Table 2 details the characteristics of the trials.

Table 2

Number of trials	France	US	US-FR[a]	Total
All trials in the sub-analysis	4	26	1	31
Intervention				
Drug	4	24	1	29
Product of human origin		2		2
Status				

Recruiting	4	26	1	31
The trial includes at least one experimental (unapproved) drug				
Yes		8		8
No	4	18	1	23
Funding source [b]				
Industry		8	1	9
Mixed	1	3		4
Other	3	15		18
Primary purpose of the intervention				
Prevention	2	7		9
Treatment	2	19	1	22
Trials evaluating the efficacy of prevention	**2**	**7**	**-**	**9**
Nature of the drug				
Drug	2	7		9
Status				
Recruiting	2	7		9
Trial includes at least one experimental (unapproved) drug				
No	2	7		9
Funding source [b]				
Mixed	1			1
Other	1	7		8
Primary completion date				
2020	2	4		6

2021		3		3
Most frequent drug under evaluation [c]				
chloroquine/hydroxychloroquine	2	6		8
Trial includes an active comparator [d]				
Yes	1			1
No	1	7		8
Trials evaluating the efficacy of treatment	**2**	**19**	**1**	**22**
Nature of the drug				
Drug	2	17	1	20
Product of human origin		2		2
Status				
Recruiting	2	19	1	22
The trial includes at least one experimental (unapproved) drug				
No	2	11	1	14
Yes		8		8
Funding source [b]				
Industry		8	1	9
Mixed		3		3
Other	2	8		10
Primary completion date				
2020	2	10	1	13
2021		8		8
2023		1		1

Most common drugs under evaluation [e]				
chloroquine/hydroxychloroquine	1	7		8
azithromycin		1		1
tocilizumab			1	1
lopinavir/ritonavir		1		1
The trial includes an active comparator [d]				
Yes		3		3
No	2	16	1	19
Primary outcome [j]				
Mortality	1	6		7
Other clinical outcome [f]	1	13	1	15
Severity of the disease [g]				
Mild		4		4
Moderate		5		5
Severe	2	9	1	12
Critical	1	4		5

Among the 31 trials, the 4 studies comparing several active treatments included only drugs that were already approved and were all funded by non-industry sponsors. The industry funded, partially or completely, 7 of the 8 trials including non-approved drugs and 6 of the 23 trials including only drugs that were approved for another condition before the pandemic, as well as 11 of the 15 studies not including hydroxychloroquine/ chloroquine, and 2 of the 16 including hydroxychloroquine/chloroquine.

Factorial Analysis and Taxonomy

The FAMD resulted in the selection of three factorial axes — which account for 31% of the variance — and the HCPC, based on the FAMD, in a 3-cluster partition (see Supplemental Digital Content 1, which details the FAMD and the HCPC).

Cluster 1 (59% of the trials) over-represents trials repurposing drugs already approved, evaluating the efficacy of a treatment against COVID-19, funded outside the industry, having a design of medium rigor, being registered in France, having either a clinical outcome that is not mortality or a surrogate outcome, comparing several active

treatments, evaluating a drug, not yet recruiting, and enrolling under the median number of patients.
Cluster 2 (19% of the trials) over-represents trials funded by the industry, evaluating an unapproved drug, recruiting, not including chloroquine or hydroxychloroquine, registered both in the US and in France, having a design of high rigor, having an outcome defined as time to clinical evolution, aiming at evaluating a treatment of COVID-19, evaluating a product of human origin, aiming at evaluating the efficacy of an intervention, not comparing a treatment to another active treatment, enrolling over the median number of patients, and having a primary completion year in 2023.
Cluster 3 (22% of the trials) over-represents trials not evaluating the efficacy of a treatment, evaluating an intervention for the prevention of COVID-19, having a primary outcome related to safety, having a design of low rigor, having a primary outcome of feasibility, being registered in the US, and not comparing a treatment to another active treatment.

Logistic Regression

The first logistic regression based on single variables shows that, at a statistical significance threshold of $p<0.05$, trials with efficacy as outcome (OR: 4.5), size of enrollment larger than the median (OR: 3.2), including a non-approved drug (OR: 2.8), and registered in France (OR: 2.5) were associated with the probability of the trial design being classified with a high rigor. With a statistical significance threshold of $p<0.10$, trials not including an active comparator (OR: 2.7) were also significantly associated with the highest level of rigor. Fit statistics show that the model explains 15% to 26% of the variance depending on the fit criteria (see Supplemental Digital Content 2, text that details the logistic regressions).
As seen in Table 3, a second logistic regression analysis, taking the clusters as explanatory variables, shows that trials belonging to cluster #2 were strongly associated with a high level of design compared to cluster #3 (OR: 3.4). Trials in cluster #1 were less likely to be classified with a design of high rigor than cluster #3, although the difference did not reach statistical significance. Fit statistics show that the model explains 6 to 9% of the variance depending on the fit criteria (see Supplemental Digital Content 2, text that details the logistic regression).

Table 3

Design = high	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Cluster #1	.749269	.2733587	-0.79	0.429	.3665141	1.531739
Cluster #2	**3.409091**	**1.611681**	**2.59**	**0.009**	**1.349661**	**8.610975**
_cons	.72	.2225668	-1.06	0.288	.3928335	1.319643
Number of obs	198					
LR chi2(2)	15.30					
Prob >chi2	0.0005					
Pseudo R2	0.0565					

Discussion

The large number of clinical trials registered in the early weeks of the pandemic illustrates substantial effort from investigators and regulatory authorities. However, only a fraction of the trials had a design with a high level of rigor that would be most likely to provide robust evidence to help clinicians and patients manage COVID-19.

The quantitative exploratory framework clusters trials by commonalities and differences, identifies and describes the characteristics that bring them in the same cluster, and analyzes the correlation between the rigor of the design and the clusters. Our analysis shows that trials most likely to be associated with a design of high rigor, as described in cluster #2, tend to evaluate the efficacy of a treatment, with a focus on unapproved drugs, compared to placebo or standard of care, and have outcome measured as a time to clinical evolution. These trials are more often funded by the industry compared to other trials of treatments for COVID-19. While these trials are designed to answer important questions, their profile will not provide evidence on critical dimensions. For example, the multiplication of rigorous trials would raise the chance to obtain reliable results about effective treatments. However, if several drugs show some efficacy, clinicians and policymakers would still require comparative data to determine which are the best. Optimally useful trials could therefore include several drugs, either in a direct comparative or adaptive design in which patients can switch enrollment from one arm to another based on the first observed results.[14] However, among trials registered in ClinicalTrials.gov, only a small fraction — 29 among the 178 trials evaluating efficacy — include several therapeutic options simultaneously. Only one trial was registered as cost-effectiveness analysis. Our results may suggest different broad patterns in the research strategy in the two countries: a publicly funded repurpose of several readily available drugs where double-blind designs are difficult and costly to run in the short-term, in France, vs. a commercial development of drugs already under development, in which doubleblind designs are crucial to obtain the regulatory endorsement of drugs not yet marketed, in the US. An analysis of the relative benefits and drawbacks of the different types of trials may support choices in a research strategy to address future pandemics.

Four characteristics of trials likely to provide relevant evidence were underrepresented in trials associated with the highest level of rigor. They include the comparison to another active treatment, an outcome defined as either reducing mortality or achieving clinical endpoint rather than reducing the time to achieve it, the repurposing of already-approved drugs, and independent funding. Trials including these features were overrepresented in cluster #1, which was not associated with high levels of rigor in trial design.

Our descriptive findings confirm previous work related to initial COVID-19 clinical trials.[15] The weakness of design in many trials has turned out to be even more problematic as clinicians, and health systems have started making decisions on the basis of the fast-track publication process before peer-review[16] and emergency use authorizations based on the limited available evidence.[17] The multiplication of trials also raises the question of the cost-effectiveness of the research itself. Although producing evidence from different independent investigators is worthwhile to ensure the reproducibility of the results, too much multiplication of similar studies risks becoming wasteful, especially if the trials do not reach a high level of rigor. The studies of hydroxychloroquine — and the even higher share of patients included in a single trial evaluating this drug — illustrate this risk, as a large number of trials, and competition among investigators undermines trial enrollment. Indeed, a French initiative to lead a European trial failed to include patients beyond France when other countries developed their own clinical trials.[18] Better cooperation in organizing the early research effort and incentives to link public funding to rigorous design might support a more cost-effective use of limited resources.

While the drugs under evaluation were private goods distributed by private companies, we found that a surprisingly low number of trials were funded by industry, while several studies were directly funded by the government or other

public funds. This may be because the most commonly studied drugs — hydroxychlo-roquine and chloroquine — are available generically or at low cost in many countries. Over four-fifths (83%) of subjects studied were included in trials funded outside the industry in the US and France. Moreover, the funding labeled as industry might include public money through the fiscal support of private research.[19] However, if a drug proves to be effective and safe enough to be used during the pandemic, there is no guarantee that the government or health insurance would be able to access the drug at a fair price. This is a particular issue for patent-protected drugs like remdesivir, which at the time of this writing remains limited to Emergency Use Authorizations and expanded access programs implemented by the firm itself in a limited number of countries.[20] Meanwhile, several other countries in the European Union have requested more extensive access.[21] Even in the case of low-price drugs, like hydroxychloroquine, the company selling a branded version of the drug in France without generic competition receives the benefit of the largely publicly funded research programs. Private companies should not be the only beneficiaries of the research they do not fund, and public support to a research program should be associated with the guarantee of fair access and price for drugs proved to be sufficiently effective and safe.

The large number of clinical trials registered in the early weeks of the pandemic illustrates substantial effort from investigators and regulatory authorities. However, only a fraction of the trials had a design with a high level of rigor that would be most likely to provide robust evidence to help clinicians and patients manage COVID-19.

An over-arching question relates to the production and diffusion of the results of the trials. The widespread availability of results will help to address the potential next waves of the current pandemic or future pandemics with other corona-viruses. Indeed, the repositioning of drugs has been facilitated by previous research on the previous outbreaks of Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). While results are supposed to be listed in ClinicalTrials.gov within a year after the primary completion date, the database has reported deficiencies in filing results,[22] and there is no guarantee that final results will become available for each trial, for several reasons, including difficulties in enrolling patients as planned given the progression of the pandemic.[23] We found that 33% of the studies were not recruiting in early May while the pandemic was showing signs of slowing down in France. It also includes the risk of the interruption of trials following results from other studies, as illustrated by the decision by the French Medicines Agency on May 26, 2020 to suspend enrollment in trials involving hydroxychloroquine,[24] or a possible lower publication rate of inconclusive or negative trials.[25] Legislators in the US and France should consider special laws to ensure that all de-identified data relating to COVID-19 trials be posted in a special registry.

Some inherent limits of our data should be considered. The SARS-CoV-2 outbreak is an evolving situation, and new trials are registered almost daily. Thus, our study focused only on the trials registered during the early months of the pandemic; later trials might show different patterns. Many trials were registered as not yet recruiting, but their status may have changed since the registration of the study. The selection of the studies does not include the trials registered as expanded access programs (the database displays 17 such studies on May 8, 2020) nor pharmacoepidemiology studies based on the use of drugs in routine practice that may give complementary answers about effectiveness and safety.[26] ClinicalTrials.gov database may not register all clinical trials, especially in France. It is however widely used in France, including by regulatory authorities.[27] Only a limited set of variables were documented in the database variables that were not included, among which the effective inclusion of patients and the outcomes of the study, would be worth to explore in future research.

Our analysis considered only protocols registered in the database. Thus, our classification of primary outcomes could not integrate any insight on the level of effect, and the meaning of a result could depend on how the outcome is measured. An example of this risk relates to the use of the 7-level ordinal scale promoted by the World Health

Organization, for which the change of one level may have a different clinical significance depending on the initial status of the patient.

Conclusion

In summary, we found a dynamic research landscape with numerous clinical trials registered in the two most active countries. However, the data collected raise concerns about the extent to which the trials will address unmet needs, as only a minority have rigorous designs likely to provide a high level of evidence. The most useful studies for comparative effectiveness, i.e., that evaluated several interventional strategies were all funded by non-industry-related sponsors, as were the studies with the largest enrollment. By contrast, studies of non-approved drugs were more likely to be funded by industry. Incentives for cooperation could help promote a more efficient research landscape with high-quality standards that would avoid unnecessary repetition, ensure the publication of the results, and guarantee fair access and price for drugs proved effective and safe based on publicly funded research.

Acknowledgments

The authors want to thank the member of the PORTAL team whose comments contributed to improving the first presentation of the research project.

Note

Additional materials are available online.

Support for this research was provided by The Commonwealth Fund. Dr. Kesselheim's work is supported by Arnold Ventures. The funders had no role in the design and conduct of the study; collection, management, analysis, interpretation, of the data; review, or approval of the manuscript; and decision to submit the manuscript for publication. The views presented here are those of the author and should not be attributed to The Commonwealth Fund or its directors, officers, or staff. Dr. Raimond in on unpaid leave from the position of senior project manager at the French Haute Autorité de santé. The authors have no conflict of interest to report.

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About This Column
Aaron Kesselheim serves as the editor for Health Policy Portal. Dr. Kesselheim is the JLME editor-in-chief and director of the Program On Regulation, Therapeutics, And Law at Brigham and Women's Hospital/Harvard Medical School. This column features timely analyses and perspectives on issues at the intersection of medicine, law, and health policy that are directly relevant to patient care. If you would like to submit to this section of JLME, please contact Dr. Kesselheim at akesselheim@bwh.harvard.edu.

DETAIL

Subjek:	Software; Registration; COVID-19; Clinical trials; Classification; Severe acute respiratory syndrome coronavirus 2; Funding; Mortality; Regulatory approval; Intervention; Pandemics; Decision making; Coronaviruses; Clinical outcomes
Ketentuan indeks bisnis:	Subjek: Regulatory approval
Lokasi:	United States--US; France
Pengidentifikasi/kata kunci:	COVID-19; Logistic regression; Hierarchical classification; Pandemic; COVID-19; Clinical Trial; United States; France; Hierarchical Classification
Judul:	Characteristics of Clinical Trials Launched Early in the COVID-19 Pandemic in the US and in France
Pengarang:	Raimond, Véronique; Mousquès, Julien; Avorn, Jerry; Kesselheim, Aaron S
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1

Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	139-151
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Columns: Health Policy Portal
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.19
ID dokumen ProQuest:	2730846983
URL Dokumen:	https://www.proquest.com/scholarly-journals/characteristics-clinical-trials-launched-early/docview/2730846983/se-2?accountid=211160
Hak cipta:	
Terakhir diperbarui:	2023-11-28
Basis data:	Public Health Database

From Exceptionalism to Essentialism in Dentistry

Simon, Lisa

ABSTRAK (ENGLISH)

Americans report more frequent financial barriers to dental care than any other health need.3 One third of Americans lack any form of dental coverage.4 Medicare beneficiaries have the lowest rates of dental insurance of any demographic, and Medicaid is not required to provide dental coverage for adults.5 Low rates of public insurance acceptance by dentists, as well as a dental workforce that is strikingly less diverse than the American population, further worsen access.6 Without dental care, patients with toothaches often seek relief in the emergency department, making up more than 1% of all ED visits nationally, but where palliation with an antibiotic and opioid prescription is all that is commonly available.7 Though corporate-run group practices make up a growing share of the dental market, more than 90% of dental practices are still run by one or a few dentists, who also make up the constituents of most professional dental associations.8 As Cajee notes, owner-dentists can be motivated by the same ethically questionable financial incentives as corporations or venture capitalists. Shifts to value-based payment models that are becoming standard in the rest of the healthcare system remain rare in dentistry, due to slow adoption of quality metrics and diagnostic codes, but primarily a reticence to change on the part of most dental practitioners.9 Although most Americans receive their dental care in the private practice setting, governmental, legislative, and health systems changes are making progress in reconciling dental delivery with wider health policy trends. The Health Resources and Services Administration (HRSA) implemented an Oral Health Strategic Framework from 2014 to 2017, the first goal of which was to integrate oral health delivery into primary care, and which resulted in increased funding for health center dental programs, dental schools, and integration pilots.10 Private payers with sufficient subscriber bases, such as Kaiser Permanente, have demonstrated the feasibility of using more integrated dental practices to identify unmet preventive health service needs, such as providing flu vaccines during a visit.11 Oregon’s Medicaid Coordinated Care Organizations (CCOs) are funding dental delivery as part of capitated payments for overall health maintenance, rather than a fee-for-service carveout. Much of the resistance for legislation that could increase oral health equity in the US has come from organized dentistry, which has waged state and national campaigns to prevent the adoption of mid-level dental providers,13 prevent the development of a single-payer health system, and to keep dental coverage out of Medicare.14 Yet in the midst of the COVID-19 pandemic, the American Dental Association released a statement affirming that dentistry was essential care, urging state regulators to allow dental practices to reopen with minimal restrictions after several months of imposed closures.15 While such a move was at least in part economically motivated to increase revenues for struggling member dentists, the rapid rebound in dental volume, at rates far greater than other ambulatory services, suggests that the public is also eager for dental care.16 Dentistry is at an ethical crossroads of its own making, made more extreme by the neoliberal market forces described by Cajee.

TEKS LENGKAP

In his article, Cajee[1] juxtaposes the response of the dental profession to Dr. Painless Parker’s dental franchises and self-promotion in the 1930s with his posthumous exoneration in 1979, when advertising by dentists had become widespread. Cajee follows this evolution of the field from a self-regulating profession to a lucrative but externally regulated industry.

Yet in 1932, when Painless Parker’s license to practice dentistry was first challenged, dentistry was already more market-driven and deregulated than medical care. The first dental school in the US, founded in Maryland by a group of physicians, had existed for 92 years, marking in many ways the first branch point separating medicine from dentistry, and delaying dental education’s adoption of a residency model of care delivery and professional identity formation. It had been three years since a group of Texas schoolteachers created the first American medical insurance model; the system of discounts and incentives that has come to be called dental insurance would not emerge until the post-World War II period.[2] Though perceived as repellent at the time, Painless Parker’s mercenary approach to dental practice is a direct link between dentistry’s origin as the trade of the barbersurgeon and the now-standard commercialization of oral healthcare. The siloization of dentistry as a profession independent of the rest of healthcare, with dental care treated as a benefit rather than a necessity, makes the field more vulnerable to

deregulation and deprofessionalization.

The impact of this separation and its shaping of the modern dental delivery system are not merely historical curiosities. In the midst of a profoundly unequal medical system, oral health outcomes remain some of the most inequitable and unjust. Americans report more frequent financial barriers to dental care than any other health need.[3] One third of Americans lack any form of dental coverage.[4] Medicare beneficiaries have the lowest rates of dental insurance of any demographic, and Medicaid is not required to provide dental coverage for adults.[5] Low rates of public insurance acceptance by dentists, as well as a dental workforce that is strikingly less diverse than the American population, further worsen access.[6] Without dental care, patients with toothaches often seek relief in the emergency department, making up more than 1% of all ED visits nationally, but where palliation with an antibiotic and opioid prescription is all that is commonly available.[7]

Though corporate-run group practices make up a growing share of the dental market, more than 90% of dental practices are still run by one or a few dentists, who also make up the constituents of most professional dental associations.[8] As Cajee notes, owner-dentists can be motivated by the same ethically questionable financial incentives as corporations or venture capitalists. The fee-for-service reimbursement system that is still near-universal in dentistry rewards more invasive and costly interventions over preventive models of management independent ofbenefit to patients. Shifts to value-based payment models that are becoming standard in the rest of the healthcare system remain rare in dentistry, due to slow adoption of quality metrics and diagnostic codes, but primarily a reticence to change on the part of most dental practitioners.[9]

Although most Americans receive their dental care in the private practice setting, governmental, legislative, and health systems changes are making progress in reconciling dental delivery with wider health policy trends. The Health Resources and Services Administration (HRSA) implemented an Oral Health Strategic Framework from 2014 to 2017, the first goal of which was to integrate oral health delivery into primary care, and which resulted in increased funding for health center dental programs, dental schools, and integration pilots.[10] Private payers with sufficient subscriber bases, such as Kaiser Permanente, have demonstrated the feasibility of using more integrated dental practices to identify unmet preventive health service needs, such as providing flu vaccines during a visit.[11] Oregon's Medicaid Coordinated Care Organizations (CCOs) are funding dental delivery as part of capitated payments for overall health maintenance, rather than a fee-for-service carveout. Even Medicaid ACOs that continue to fund dental care through parallel fee-for-service systems, such as Massachusetts, are implementing oral health quality metrics that put the onus for compliance on the medical system, bypassing dentist reluctance. A commonality of these integrative initiatives is their origin outside of dentistry itself, representing in some ways a shift towards external professional regulation just as potentially transformative as venture capital-owned dental practices.

Dentistry is at an ethical crossroads of its own making, made more extreme by the neoliberal market forces described by Cajee. Is dental care a valuable commodity on the open market, or essential health care? The conclusions reached by the profession and by the public will drive the future of oral health.

Initiatives to reintegrate oral healthcare back into the broader healthcare system are often justified by claiming that doing so will improve health outcomes for patients with chronic conditions such as diabetes or during pregnancy, or will ultimately result in cost savings for payers. Yet studies have been at best inconclusive.[12] That the pain, shame, and suffering caused by poor oral health impacts well-being should be intuitive; the fact that this is not considered sufficient justification for more robust dental infrastructure and access is a testament to the completeness of the historical rupture between dentistry and medicine.

Painless Parker was known to wear a necklace of 357 teeth that he claimed to have extracted in a single day. There are modern echoes of such dehumanizing sensationalism in newspaper aerial photographs of the volunteer dental clinics held in gymnasia or on race tracks across the country, where thousands wait hours for a free tooth extraction conducted on folding chairs.

Much of the resistance for legislation that could increase oral health equity in the US has come from organized dentistry, which has waged state and national campaigns to prevent the adoption of mid-level dental providers,[13] prevent the development of a single-payer health system, and to keep dental coverage out of Medicare.[14] Yet in the

midst of the COVID-19 pandemic, the American Dental Association released a statement affirming that dentistry was essential care, urging state regulators to allow dental practices to reopen with minimal restrictions after several months of imposed closures.[15] While such a move was at least in part economically motivated to increase revenues for struggling member dentists, the rapid rebound in dental volume, at rates far greater than other ambulatory services, suggests that the public is also eager for dental care.[16]

Dentistry is at an ethical crossroads of its own making, made more extreme by the neoliberal market forces described by Cajee. Is dental care a valuable commodity on the open market, or essential health care? The conclusions reached by the profession and by the public will drive the future of oral health.

Note

The author has no conflicts to disclose.

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DETAIL

Subjek:	Emergency medical care; Medicaid; Oral hygiene; Health care policy; Dental insurance; Ethics; Dental care; Neoliberalism; Insurance coverage; Medicare; Associations; Dentists; Prevention; Public health; Dentistry; Regulated industries; Primary care; Essentialism; COVID-19; Exceptionalism; Influenza; Private practice; Legislation; Ambulance service; Health disparities; Adults; Market shares; Private schools; Antibiotics; Companies
Ketentuan indeks bisnis:	Subjek: Medicaid Insurance coverage Medicare Regulated industries
Lokasi:	United States--US
Perusahaan / organisasi:	Nama: Kaiser Permanente; NAICS: 524114, 622110
Pengidentifikasi/kata kunci:	Health Equity; Dentistry; Health equity; Exceptionalism; Dental insurance; Health policy; Essentialism; Medicaid; Oral Health; History of Dentistry; Access to Care; Health Care Policy
Judul:	From Exceptionalism to Essentialism in Dentistry
Pengarang:	Simon, Lisa
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	89-91
Tahun publikasi:	2021

Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles: Commentary
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Commentary
DOI:	https://doi.org/10.1017/jme.2021.14
ID dokumen ProQuest:	2730846905
URL Dokumen:	https://www.proquest.com/scholarly-journals/exceptionalism-essentialism-dentistry/docview/2730846905/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

INTRODUCTION: Public Sector and Non-Profit Contributions to Drug Development — Historical Scope, Opportunities, and Challenges

Sarpatwari, Ameet; Kesselheim, Aaron S

ABSTRAK (ENGLISH)

Medication affordability is a persistent public health problem in the US. Per capita US spending on prescription drugs totaled $1,024 million in 2017, $319 million (45%) more than the next highest country.1 An important contributor to this spending has been high drug prices, which can lead patients to skip or stretch out their prescriptions and forego other essential items. Such prices have been driven in part by new drugs. In 2017, the first gene therapies entered the US market. The chimeric antigen receptor-T cell (CAR-T) treatments tisagenlecleucel (Kymriah) and axicabtagene ciloleu-cel (Yescarta) were initially priced at $475,000 and $373,000, respectively,2 while the inherited retinopathy gene therapy voritigene neparvovec-rzyl (Lux-turna) was listed at $850,000 ($425,000 per eye).3 Two years later, Novartis announced that it would charge $2.1 million for onasemnogene abeparvovec-xioi (Zolgensma), a gene therapy for spinal muscular atrophy.4 Higher launch prices have similarly been observed for non-gene therapies as well. In 2019, the US Food and Drug Administration (FDA) approved two new drugs for sickle cell disease, crizanlizumabtmca (Adakveo) and voxelotor (Oxbryta), which each launched at about $100,000 per year.5 Other drugs have been the subject of substantial price mark-ups. The TNF-alpha inhibitor adalim-umab (Humira, first approved in 2002) and recombinant insulin (Lantus, 2000), have each more than doubled in list price since launch.6 One investigation found that price increases on existing drugs accounted for 60% of increased revenues between 2014 and 2017.7

Particular concern has emerged because some of the new drugs and treatments emerging at high prices in the US, or that have been subject to some of the most substantial price increases over time, have benefitted in their development from critical public sector support.8 Galkina Cleary et al. found that funding from the US National Institutes of Health (NIH), which had a budget of over $42 billion in 2020,9 contributed at some level to all new drugs approved between 2008 and 2017.10 While many of these contributions were to the underlying basic science, a growing number of drugs can trace their existence to late-stage contributions originating from the public sector. Of all new small-molecule drugs approved between 2008 and 2017, a quarter were based in part on patents or other late-stage links to publicly supported research institutions.11 If contributions from US taxpayers reduce the risk of private investment in development, should that be reflected in the price charged to US patients?

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Particular concern has emerged because some of the new drugs and treatments emerging at high prices in the US, or that have been subject to some of the most substantial price increases over time, have benefitted in their development from critical public sector support.[8] Galkina Cleary et al. found that funding from the US National Institutes of Health (NIH), which had a budget of over $42 billion in 2020,[9] contributed at some level to all new drugs approved between 2008 and 2017.[10] While many of these contributions were to the underlying basic science, a growing number of drugs can trace their existence to late-stage contributions originating from the public sector. Of all new small-molecule drugs approved between 2008 and 2017, a quarter were based in part on patents or other late-

stage links to publicly supported research institutions.[11] If contributions from US taxpayers reduce the risk of private investment in development, should that be reflected in the price charged to US patients?

Such de-risking featured prominently in the three gene therapies approved in 2017. Tisagenlecleucel had its origins in work done by Dr. Carl June at the University of Pennsylvania.[12] It was only after his team published a National Cancer Institute (NCI)-funded pilot trial, which documented remission of chronic lymphocytic leukemia in a patient who had received that therapy[13] that Novartis acquired the drug.[14] Development of axicabtagene ciloleucel started at the NCI by a team led by Dr. Steven Rosenberg.[15] After publication of the results of treatment in 8 patients with advanced, progressive B-cell malignancies,[16] Kite Pharma executed a series of cooperative research and developments agreements with NCI to improve and advance the drug before ultimately acquiring it.[17] In the case of voritigene neparvovec-rzyl, grants from the National Eye Institute and non-profit sources supported a pilot trial,[18] after which university researchers formed the spin-off Spark Therapeutics to commercialize the therapy.[19] In each case, private investment played an essential role in supporting the pivotal clinical trials necessary for securing FDA approval. However, the manufacturers most prominently figured in the development programs after taxpayer-funded scientists worked through the challenging early stages.

To discuss the historical scope, opportunities, and challenges of public sector and non-profit contributions to drug development, including approaches to better account for public funding in the price of a drug resulting from that investment, the Program On Regulation, Therapeutics, And Law (PORTAL) in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital/Harvard Medical School convened a two-day Exploratory Seminar at the Radcliffe Institute for Advanced Study with experts in drug development and production, technology transfer, pharmaceutical policy, economics, and law. The six articles in this symposium issue stem from that meeting.

Does such public support mean that Americans are "paying twice" for their medications? The COVID-19 pandemic has underscored this concern while also revealing the promise of more assertive governmentled drug discovery. By December 2020, Operation Warp Speed had spent $12.4 billion on COVID-19 vaccines.[20] Of this funding, nearly $4.1 billion went to Moderna, including almost $1 billion for research and development costs, with the rest to advanced market commitments.[21] The NIH also served as an active collaborator in the phase III trial for the vaccine, [22] which has proven to be extremely effective. Yet. despite extensive public support, the company is charging the federal government around $15 per dose.[23] Analysts forecast that Moderna's revenues from its vaccine could total $32 billion in 2021 alone,[24] and several Moderna executives have cashed out hundreds of millions of dollars in stock deriving its value primarily from public backing.[25]

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In the first article, Sampat traces the historical debate over public and private sector roles in drug development, summarizes evidence on the relative contributions of these sectors, and details a research agenda to identify optimal reforms to the existing system.[26] Marko and Miller follow with a case study on the development of photodynamic therapy and antivascular endothelial growth factor drugs —two revolutionary treatments for retinal diseases —highlighting the need for greater federal funding of "proof of concept" trials.[27] Next, Baker critiques patent monopolies, proposing several ways that states and private actors can lower drug prices closer to free market levels, including importation, medical tourism, and state and philanthropic drug development funding.[28] In the fourth article, Liljenquist et al. discuss the vulnerability of the US generic drug supply, calling for a greater role for non-profit drug manufacturers, which they argue can more freely engage in transparent, cost-plus pricing.[29] Kapczynski subsequently examines government patent use, identifying its strengths in contrast to Bayh-Dole "march-in rights"

and how it could be implemented using the case of COVID-19 drug remdesivir (Veklury).[30] Finally, Mazzucato and Li identify four key problems with the pharmaceutical market —unmet needs, inefficient collaboration, high prices, and overly-financialization —and call for a fundamental reframing of the role of the state from market-fixing to market co-creation and co-shaping.[31]

We hope this symposium issue will advance the debate on how to improve equitable access to prescriptions for drugs while promoting clinically meaningful innovation. This undertaking would not have been possible without generous support from the Open Society Foundations, Arnold Ventures, and Radcliffe Institute for Advanced Study.

Note

The symposium and symposium issue was funded in part by the Open Society Foundations, Arnold Ventures, and the Radcliffe Institute for Advanced Study. Dr. Kesselheim is the Editor-in-Chief of the Journal of Law, Medicine &Ethics. Dr. Sarpatwari reports receiving consulting fees from West Health.

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Innovation Towards the Public Interest ", Journal of Law, Medicine &Ethics 49, no. 1 (2021): 39–49.

DETAIL

Subjek:	Gene therapy; Profits; Prescription drugs; Immunization; Public sector; FDA approval; Pharmacoeconomics; Medical research; Coronaviruses; COVID-19 vaccines; Drug prices; Investments; Funding; Technology transfer; Insulin; Research &development--R &D; Pharmaceuticals; Food; Public health; Expenditures; Medical treatment; Patents; Patients; Institutes; Monoclonal antibodies; Sickle cell disease; Neuromuscular diseases
Ketentuan indeks bisnis:	Subjek: Profits Public sector FDA approval Drug prices Technology transfer
Lokasi:	United States--US; New York
Perusahaan / organisasi:	Nama: Harvard Medical School; NAICS: 611310; Nama: Open Society Foundations; NAICS: 813211; Nama: Food &Drug Administration--FDA; NAICS: 926150; Nama: Radcliffe Institute for Advanced Study at Harvard University; NAICS: 611310; Nama: New York Times Co; NAICS: 513110, 516110, 516120; Nama: National Institutes of Health; NAICS: 923120
Pengidentifikasi/kata kunci:	Pharmaceutical Development; Drug; Public sector; Insulin; Drug development; Medication; Medication costs; Public policy; Ad alimumab; Insulin glargine; Public health; Innovation; Government; Non-Profit; Drug Pricing
Judul:	INTRODUCTION: Public Sector and Non-Profit Contributions to Drug Development — Historical Scope, Opportunities, and Challenges
Pengarang:	Sarpatwari, Ameet; Kesselheim, Aaron S
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	6-9
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston

Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Commentary
DOI:	https://doi.org/10.1017/jme.2021.2
ID dokumen ProQuest:	2730846871
URL Dokumen:	https://www.proquest.com/scholarly-journals/introduction-public-sector-non-profit/docview/2730846871/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-28
Basis data:	Public Health Database

A Market Shaping Approach for the Biopharmaceutical Industry: Governing Innovation Towards the Public Interest

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Link dokumen ProQuest

ABSTRAK (ENGLISH)

Enhancing research and development and ensuring equitable pricing and access to cutting-edge treatments are both vital to a biopharmaceutical innovation system that works in the public interest. However, despite delivering numerous therapeutic advances, the existing system suffers from major problems: a lack of directionality to meet key needs, inefficient collaboration, high prices that fail to reflect the public contribution, and an overly-financialized business model.

TEKS LENGKAP

Introduction

Countries across the world recognize the vital importance of both enhancing research and development (R&D) and ensuring equitable pricing and access to cutting-edge treatments. However, despite delivering numerous therapeutic advances, the existing system of biopharmaceutical innovation suffers from at least four major problems in achieving these goals: a lack of directionality to meet key needs, inefficient collaboration, high prices that fail to reflect the public contribution, and an overly-financialized business model. COVID-19 —one of the gravest public health challenges in modern times —has magnified and focalized these challenges, as the development, manufacturing, and distribution of effective therapeutics and vaccines are critical to any exit strategy from the pandemic.

In this paper, we review the major problems impacting the biopharmaceutical industry, and argue that overcoming them requires a fundamental reframing of the role of the state in innovation from market-fixing to market co-creation and co-shaping, in which risks and rewards are shared across a symbiotic public-private relationship.

Problems of the Existing Biopharmaceutical Innovation System

First, many areas of medical need —especially in public health —are unmet and underfinanced. The system is skewed towards revenue-rich ailments.[1] There is little evidence on the magnitude and direction of such disparities. In this paper we measure inequality in innovation, by comparing R&D activity with population health and GDP data across 493 therapeutic indications to globally measure: (Diseases relevant to high-income countries are 7-8 times more likely to be investigated than those that mainly affect low- and middle-income countries.[2] Disease groups that present smaller financial returns are largely overlooked. The development of drugs and vaccines for neglected tropical diseases, for example, accounted only 1% of clinical trials registered between 2011 and 2016.[3] But neglected diseases are not confined to tropical diseases: Central nervous system disorders, a therapeutic are for which there has been low probability of clinical trial success, have been increasingly marginalized from many companies' research and development pipelines, leading to an increasing disconnect between unmet medical need and investment.[4]

Lack of innovation in vaccines against infectious diseases of pandemic potential —exemplified by coronaviruses —follows this trend.

The emergence and alarming consequences of severe acute respiratory syndrome (SARS) coronavirus in 2002 and Middle East respiratory syndrome (MERS) coronavirus in 2012 were insufficient to spur R&D efforts on vaccines. Overall coronavirus R&D funding —mostly from public sources —was been paltry, totalling $27 million in 2016, increasing to $50 million in 2017, and then falling significantly to around $36 million in 2018.

Due to a lack of resources, the vaccine R&D projects launched after the outbreak of SARS-CoV1 in 2003 were abandoned before successful completion, despite the availability of a number of promising candidates and awareness of the risk these pose on humans due to a lack of resources. It took a sweeping pandemic almost two decades later to spur necessary action.

Firms also often pursue low-risk strategies that can more easily yield commercial success instead of developing innovations to address unmet needs. Two major strategies to achieve this include ever-greening (extending the monopoly period on a drug by artificially extending the life of a patent or other exclusivity), and developing the me-too drugs (drugs that are structurally related to a first-in-class compound and share the same therapeutic purposes, but with only minor differences in the pharmacological profile that provide, at best, incremental innovation).[5] Between 2005 and 2010, nearly 78% of drugs approved by the United States Food and Drug Administration (FDA) corresponded to existing drugs on the market.[6] In Europe, an analysis of 1345 new medicine approvals between 2000 and 2014 revealed that 51% of newly approved medicines were modified versions of existing medicines that did not have evidence of additional health benefits.[7]

Lack of innovation in vaccines against infectious diseases of pandemic potential —exemplified by coro-naviruses —follows this trend. The emergence and alarming consequences of severe acute respiratory syndrome (SARS) coronavirus in 2002 and Middle East respiratory syndrome (MERS) coronavirus in 2012 were insufficient to spur R&D efforts on vaccines. Overall coronavirus R&D funding —mostly from public sources —has been paltry, totalling $27 million in 2016, increasing to $50 million in 2017, and then falling significantly to around $36 million in 2018.[8]

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Second, reinforcement of the intellectual property rights (IPR) system has increasingly come at the expense of effective collaboration. The current innovation system is highly disintegrated, unsuitable to solve complex problems that arises from the non-modular nature of biopharmaceutical innovation, in which the product development and manufacturing processes are becoming increasingly intertwined.[10] As the need for the transfer of knowledge and know-how becomes greater, the constraints of patents in incentivising and facilitating dynamic models of knowledge exchange and production becomes more evident. As the major incentive for innovation in our current system, the IPR system encourages a protectionist attitude around research, with each actor working in secrecy and isolation. This creates further barriers to addressing the existing insufficiencies in effective and transparent data sharing in both public and private research institutions,[11] which can result in wasted financial resources and duplication of scientific efforts.[12] Additionally, patenting is increasingly too wide (broadly defined patentable subject matter), too strong (hard to licence), and too upstream (privatizing the tools for research), so that not only are products being patented, but also the tools and processes for research that might lead to those discoveries, blocking the ability of new, basic science to be fully disseminated, diffused, and translated into future innovation.[13] For example, the intense patenting activities around the CRISPR-Cas9 (clustered, regularly interspaced, short palindromic repeats and its associated enzymes such as CRISPR-associated protein 9) technology platform for genome editing by different institutions can lead to significant fragmentation of its intellectual property rights landscape; if the knowledge holders cannot find effective ways to cooperate, the potential of this technology could become more limited. This is a classic case of the anticommons problem, in which a resource is prone to underuse when multiple owners each have a right to exclude others from a scarce resource and no one has an effective privilege of use.[14] This makes the research process less efficient and exposes research and its outcomes to bias in favor of actors' specific interests (be they financial or scientific). Limited sharing of information and tools pertinent to COVID-related health technologies can risk derailing coordinated efforts on clinical trials, creating unnecessary drag to the speed of R&D and excluding low- and middle-income countries from the process. The societal and economic cost of such delay would be enormous.

Third, high drug pricing forms a major barrier to access to medicines across the world. Even though most treatments are heavily paid for by the taxpayer, with public funds from organizations like the US National Institutes of Health (NIH), when breakthrough treatments do make it to market, they often have price tags that are beyond the reach of the taxpayers themselves. This puts pressure on health systems in high-, middle- and low-income countries. The ability to charge high prices is based on the monopoly protection granted through patents on new drugs. Despite substantial public funding of R&D —globally, some estimate that the public pays for between one- to two-thirds of upfront drug R&D costs[15] –there are no guarantees that drugs developed from publicly funded research will be affordable and accessible. Sofobu-vir, an antiviral treatment for hepatitis C, provides a notable case of socialization of risks and privatisation of rewards. First developed by Pharmasset, the drug benefited significantly from on more than 10 years of Veterans Affairs and NIH-funded research at Emory University as well as from an NIH-small business innovation grant.[16] After its acquisition by Gilead Sciences, the product was priced at about $90,000 per three-month treatment course at the launch.

As R&D efforts for vaccines and treatments for COVID-19 intensify, similar concerns have arisen about their pricing and the extent to which it reflects public contribution. Between 2002 and 2020, the NIH spent nearly $700 million on coronavirus R&D, leading to a number of promising drug candidates.[17] It is estimated that the public funding for the antiviral treatment remdesivir —also a product from Gil-ead Sciences —was at least $70.5 million as of May 2020.[18] While Gilead's pricing of the drug —$3,120 for a 5-day treatment course in the United States —is in line with the value-based estimates from the Institute for Clinical and Economic Review (ICER),[19] this pricing continues to ignore the collective nature of value creation, and the lack of safeguards for drug pricing *ex ante* as well as the imbalance in

price setting and bargaining power between the public sector and the private sector remains unchallenged.[20] Fourth, companies have become overly financialized, limiting reinvestment into production and innovation, and focusing on short-term return. One of the most common symptoms of this problem is the extent to which share buybacks are used, in which companies purchase their own stocks to boost the value of the remaining ones to shareholders in equity markets.[21] From 2007 to 2016, the 19 pharmaceutical companies included in the S&P 500 Index in January 2017 (and publicly listed from 2006 through 2015), spent $297 billion repurchasing their own shares, equivalent to 61% of their combined R&D expenditures over this period.[22] At the same time, increasing financialization contributes to the rising trend of externalization of R&D and manufacturing. Big biopharmaceutical firms increasingly disinvest from riskier upstream research, and instead focusing more on acquiring products that are already in later clinical trial stages from biotech companies.[23] As biotech start-ups seek boost market valuation, pushing for high drug pricing becomes an essential approach to project high profitability.[24] High expectation in vaccines for COVID-19 in several biotech companies have seen their share price more than double.[25] However, the drive to cut costs by outsourcing manufacturing overseas have come at the cost of local capabilities and the underlying industrial commons.[26] Coupled with the contraction elsewhere in the world, concentration of manufacturing capacity has substantially reduced the resilience of supply chains, which is particularly exposed during systemic shocks. Lack of preparedness in manufacturing has led to shortages of drugs essential for managing COVID-19, from pain relief for mild symptoms such as paracetamol, to powerful anaesthetics used to sedate patients on ventilators, such as propofol, midazolam, and fentanyl; and more widely, drugs that were already at risk of shortages before the pandemic due to lack of financial incentives to market, vulnerabilities in supply chain and manufacturing difficulties.[27]

From Market-Fixing to Market Co-Creating and Co-Shaping

Addressing these persistent problems in the biopharmaceutical innovation system requires a different framing of the role of the public sector from that governments have chosen: market fixer.[28] This role stems from prevailing economic theory, which does not consider the state a key driver of market creation.[29] State intervention is thus justified only in areas characterized by market failures —such as coordination or information failures,[30] imperfect competition, underprovision of positive externalities and over-provision of negative externalities,[31] and under-provision new knowledge arising from basic research —with actions restricted to levelling the playing field so that industry and competition can thrive; devising market mechanisms to internalize external benefits or costs; and funding basic public goods, such as science, infrastructure, and education.

This view has significantly limited policymakers' understanding and choice of tools for addressing problems with the biopharmaceutical innovation sys-tem.[32] Governments establish intellectual property rights to consolidate the appropriability of benefits from knowledge production and exchange to incen-tivise private innovative activities. However, they are reluctant to shape the rules in the public's interest despite the high social cost of maintaining the status quo. So too are governments reticent to make strategic choices and building proactive industrial policy agendas, which are seen as distorting the functioning of the market and crowding out private-sector actors. Instead governments justify the economic rents and supranormal returns for private investors in innovation as the necessary rewards for high risk-taking, and at the same time significantly under-play their own, more substantial role in high risk-taking as an *investor* of first resort throughout the innovation chain, to a lender of last resort. In addition to inflating the return on private investment, governments do not proactively consider the return for the public on the investment in innovation by the public, and instead frames the spending on public goods like science as de-risking the activities of private innovators.

Yet, throughout the history of capitalism, the state has often been responsible for actively shaping and creating markets, not just fixing them.[33] The impact of the state's role in investing in the production and translation of scientific knowledge has been well documented and quantified. It has been demonstrated that over the past 90 years, almost one-third of patents in the US rely on federal research.[34] In addition, the state has been engendering some of the most important general-purpose technologies, from mass production, to aerospace, and information and communications technology through its innovative insti-tutions.[35] The Defense Advanced Research Projects Agency

(DARPA) developed foundational technologies for Apple's i-products; the US Navy was behind the development of the global positioning system (GPS); and the Central Intelligence Agency (CIA) created the touchscreen display that is now commonplace.[36] Importantly, public investments in these examples went beyond any typical "public good" in market failure theory (Arrow, 1962; Nelson, 1959). The nature of these investments is not merely a matter of narrative and framing. Multiple well-documented examples from across different sectors and countries have shown that government agencies have been funding areas along the entire innovation chain: both basic *and* applied research and, in many cases, provided downstream early stage high-risk finance to companies deemed too risky by the private financial sector.[37] In addition, market co-shaping and co-creation have also occurred through demand-side policy instruments based on mass government procurement programs (e.g. in semiconductors and in vaccines). Although private investments are crucial to sustaining the level of risk-taking and capital intensity required in innovation, they are conditional on the groundwork laid by the public sector —a fact that has been historically overlooked.

In the biopharmaceutical sector, the public sector has been responsible for funding some of the highest-risk research in biomedical R&D, which leads to most innovative and crucial biomedical innovations.[38] Public sector investment often underlies therapeutic advances that are truly innovative and impactful to human health[39] and creates positive fiscal impact for the private sector through generating further investments ("crowding in")[40] and substantial drug sales revenue.[41]

Market-Shaping Approaches to Biopharmaceutical Innovation

Realization of these contributions has critical implications for the distributions of risks and rewards in innovation.[42] Unlike private investors, who receive tangible financial rewards, the state generally accrues return on its investment through the knowledge spillovers that are created, and via the taxation system due to new jobs being generated, as well as taxes being paid by companies benefiting from the investments. However, public returns through these mechanisms are offset in several ways. First, knowledge spill-over is significantly hindered by strong mechanisms of knowledge appropriation.[43] Second, corporate taxation has been falling globally, and corporate tax avoidance and evasion rising. Tax cuts, such as those promoted by the Tax Cut and Jobs Act of 2017, are touted as an incentive to encourage companies to repatriate their overseas capital; however, their intended impact —increased domestic investment in R&D and job creation —have hardly materialized, while stock buyback and dividends have increased.[44] Third, in the case of health, the economic, welfare and health benefits of biopharmaceutical innovations are also further deterred by barriers to access innovative treatments posed by high pricing.[45] In this context, the emphasis on maximizing financial capital to deliver shareholder value over stakeholder value in the current model of capitalism has served to reinforce the inherent flaws in the risks-rewards nexus, tilting it further towards private financial gains away from public interest.

Rectifying the balance between risks and rewards requires a new understanding of the role of the state in the governance of biopharmaceutical innovation as a proactive market co-creator and co-shaper: steering innovation, getting fair prices, ensuring that patents and competition work as intended, setting conditions for reinvestment, and safeguarding medicine supply. In other words, the responsibility to create a more symbiotic relationship with the private sector and an innovation system that aligns with societal benefit significantly rests on the state overcoming the conceptual confines of the market-fixing role.

While no single or straightforward set of policies can thoroughly address all the problems in biopharmaceutical innovation across varying health system context, we highlight a subset of practice-based policies that emphasise systemic market-shaping principles and examine briefly the impact of COVID-19 on the progress and prospect for policy implementation.

Deploying Mission-Oriented Innovation

To direct biopharmaceutical innovation towards public health priorities, the public sector must be guided by a mission-oriented framework, similar to how it is during war time. Strongly problem-oriented in nature and problem-solving in purpose, the mission-oriented approach to innovation is a way to bridge top-down agenda driven by societal challenges and bottom-up explorative approaches to deliver innovations in an outcome-focused, milestone-

driven, and time constrained manner.[46] The concept of mission has been adopted as the central construct for policy making in industrial policies and research and innovation policies at national and international levels.[47]

Unique catalysts for mission-oriented innovation are mission agencies, which enhance the role of the state in coordinating public and private sectors and create new markets by inducing procurement.[48] For example, the "ARPA" agencies, including the US Defense Advanced Research projects Agency (DARPA) and Advanced Research Projects Agency –Energy (ARPA-E),[49] help to strategize innovation investment, harmonize and manage horizontal collaboration across sectors and actors, and coordinate the vertical integration of product development. In health, the recently proposed Health Advanced Research Projects Agency (HARPA) offers a feasible model for lean and autonomous bureaucratic structures that provide freedom to pursue blue-sky innovations (and in the process lead to significant spill-out effect on other sectors) while also being driven by outcomes towards specific missions.[50] The US Biomedical Advanced Research and Development Authority (BARDA) demonstrates another key attribute of mission-oriented agencies in public procurement: when missions create innovative solutions, they also directly create market demand that self-enforces the need for further innovations.[51]

DARPA and BARDA have seeded and directed new technological trajectories in DNA and mRNA vaccine technologies, which may prove to be an important platform for vaccines against COVID-19.[52] There has been increasing interests in advanced countries in increasing R&D investment and setting up or broadening of scope of ARPA-type programs as part of a post-pandemic recovery plan.[53] It is critical that these programs are designed and implemented along with substantial changes in the healthcare and innovation systems that can broaden access to technology, lower pricing, enhance knowledge transfer, and connect procurement at an international level, rather than simply focus on competitive and economic advantages. In addition, innovations must not be confined to a narrow and siloed technological focus, but instead connect with and strengthen wider public health infrastructures and social innovations. A holistic mission-oriented approach to innovation must take a systems perspective when applied to "wicked" problems that have complex socio-economic and technological dimensions. This requires the proposals to develop cutting-edge biopharmaceutical technologies be nested within the myriad different moving parts —such as innovations in other aspects of healthcare, infrastructures, social enterprises, and institutions —in an inter-related network of actors and institutions, with the overarching goal of generating stronger systemic resilience.[54] Furthermore, national efforts must be aligned with international efforts to maximize the leverage of international procurement mechanisms (such as Gavi, the Vaccine Alliance) and avoid inefficiency.

Reshaping Knowledge Governance for Public Value

Patents must be seen through a knowledge governance perspective, not an innovation incentive perspective, so that the monopoly profit given to a company during the patent term should be governed to make sure that the patent produces productive entrepreneurship. On one level, patentability criteria should be made more stringent. To incentivise innovation, patents should protect only the area that is fundamentally new, and be focused downstream so as to avoid tools and processes being privatised while at the same time enabling licensing and diffusion.[56] On another level, governments should more actively use policy instruments designed to uphold equitable knowledge governance and improve access to medicines especially during public health crisis, such as voluntary licencing arrangements (e.g. through Medicines Patent Pools), assertion of government rights over patents (e.g. compulsory licencing under the flexibilities of the Trade-Related Aspects of Intellectual Property Rights, March-in Right under the Bayh-Dole Act, and government patent use through 28 U.S.C. §1498).

In addition to strengthening the role of the state in enforcing IPR for public health, government should more actively explore and foster alternative models of innovation that better facilitate knowledge exchange, maximizes use of existing knowledge, and reduces transaction costs. Open innovation, which can be generally defined as "the process of innovating with others for shared risk and reward to produce mutual benefits for each organisation, creating new products, processes or ideas that could not otherwise have been achieved alone, or enabling them to be achieved more quickly, cheaply or efficiently,"[57] describes an important group of models. Although the willingness of private sector collaborators to abdicate the pursuit and control of IPR varies, loosening the constraint imposed by IPR is a key element to the various forms of open innovation in general.[58] While some models are better to be characterized

as public-private partnerships where only the research problem is in the public domain and the solutions remains subjected to the structures of IPR,[59] other models have sought to establish a norm of collaboration and sharing in the absence of patents, and demonstrated the potential to create flexible forms of market-creating collaboration beyond simply buttressing the classic market-fixing and de-risking stereotype for public sector. The need to address disease spaces that lack economic incentives —especially infectious diseases —has led to the creation of not-for-profit product development partnerships, such as the Drugs for Neglected Diseases initiative, the Global Antibiotic Research and Development Partnership the Medicines for Malaria Venture, and the Global Alliance for Tuberculosis Drug Development. These models channel public and private efforts into delivering specific target product profiles that represent the public R&D priorities, and explicitly set out IPR policies that ensure the sharing of patented knowledge and affordable access of the resultant products.[60] On the patent-free end of the spectrum, open science —exemplified by the Structural Genomics Consortium[61] and the Open Source Drug Discovery project[62] —provides a model for building platforms for knowledge commons that would not have been permitted under the patent system, and for illuminating on possible routes for open source drug development of the future, whereby new drugs can be taken all the way from basic research to clinical trials without the filing of patents.[63]

In tackling COVID-19, countries are increasingly aware of the potential of compulsory licensing. For example, Israel issued compulsory licensing to enable import of generic alternatives of lopinavir/ritonavir due to concerns in their supply (rather than their pricing, which is a more common rationale for invoking compulsory licensing).[64] Several other countries, including Chile, Ecuador, Canada, and Germany have also initiated the legal and legislative steps to create a national framework for using of compulsory licensing to facilitate access to health products and other technologies for managing COVID-19.[65]

At the same time, new policy instruments exemplified the WHO COVID Technology and Access Pool (C-TAP) provides an enabling platform for voluntary sharing of data, know-how and patents related to any COVID-related health technology.[66] Beyond its public interest case, C-TAP has a robust economic case: the quicker effective vaccines, therapeutics, and diagnostics are available, the quicker the world can exit from the pandemic and minimize its damage. Despite their support for more conventional public-private partnerships at global and national levels, major advanced countries, non-profit funders, and the biopharmaceutical industry (bar 2 executives) have chosen to distance themselves from the more transformative C-TAP. In particular, the industry has dismissed and distorted the basic rationale of the initiative —a voluntary sharing mechanism that protects patents and allow companies to retain control over critical technologies and data —to one that threatens existing IPR. Given the determination of the biopharmaceutical industry to buttress the existing IPR regime, prospects for genuinely transformative open innovation projects to scale at a systems level may remain challenging. To build greater leverage and more meaningful dialogue, public funders must formulate and enforce conditionalities on publicly funded R&D, which is covered next.

Putting in Place Conditionalities for Public Interest

Government agencies must put in place conditionalities for public return when making public investment into biopharmaceutical innovation and procurement. To ensure that public contribution to biopharmaceu-tical R&D is taken into account of price setting *ex ante*, conditions on affordability and access must be attached to public funding. Commitment of the public sector in ensuring public return must be brought back. In 1995, NIH rescinded a “fair pricing clause” in its collaboration and licensing arrangements under cooperative research and development agreement (CRADA), which sought to ensure products resulting from public funding, in an attempt to ease the fears of private sector collaborators and stimulate commercialisation.[67] Given that the outsourcing model of innovation has led the private sector to more heavily rely on publicly funded R&D, a revised clause updated for the current innovation context with better clarity, more consistent application, broader scope, and clearer indication of the reward for genuine innovation could have significant potential to ensure affordability of innovative products.[68] Additionally, conditions can include commitment for reinvestment of a share of the company’s profits into productive economic activities or a public innovation fund.[69]

Additionally, the public sector can more proactively manage its ownership of IPR and its associated knowledge and

financial returns, whether by retaining stakes in the companies concerned, holding intellectual property rights, or receiving royalties on sales. While public funding should encourage open access to data and knowledge where possible, governments could also retain a “golden share” of patents developed with public funding, with patents governed in such a way to allow companies to recover their costs while spurring greater use of that specific innovation. Ultimately, such a “golden share” would allow the public to convert a property right previously granted into a general public licence, should the owner refuse to license broadly and fairly.[70] Royalties can be used to finance future innovation or to help cover the losses that inevitably arise when investing in high-risk areas.[71]

The highly substantial public investments in the R&D of COVID-19-related health technologies have put conditionalities in much sharper relief.[72] Underpinned by the rationale to create a symbiotic relationship between public and private actors in the context of COVID-19, 140 public figures, including 50 former world leaders, have led the call for a “People’s Vaccine”: a “global guarantee which ensures that, when a safe and effective vaccine (and other technologies for COVID-19) is developed, it is produced rapidly at scale and made available for all people, in all countries, free of charge.”[73]

Yet, even though the arguments for conditionalities are strong, their substantive relevance remain finely in the balance in the complex political economy of biopharmaceutical innovation. It remains to be seen whether any high-profile public-private partnerships at global and national levels will make firmer and more specific commitments that enable vaccines to be universally available according to needs and free at the point of use, beyond commonplace statements of principle and generic pledges. At the same time, it is essential that these partnerships be more transparent about negotiations on pricing, procurement and potential conflict of interests. Mismanagement of issues around these areas will damage public trust and public health. Nevertheless, increased willingness for state investment to translate into partial public ownership of companies and/or their public-funded innovations —partly driven by nationalistic concerns —may open up new policy opportunities for the state to shape the pricing, manufacturing, and distribution of vaccines.

De-Financialising Biopharmaceutical Innovation: Corporate Governance Reform and Manufacturing Revival

Large pharmaceutical companies have become overly financialized in recent decades. Active measures can be taken to promote corporate governance models that share that value fairly between all stakeholders, not just shareholders.[75] While the pharmaceutical sector remains one of the most financialized industries, short-termism and financialization is not unique to the biopharmaceutical innovation, and reforms to corporate governance must apply to the wider economy as a whole. Initial measures can focus on addressing the symptoms of shareholder value. Limiting the practice of share buybacks for firms who have benefited from publicly funded research is a first step. In the US, companies have been allowed to repurchase their shares on the open market with virtually no regulatory limits since 1982.[75] Shifting managerial incentives away from share buyback requires executive compensation to be based on means other than stocks. In the case of pharmaceutical companies, new rules can require that any performance-related bonuses reward, for example, the success of the company in generating new medicines that deliver therapeutic advance, at affordable prices.

Deeper reforms to align corporate governance with public values involve ensuring companies incorporate public interest into their ethos, decisions, and actions. One possible approach is to place stakeholders representing taxpayers, workers, and patients directly on corporate boards of publicly listed pharmaceutical companies. Governments could encourage or mandate companies to allocate a certain number of board positions to such stakeholder representatives. Another approach is to amend the legal duties of *all* company directors so that they are obliged to serve the interests of a range of stakeholders, rather than to prioritise shareholders; these two approaches can go hand in hand.[76] Reforms geared towards increasing productive investments —for example, prohibiting share buy backs or setting conditionality of reinvestment —can play a vital role in reversing the vicious cycle caused by financialization.[77]

Key concerns about the impact of these initiatives and their prognosis beyond the pandemic remain. At their core is the question: Can the public sector finally rise up to the challenge to reset their relationship with the private sector, and prepare societies for even sterner tests to come? This requires a change in its remit, governance, and ways to

understand and assess “value.” We hope the paper can inform this process.

In addition, to nurture a resilient and responsive industrial ecosystem capable of ramping up production during crisis times, countries must take the lead in actively building and buttressing public manufacturing capabilities across a range of sectors critical essential medical supplies, from PPE, ventilators, and testing to biopharmaceutical products.[78] Across all countries, stronger global supply chain resilience has to be built upon stronger local productive capacity and the regeneration of industrial commons —the collective capabilities and infrastructures of “R&D know-how, advanced process development and engineering skills, and manufacturing competencies related to a specific technology” resulting from the clustering of upstream and downstream actors from both public and private sectors.[79] The measures in these areas are farther-reaching and will require deep restructuring of the relationships between finance, productive activities, and labor. With regard to de-financialization, countries have learned lessons from the previous financial crisis, and are more willing to impose bail-out conditions with restrictions on share buy-back and executive pay. However, the implications of these broader developments on the over-financialized biopharmaceutical industry is difficult to ascertain. Biopharmaceutical stocks have weathered the storm well relative to the overall market and have become the centre of speculation.[80] The industry itself is keenly aware of its highly critical role in the pandemic, and will likely tread on the economic and political issues pertinent to vaccines and treatments, and manage its role in serving commercial, national, and global interests in order to resist any systematic shock to its business model with caution, especially in the moments where the momentum for change is greatest. Sustained, intense public scrutiny and advocacy across different sectors —health, climate, finance —will be needed to rigorously hold the industry to account and push for systemic change.

In terms of manufacturing, countries are driven by current needs, alerted by the fragilities in global supply chain, and finally paying long-overdue attention to strengthening local capacities. In the United States, this is a policy issue gaining increasing bi-partisan support, such as Senators Warren and Rubio’s legislation to review the pharmaceutical supply chain in the wake of COVID-19.[81] In the biopharmaceutical sector, the renewed focus on manufacturing will benefit not only innovative products, but also conventional products that are in shortage. There is a strong case for a public option in pharmaceuticals: government provided, quality assured medicines that are universally available at a reasonable and fixed price, which coexist with products from the private sector.[82] This can range from the creation of a new business model dedicated to creating a functional, competitive market for pharmaceuticals in shortage (e.g. Civica Rx), to the state becoming directly involved —and taking a substantial stake —in coordinating and executing the full range of activities in drug innovation and manufacturing and to retain a sufficient level of control.[83] As persistent market failures and lack of political and economic imagination in solutions outside creating and aligning incentives for the private market to address the gaps in innovation and pharmaceutical supply becomes a repeated phenomenon, the drive to marry innovation, manufacturing, and social policies may well provide new impetus for public-sector solutions.

Conclusion

How the public sector governs the health innovation system and creates symbiotic public-private relationships will come to define the innovation-led welfare state of the 21st century. The COVID-19 pandemic has presented a critical window and created significant momentum for countries to move away from market-fixing approaches to biopharmaceutical innovation towards market shaping approaches. At a global level, this will require countries’ joint efforts to impose firm rules regarding IPR, pricing, and manufacturing, designed and enforced in ways that value international collaboration and solidarity, rather than competition between countries. Key concerns about the impact of these initiatives and their prognosis beyond the pandemic remain. At their core is the question: Can the public sector finally rise up to the challenge to reset their relationship with the private sector, and prepare societies for even sterner tests to come? This requires a change in its remit, governance, and ways to understand and assess “value.” We hope the paper can inform this process.

Note

The authors have no conflicts to disclosed.

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DETAIL

Subjek:	Public interest; Middle East respiratory syndrome; Respiratory diseases; Coronaviruses; Product development; Innovations; Research &development--R &D; Pharmaceutical industry
Ketentuan indeks bisnis:	Subjek: Product development
Lokasi:	Middle East; United States--US
Perusahaan / organisasi:	Nama: Food &Drug Administration--FDA; NAICS: 922190
Pengidentifikasi/kata kunci:	Pharmaceutical; Public interest; Research and development; Innovation; Biopharmaceutical; Innovation; Pricing; Access; Governance
Judul:	A Market Shaping Approach for the Biopharmaceutical Industry: Governing Innovation Towards the Public Interest
Pengarang:	Mazzucato, Mariana; Li, Henry Lishi
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1

Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	39-49
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.8
ID dokumen ProQuest:	2730846867
URL Dokumen:	https://www.proquest.com/scholarly-journals/market-shaping-approach-biopharmaceutical/docview/2730846867/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

Realizing Public Rights Through Government Patent Use

Kapczynski, Amy

ABSTRAK (ENGLISH)

A substantial portion of biomedical R&D is publicly funded. But resulting medicines are typically covered by patents held by private firms, and priced without regard to the public's investment. The Bayh-Dole Act provides a possible remedy, but its scope is limited.

TEKS LENGKAP

The novel coronavirus that emerged in 2020 has led to extraordinary social and economic dislocation. By late September, it had caused an estimated one million deaths around the world.[1] Governments are taking unprecedented steps to try to accelerate the development of effective therapies and vaccines, and in a matter of months have allocated almost $9 billion in research funding toward this end, much of it to private companies.[2] As of early August, an estimated 150 therapeutics were under clinical investigation worldwide, and 27 vaccine candidates were in clinical trials.[3] But only one anti-viral drug had yet shown some efficacy: remdesivir.

Patented and sold by Gilead Sciences, remdesivir is far from a game-changer. No peer reviewed studies have yet shown a mortality benefit. But the drug has been shown to reduce hospitalization time,[4] and it has become the standard of care in the US for many of those hospitalized with COVID-19.[5] However, there are significant questions about whether Gilead has priced it appropriately and will be able to provide adequate supply.

The price of remdesivir in the US was set at $2340 to $3120 for a five-day course.[6] However, generic prices today are $320 or less, and the cost of manufacturing has been estimated at far less, at $5 for a five day course.[7] A leading independent non-profit that performs technology assessments in the US, ICER, determined that a fair price for the medicine could be as little as $10-600 if only covering marginal manufacturing cost, or $1010 to $1600, accepting the company's forecasted development costs.[8] These prices, it assumed, may be appropriate because any past company R&D costs appear to have been recovered, since the line of research that resulted in remdesivir also yielded Gilead's lucrative Hepatitis C medicines.[9] ICER also estimated that, using traditional, cost-effectiveness analysis, the appropriate price would be below the current US price unless the medicine was shown to have a mortality benefit, which has yet to be shown.[10]

Additionally, over the summer, shortages of remdesivir have emerged in hotspots around the United States. An independent analysis found that shortages were reported in 38 hospitals around the country, and in 12 states.[11] This is so even as Gilead had directed almost all its available worldwide supply to the US.[12]

Given these concerns, it is notable that remdesivir benefitted from substantial public sector funding and research collaboration.[13] The US government funded and helped design the phase III trial for remdesivir and also was significantly involved in the earlier period of the medicine's development.[14] The early clinical research of remdesivir as a possible treatment for Ebola was funded by the US government.[15] Government researchers with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Centers for Disease Control and Prevention (CDC) in fact appear to have contributed to the discovery of remdesivir's anti-viral properties, and perhaps even to the selection of it as a candidate to treat SARS-CoV2.[16] An independent analysis suggests on this basis that the US government may be legally entitled to claim co-ownership over key pat-ents.[17] No such rights have to date been recognized or asserted. Gilead alone appears to hold the patents, which give it a general entitlement to prevent all other companies from making, using, selling, or importing the compound into the United States. Despite the substantial investment made by taxpayers, then, the public exerts no direct control over the price or supply of the medicine.

Patented and sold by Gilead Sciences, remdesivir is far from a game-changer. No peer reviewed studies have yet

shown a mortality benefit. But the drug has been shown to reduce hospitalization time, and it has become the standard of care in the US for many of those hospitalized with COVID-19. However, there are significant questions about whether Gilead has priced it appropriately and will be able to provide adequate supply.

This is in fact commonplace. The US government invests billions of dollars in research each year, research that one study showed underpinned the development of all of the drugs approved from 2010 to 2016.[18] The Bayh-Dole Act reserves the US government "march-in" rights, which allow it to give any company the right (or a "license") to make an invention covered by a patent, even against the wishes of the patent-holding firm.[19] It also gives the government the right to make or use the invention without permission, for its own benefit.[20] These rights only attach where the government's funding meets certain restrictive criteria, however. They only reach inventions very proximately developed with government funding, namely inventions "conceived or first actually reduced to practice in the performance of work under a funding agreement."[21] A great deal of government funding supports drug development, for example by identifying biomarkers or clarifying the nature of a disease, that does not result in Bayh-Dole rights because these grants did not directly fund the development of the marketable technology. The NIH and HHS have also taken the contested view that these rights can only be used in very limited ways. The law states that the government can march-in on patents if the action is "necessary to alleviate health or safety needs."[22] But some have argued that this does not cover the problem of excessive pricing, but only reaches problems like failure to commercialize.[23] No march-in petition has ever, in fact, been formally granted.[24] In addition, the agency leading the allocation of COVID-19 research funding, BARDA, has used contracts that seem to eliminate even these limited obligations for recipients of its funding.[25]

Remdesivir shows the limits of the Bayh-Dole approach. It is not clear that Bayh-Dole rights attach to the relevant patents, despite the significant public investment in the drug.[26] In addition, the BARDA contracts might restrict the government's march-in rights —even assuming NIH would be inclined to use them.

Is there a way to recognize government funding more comprehensively than through the limited means of government patenting and Bayh-Dole rights? The question is likely to present itself urgently as more effective COVID-19 therapies and vaccines come online. Given the government's major investment in research in ordinary times, and the acknowledged impact of high drug prices on patients and health in the United States, the question also has broader importance.

Any system of fair pricing passed by Congress could include, as a factor in the definition of fair price, an accounting of public sector contributions. Some leading proposals for drug price reform in the US have this design. The proposed Medicare Negotiation and Competitive Licensing Act (H.R. 1046 [2019]), for example, would treat private sector research and development expenditures as one consideration, which incorporates public funding indirectly (because public funding will diminish private expenditures). Public funding could also be directly considered to reduce the price that the company could command in negotiations. Such an approach makes sense: if government investment has reduced the research and development (R&D) cost and risk of a drug's development, then as a matter of both fairness and efficiency, the price should reflect this input.

The government patent use right works similarly: it permits the federal government to override a patent and purchase a product competitively. The law has been extensively used by the federal government, for example to procure equipment for defense at fair prices and without the complexity of evaluating patent claims when assessing responses to a government bid. Section 1498 was also used repeatedly by the Department of Defense and other agencies in the 1960s and 1970s to procure generic medicines such as tetracycline hydrochloride. It was also invoked in 2001, after the government sought to procure surge supplies of an antibiotic in the aftermath of the anthrax attacks: in response, the patent-holding company agreed to cut the price in half and to ensure adequate supply.

Existing law also provides an ex post procedure that can be deployed to a similar end. In the United States, patent holders have never been entitled to prevent the federal government from using, making, or importing a patented technology —instead, it can use the technology freely, paying only a royalty. Initially, this right of "government patent use" was an outworking of the organization of courts and the logic of sovereign immunity. The right has also been

likened to eminent domain, a process that allows government to take private land for public use in exchange for fair compensation. This right permits the government to avoid situations where private rightsholders can hold up the public for more than reasonable compensation, as might happen, for example, where an owner holds the last plot of land needed to complete a new railroad line.

The government patent use right works similarly: it permits the federal government to override a patent and purchase a product competitively. The law has been extensively used by the federal government, for example to procure equipment for defense at fair prices and without the complexity of evaluating patent claims when assessing responses to a government bid.[27] Section 1498 was also used repeatedly by the Department of Defense and other agencies in the 1960s and 1970s to procure generic medicines such as tetracycline hydrochloride.[28] It was also invoked in 2001, after the government sought to procure surge supplies of an antibiotic in the aftermath of the anthrax attacks: in response, the patent-holding company agreed to cut the price in half and to ensure adequate supply.[29]

Codified at 28 U.S.C. §1498, this right immunizes not only federal agencies and programs but anyone acting “by or for” the US, including contractors and other state actors under certain circumstances.[30] Patent holders are entitled to compensation, although not, courts have suggested, the full replacement of anticipated profits.[31] Instead, caselaw suggests that courts should set royalties that take into account a variety of factors, including existing license terms (if there are any), and investments into R&D by the patent-holder.[32]

Practically, government patent use is a straightforward process: federal procurement agents are entitled to accept bids to contracts regardless of patent status, and patent holders cannot prevent their effort.[33] Their only remedy available to rightsholders is a suit for compensation, beginning in the Court of Federal Claims. Drug regulatory requirements can create additional complexity. The FDA does have some enforcement flexibility to permit unapproved medicines into the US, and the government can seek to expedite the process of generic drug approval by asserting its government use rights in proceedings brought by drug companies to try to prevent approval, for example under procedures set out in the Hatch-Waxman Act.[34] If a drug is new and enjoys data exclusivity, which prevents for a period of time the registration of generic versions that rely on the originator’s data, generics face a significant but not insurmountable barrier to entry.[35] Particularly in a pandemic, emergency use authorization —the process under which Gilead was permitted to market remdesivir absent new drug approval —may permit use with limited data and avoid any barrier of data exclusivity. (Drugs issued an EUA also are not awarded data or market exclusivity for the use, which attaches only to approvals.) Government agencies may also possess data needed to approve a drug. In the remdesivir case, for example, the trial that showed efficacy was conducted by the NIH.[36] This normally would allow the government to give such data to third parties or even make such data public, as long as they have not promised companies involved in the trial that they will keep the data confidential.

How might government patent use work in practice to help ensure taxpayers receive the benefits of their investment? Remdesivir provides an example. Suppliers of generic remdesivir exist in India, Bangladesh, and China. The Department of Health and Human Services, which is distributing the existing supply, could put out a competitive tender to seek additional competitive bids for high quality remdesivir, and accept any bids that appeared advantageous, on the condition that they seek an EUA or approval. Gilead would be able to request compensation, and the government could negotiate a fair royalty, taking into account both the government’s investment, and Gilead’s. If no agreement was made, Gilead could seek compensation in the Court of Federal Claims, and a court could determine compensation using a similar means. Because the fair price, when accounting for research and development costs, may well be significantly below Gilead’s price, the government might well also save substantially by invoking section 1498.[37] Even if the government were to pay Gilead the same as it currently is, the public would still have the benefit of adequate and more reliable supply —a significant one, particularly in pandemic times.

Critics of Bayh-Dole often argue that fair-pricing clauses will distort investment away from drug candidates that emerge from federal funding. An ex post or ex ante system for negotiating drug prices would not trigger such concerns, and has the additional benefit that it can be deployed to ensure fair prices for medicines that are not substantially funded by the federal government. Finally, invoking the ex post remedy of government patent use is

especially attractive in a case where there is urgent public health need a substantial public investment, as in remdesivir —it may create the urgency needed to set precedents for the administrative and judicial treatment of this approach, that can assist in decision-making in more ordinary times. The knowledge that the remedy can and will be used may help discipline drug makers seeking excessive returns on their products in the future.

Note

The author has no conflicts to disclose.

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DETAIL

Subjek:	COVID-19 vaccines; Medicine; Mortality; Research &development expenditures; Research funding; Medical research; Federal government; Patents; Prices; Research &development--R &D; Coronaviruses; Public sector; Biomedicine; Health care policy
Ketentuan indeks bisnis:	Subjek: Research &development expenditures Patents Public sector
Lokasi:	United States--US
Perusahaan / organisasi:	Nama: Department of Defense; NAICS: 928110; Nama: Gilead Sciences Inc; NAICS: 325412, 541714
Pengidentifikasi/kata kunci:	Patents; Patent; Pharmaceuticals; Drug Pricing; Bayh-Dole; Government Patent Use
Judul:	Realizing Public Rights Through Government Patent Use
Pengarang:	Kapczynski, Amy
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1

Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	34-38
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.7
ID dokumen ProQuest:	2730846857
URL Dokumen:	https://www.proquest.com/scholarly-journals/realizing-public-rights-through-government-patent/docview/2730846857/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-28
Basis data:	Public Health Database

Ethical Allocation of Scarce Food Resources During Public Health Emergencies

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ABSTRAK (ENGLISH)

Escalating demands for limited food supplies at America's food banks and pantries during the COVID-19 pandemic have raised ethical concerns underlying "first-come, first-served" distributions strategies. A series of model ethical principles are designed to guide ethical allocations of these resources to assure greater access among persons facing food insecurity.

TEKS LENGKAP

Over the course of the COVID-19 pandemic from 2020-2021, scarcities have emerged as a unifying threat to the public's health. Scarcities of tests, protective equipment, masks, hospital beds, ventilators, medical personnel, and vaccinations have all contributed significantly to excess morbidity and mortality.[1]

Deleterious impacts of scarcities tied to the pandemic extend well beyond medical settings. Tens of millions of Americans have lost their jobs, business interests, health insurance, financial support, and livelihoods.[2] Resulting poverty coupled with homelessness and other spiral-ing, economic trends have found millions of persons experiencing limited or uncertain access to food.[3] At the initial height of the pandemic in late April 2020, greater than 50 million Americans were food insecure, many for the first time.[4] More than 20% of all U.S. households reported insufficient resources to buy food.[5]

Significant physical and mental health outcomes extend across affected populations.[6] As households stretch budgets to provide basic food needs, failures to assure other necessities (e.g., medications, safe childcare, stable housing) exacerbate public health impacts.[7] Older adults with chronic health conditions (e.g., diabetes, heart disease) experience heightened health risks when specific nutritional needs are unmet.[8] Food insecure children face higher rates of hospitalizations, behavioral issues, and developmental impairments.[9]

Immediate assistance to remedy food scarcities arose through multiple public and private sector sources,[10] including laudable efforts from America's network of food banks/ pantries (FBPs). In response to significant spikes in demand and diminishing supplies,[11] many FBPs resorted to "first-come, first-served" distribution strategies. Though efficient in serving long lines of recipients in vehicles or on foot, hundreds of thousands of Americans were turned away or otherwise lacked access to FBP resources for multifarious reasons. Escalating cases of COVID-19 in 2021 prolong food distribution challenges.

Profound and unique ethical implications underlie FBPs' emergency distributions impacting the health of at-risk Americans. As presented in Figure 1 and elucidated below, consideration and utilization of a model series of ethical principles guiding FBP distributions may help assure greater access to essential food and sustenance among vulnerable populations during public health emergencies (PHEs).

Model Ethics Principles: Food Bank/Pantry Distributions in Public Health Emergencies

James G. Hodge, Jr., J.D., L.L.M., Principal Investigator | Sarah Wetter, J.D., M.P.H., Lead Investigator

OVERVIEW. Profound ethical dilemmas arise for FBPs whose scarce food supplies are insufficient to meet heightened demands during sustained PHEs. Use of rapid distribution strategies during exigencies are efficient but may negatively impact the health of persons in need who cannot access limited supplies. Equitable distributions of scarce food resources may be guided by specific principles incorporating the following definitions:

Decision-maker: Person tasked with key roles and responsibilities in food distribution operations within FBPs.
Distribution: No-cost allocations of FBP food resources to recipients.
Donors: Individuals and entities donating food, money, or other resources to facilitate distributions among FBPs.
Food bank/pantry (FBP): A non-profit or charitable organization storing food in bulk quantities to allocate largely to specific agencies or programs, including pantries where recipients access resources directly.
Food insecurity: The inability to provide sufficient food over time to support healthy lifestyles.
Food producers: Grocers, restaurants, caterers, or other entities that produce and potentially distribute food to FBPs.
Food sovereignty: One's ability to obtain food resources in furtherance of nutrition, special dietary needs, and cultural/religious beliefs and practices.
Personnel: Regular or temporary employees or volunteers who further FBPs' mission, management, or operations.
Public health emergency (PHE): An occurrence or imminent threat of illness or adverse health outcome posing a substantial risk of death or disability to significant numbers of persons.
Recipient: One determined by FBPs as eligible for food distributions.
Scarcity: The limited availability of FBP food and other sustenance such that supplies are insufficient to meet immediate or long-term demands among recipients.
Stakeholder: An individual or entity interested in or affected by FBPs' food distribution strategies, including personnel, donors, other suppliers, recipients, and community partners.
Vulnerable populations: Communities or persons at greatest risk of food insecurity leading to deleterious health impacts.

MODEL PRINCIPLES. The following ethics principles and subsidiary practice-based applications are listed below in no order of priority.

4. EQUITY IN FOOD DISTRIBUTIONS. Scarce food resources must be managed during PHEs to prevent and mitigate food insecurity among vulnerable populations.
- **4.1. Needs-based prioritization.** In prioritizing distributions, decision-makers may consider factors including household size/income, food access from other sources, health factors, other need-based indicators, and impacts on recipients.
- **4.2. Information collection.** Where possible, personnel may ask recipients whose needs are unmet to provide contact information to be prioritized for future distributions.
- **4.3. Limited application and duration.** Food supplies should be reserved for vulnerable populations only as needed. Prioritization of food resources should be limited in duration and discontinued when supplies sufficiently meet demand.

5. LIMITING FOOD ACCESS BARRIERS. Discrimination, stigmatization, or other access barriers to food among vulnerable populations during PHEs must be ameliorated to the extent possible.
- **5.1. Protections for recipients.** FBPs must create an environment that is safe and respectful of all recipients through supportive policies (e.g., line safety management) and personnel trainings promoting recipients' dignity and privacy.
- **5.2. Enhancing access.** Vulnerable populations may be provided distinct times or unique opportunities to access FBPs to receive food set aside for their immediate access.
- **5.3. Transportation barriers.** Vulnerable populations lacking transportation to FBPs may be provided special access to transportation services.

6. AMELIORATING FOOD INSECURITY. FBPs must be prepared to diversify their allocation strategies to meet communal needs, especially among vulnerable populations.
- **6.1. Flexibility.** As conditions shift rapidly during PHEs, decision-makers should regularly revisit and revise distribution strategies to ameliorate food insecurity.
- **6.2. Maximizing resources.** Personnel must work to maximize available supplies through additional donations and coordination among other FBPs to direct supplies to specific locations in need.
- **6.3. Avoiding waste.** To avoid waste, donated food items that do not conform to FBPs' specific packaging or other requirements may be provided to entities able to accept and safety distribute them.

7. RESPECT FOR FOOD SOVEREIGNTY. Even during periods of scarcity, personnel should acknowledge unique dietary needs and preferences of recipients where possible.
- **7.1. Amenable services.** To maintain efficiency while promoting food sovereignty, personnel should devise strategies amenable to recipients with unique dietary needs or preferences, including separate lines, sequestered food resources, or delivery options.

1. PROTECTING FBP PERSONNEL & RECIPIENTS. Decision-makers are responsible for ensuring a safe and healthy work environment for FBP personnel and recipients.
- **1.1. Risk assessment.** Decision-makers must regularly re-assess the health risks to personnel distributing food to recipients under evolving circumstances.
- **1.2. Evidence-based practices.** Emergency food distribution policies, sanitation procedures, and social distancing requirements should be based on "best practices" to avoid harmful impacts among personnel and recipients during PHEs.
- **1.3. Personnel protections.** Personnel should be provided appropriate protective equipment and services (e.g., paid sick leave, workers' compensation) during PHEs.

2. STEWARDSHIP OF FOOD RESOURCES. Decision-makers must anticipate food shortages during PHEs and strategize to ethically distribute food resources to mitigate scarcity.
- **2.1. Identify community needs.** Prior to impending PHEs, personnel should ascertain the composition and needs of the community served and identify vulnerable populations.
- **2.2. Mitigation.** Personnel should identify potential issues during PHEs (e.g., shortages of personnel or food) and align with entities (e.g., food producers) to acquire additional personnel and distribute excess supplies to recipients.
- **2.3. Allocation plan.** A written distribution plan should clearly describe considerations for prioritizing recipients in PHEs when demands exceed supplies.

3. CIVIC ENGAGEMENT IN POLICIES. Developing food distribution plans or policies should incorporate input from diverse stakeholders to promote practicality and public trust.
- **3.1. Community partnerships.** FBPs should establish diverse community partnerships with (a) food producers, (b) stakeholders, (c) government entities able to connect FBPs to persons at risk of food insecurity, and (d) entities that may assist with transporting persons or food during a PHE (e.g., USPS, ride share services).
- **3.2. Deliberative and inclusive process.** Interested persons and entities should have an advance opportunity to participate in planning processes for distributing scarce food resources during PHEs via public meetings, advisory boards with diverse stakeholders, or other means.
- **3.3. Recognizing injustice.** Community engagement should help (a) uncover historic or contemporary inequities that led to food insecurity and (b) justify prioritization plans.
- **7.2. Medical/health needs.** FBPs may distribute food supplies tailored to unique dietary and nutritional needs due to health factors (e.g., food allergies, diabetes, pregnancy) of recipients.
- **7.3. Religious, cultural, and personal practices/ preferences.** To avoid waste, promote food sovereignty, and address limitations (e.g., lack of stable housing, refrigeration, or appliances), personnel should accommodate specific recipients' practices and preferences.

8. TRANSPARENT & ACCESSIBLE COMMUNICATIONS. Distribution policies in times of scarcity should be open, accessible, and publicized prior to and during implementation in PHEs.
- **8.1. Communication systems.** FBPs should design communication strategies to reach vulnerable populations, including those lacking online access, through varied media (e.g., social media, email, websites, toll-free hotlines, broadcasts, and printed materials) circulated among stakeholders.
- **8.2. Openness.** Public communications should clarify FBP distribution policies, including prioritized populations, documentation to receive scarce food resources, and service methods. Two-way communication systems allowing potential recipients to share concerns are preferred.
- **8.3. Shifts in policies.** The public must be regularly informed of shifting distribution policies in PHEs through established communication channels.

9. ACCOUNTABILITY. Decision-makers are publicly accountable for assuring that personnel apply distribution policies fairly and appropriately.
- **9.1. Consistency.** Allocation procedures must be standardized and applied consistently to promote equality and achieve best outcomes across vulnerable populations.
- **9.2. Progress reports.** Decision-makers should monitor and report progress on a timely basis in meeting community needs, identifying successes, and rectifying failures of distribution practices.
- **9.3. Publication.** Progress reports should be shared with donors and made publicly accessible with opportunities for input.

10. PRIORITIZATIONS. Following distribution events during scarcity, personnel should seek to identify persons with unmet needs and prioritize them for additional available supplies.
- **10.1. Assessing unmet needs.** Personnel should conduct post-distribution efforts and data gathering to assess and record unmet needs.
- **10.2. Obviating needs.** Persons identified as having unmet needs should be prioritized for future available supplies via advance invitations or direct deliveries.
- **10.3. Advocacy.** Personnel should seek innovations in food distribution strategies to reduce food insecurity and enhance equity among vulnerable populations.

Perbesar gambar ini.

Food Demands and Distributions During COVID-19

Americans' demand for food assistance rose at an extraordinary rate during the COVID-19 pandemic.[12] Despite

infusions of federal and state emergency funds supporting multiple food access programs (e.g., SNAP benefits, school lunches) Americans' needs were insatiable.[13] Unprecedented levels of hunger presented unique challenges for FBPs faced with depleted supplies, receding volunteers, and extensive public health infection control requirements during the pandemic. Feeding America, the nation's largest network of food banks, reported in November 2020 that over 80% of FBPs across the country were serving more people than they did a year ago, yielding a 50% increase in food distributed nationally.[14]

Profound and unique ethical implications underlie FBPs' emergency distributions impacting the health of at-risk Americans. As presented in Figure 1 and elucidated below, consideration and utilization of a model series of ethical principles guiding FBP distributions may help assure greater access to essential food and sustenance among vulnerable populations during public health emergencies (PHEs).

Spikes in demand were compounded by supply-side limitations. FBPs experienced significant supply shortages. Private sector grocers, normally a reliable source for substantial inventories among FBPs, donated fewer food items as consumers depleted their shelves.[15] Direct food acquisition costs from manufacturers increased substantially for FBPs as well, lending to a national supply gap of 10 billion pounds of food estimated across FBPs between September 2020 to June 2021.[16] Whenever FBP supplies cannot meet demand, some persons seeking emergency food resources may leave empty-handed. Recognizing the exigencies, FBPs adjusted their normal practices and modified distribution strategies to rapidly distribute food to as many persons as possible.[17] In lieu of usual on site, grocery-store style services, many pantries hosted mobile food pantry events to bring goods directly to consumers.[18] Pre-pandemic eligibility requirements, typically used to vet need-based recipients, were eased or waived.[19]

Many FBPs also began distributing food via pre-determined drive through sites (e.g., fairgrounds, stadiums, parking lots) allowing contactless service consistent with social distancing requirements.[20] Persons with means of transportation arrived early to receive pre-assembled boxes of food placed in their vehicles. In places like San Antonio in April 2020, persons waited for hours in lines over 6 miles long and 10,000 cars deep.[21] Those first in line were first to receive food.[22] In some case, FBPs rationed supplies further by limiting the number of food boxes distributed per vehicle, even if a vehicle contained members of several families.[23]

Food Access Barriers and Ethical Conundrums

Access limitations and other challenges related to FBPs use of rapid food distribution approaches during the pandemic profoundly affected at-risk individuals and families seeking assistance. Hundreds of thousands of Americans "lost out" either because (1) they were at the end of the line when supplies ran dry; (2) distinct access barriers kept them from lining up at all; or (3) the supplies they received were insufficient in providing sustenance. FBPs across multiple states (e.g., California, Illinois, Michigan, Ohio, Pennsylvania, Texas) reported turning people away in the Spring 2020 due to insufficient food supplies.[24] Many in-need of food were unable to travel to FBPs or wait in lines due to their health (e.g., seniors, disabled persons), care-taking needs (e.g., mothers with infants), or transportation barriers (e.g., homeless persons). Fear of stigma or discrimination, especially among immigrant populations, posed additional barriers. Rumors of federal Immigration and Customs Enforcement (ICE) raids thwarted undocumented immigrants from seeking food assistance in Texas even prior to the pandemic.[25] Others arriving at FBP drive throughs did not acquire foods necessary to fulfill their health needs (e.g., persons with diabetes, allergies, or who are pregnant), or aligned with their cultural/ religious practices due to FBP limitations on pre-boxed food selections.[26]

Persons at highest risk of food insecurity and related health consequences likely faced the greatest hurdles to accessing FBP resources, lending to significant disparities. Similar issues underscore the development of ethical plans for distributing other scarce resources, such as medical supplies, services,[27] and vaccines during PHEs.[28] Ethical allocations of these limited resources during the pandemic accommodate populations most in-need and likely to benefit. As an essential resource for health and well-being, food distributions during periods of scarcity in PHEs should ensure vulnerable populations are not further disadvantaged.

Ethical Norms Underlying the Distribution of Scarce Food Resources

Specific ethics principles may help guide FBPs' distribution of limited food resources to quell rates of food insecurity

in emergencies. With contributions from our project advisory group, we developed a series *of Model Ethics Principles: Food Bank/Pantry Distributions in Public Health Emergencies* ("Model Principles") (see Figure 1). These principles were derived from initial research and applications focused on prevailing ethics approaches to emergency distributions of scarce health/medical resources (e.g. ventilators, ICU beds, vaccines). From these analyses arose multiple precepts with input from experts in health and food/nutrition policy, emergency preparedness, FBP operations, and ethics.

The resulting Model Principles set forth core ethics statements (e.g., 1, 2, 3) underlying the distribution of scarce food resources supplemented by correlated, practical guidance (e.g., 1.1, 1.2, 1.3) for their implementation. The principles are not intended to create legal standards or set affirmative duties or obligations. Rather they guide FBP decision-makers and personnel at all levels toward more equitable food distribution policies and practices during periods of scarcity in PHEs.

Acknowledging the complex, laudable objectives of FBPs seeking to mete out food supplies in exigencies, the Model Principles proffer alternatives to typical distribution strategies that can unfairly disadvantage vulnerable populations facing barriers to accessing limited FBP resources. Assuring the health and safety of all persons involved in distributions, including FBP staff, volunteers, and recipients, is preeminent (Principle 1). FBP decision-makers must create a safe and healthy environment at distribution sites and ameliorate diverse risks ranging from infection spread to stigma and discrimination. This includes implementing evidence-based practices and protections for FBP personnel and recipients through line safety management (Principle 1) and personnel trainings on anti-discrimination and anti-stig-matization (Principle 5).

Advance planning and stewardship of food resources (Principles 2, 3) facilitate expedited, flexible distributions amid changing environments. Mechanisms for building public trust interwoven in the Model Principles strike an intricate balance between promoting individuals' needs for adequate food and FBP efficiencies in serving the greatest number of persons. Data collection and record keeping enable FBPs to calculate and better predict recipients' demands and promote public accountability through dissemination of progress reports and opportunities for stakeholder input (Principles 9, 10).

Equitable allocation of FBP resources during scarcity is also key (Principles 4, 5). Needs-based prioritization schemes should promote equity and social justice by serving populations at heightened risk of food insecurity and those facing specific food access barriers such as lack of transportation. Use of pre-packaged food boxes may be efficient during periods of scarcity, but individuals' dietary needs and cultural/religious preferences should also be respected where possible (Principle 7).

Serving the greatest numbers of persons possible in emergencies entails identification, communication, and prioritization of vulnerable populations for FBP distributions (Principle 10). FBP partners and other stakeholders should devise distribution policies and communicate them transparently leading up to and during periods of food scarcity. Communication systems should include alternatives to reach at-risk individuals, including those lacking regular access to electronic media (Principle 8).

Active engagement in diverse community partnerships allows FBPs to connect with additional persons or supplies that can help obviate shortages (Principle 3). While decision-makers are accountable to donors and recipients to implement distribution policies fairly (Principle 9), they must also adapt to shifting circumstances through diverse distribution strategies that maximize resources and avoid waste (Principle 6). Following food distribution events where supplies are insufficient to meet community needs, for example, FBPs should identify and advocate for underserved persons, prioritizing them for future distributions (Principle 10).

Collectively the Model Principles are crafted to guide emergency distributions of scarce food resources through FBPs to assure equitable allocations and limit deleterious impacts specifically among vulnerable populations. How these principles are operationalized in the field among FBPs may vary significantly depending on (a) existing policies and available resources, (b) extent, type, and duration of the emergency, (c) size of the community, and (d) scope of needs experienced among community members. Irrespective of the unique settings or invocations of these principles, the goal remains the same: *assuring equitable access on expedited bases to as many food insecure*

Americans as possible to limit or prevent correlated public health harms.

Acknowledgments

Support for this research and findings was provided through a Presidential Award grant dated September 9, 2020 from The Greenwall Foundation, New York, NY, to the Sandra Day O'Connor College of Law, ASU. The authors thank the members of the project advisory group for their input and guidance: Leila Barraza, J.D., M.P.H.; Ruth Gaare Bernheim, J.D., M.P.H.; Ruth Faden, Ph.D., M.P.H.; Lance Gable, J.D., M.P.H.; Amanda Karls, J.D.; Jill Mahoney, J.D., M.P.H.; Michael McDonald, M.I.B.; Stephanie Morain, Ph.D., M.P.H.; Daniel Orens-tein, J.D., M.P.H.; Jennifer Piatt, J.D.; Anne Readhimer, M.S.; Sarah Roache, L.L.M., L.L.B.; Lainie Rutkow, J.D., Ph.D.; Sallie Thieme Sanford, J.D.; Kristopher Tazelaar; Carrie Waggoner, J.D.; Erica White; and Lawanda Williams, M.P.H., L.C.S.W.-C.

Note

The author has no conflicts to disclose.

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About This Column

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DETAIL

Subjek:	Ethics; Public health; COVID-19 vaccines; Diabetes; Principles; Ventilators; COVID-19; Food programs; Emergency preparedness; Scarcity; Homeless people; Pandemics; Emergencies; Banking; Older people; Medical supplies; Food security; Coronaviruses; Vehicles
Ketentuan indeks bisnis:	Subjek: Scarcity
Lokasi:	Texas; United States--US
Pengidentifikasi/kata kunci:	Emergency Preparedness; Food banks; COVID-19; Food bank; Public Health Emergency of International Concern; Food security; Public health; Public Health; Food Insecurity; Ethics; Policy
Judul:	Ethical Allocation of Scarce Food Resources During Public Health Emergencies
Pengarang:	Wetter, Sarah; Hodge, James G; Carey, Emily
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	132-138
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Columns: Public Health and the Law
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105

e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.18
ID dokumen ProQuest:	2730846854
URL Dokumen:	https://www.proquest.com/scholarly-journals/ethical-allocation-scarce-food-resources-during/docview/2730846854/se-2?accountid=211160

Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database

Improving the Ethical Review of Health Policy and Systems Research: Some Suggestions

Persad, Govind

ABSTRAK (ENGLISH)

Consistent and well-designed frameworks for ethical oversight enable socially valuable research while forestalling harmful or poorly designed studies. I suggest some alterations that might strengthen the valuable checklist Rattani and Hyder propose in this issue of *Journal of Law, Medicine &Ethics*1 for the ethical review of health policy and systems research (HPSR), or prompt future work in the area.

TEKS LENGKAP

Consistent and well-designed frameworks for ethical oversight enable socially valuable research while forestalling harmful or poorly designed studies. I suggest some alterations that might strengthen the valuable checklist Rattani and Hyder propose in this issue of *Journal of Law, Medicine &Ethics*[1] for the ethical review of health policy and systems research (HPSR), or prompt future work in the area.

Institutional Versus Individual Interventions

Rattani and Hyder describe HPSR as "investigation, evaluation, and/or implementation of healthcare strategies or issues at the institutional or systems-level."[2] But their case study involves an *individual-level* intervention —a conditional cash transfer —for which individual informed consent was obtained, just as in traditional clinical research. In contrast, much HPSR involves changes to *institutional* rules or policies, such as changes to health system budgets, staffing, or supply chains, where individual consent is infeasible. More detail about how the checklist applies to institutional HPSR, and who should review it, would strengthen the project. It is not obvious that research ethics committees should review institutional-level HPSR,[3] and current law in the United States exempts some types of HPSR —such as research on the design of benefit programs —from research ethics committee review, though not from review altogether.[4]

The distinction between individual and institutional HPSR might also help clarify the proper role of gatekeepers. When individual consent is feasible, respect for autonomy supports a presumption in favor of leaving enrollment decisions in the hands of potential participants, not gatekeepers. By contrast, the infeasibility of individual consent for institutional HPSR makes representatives more relevant. Yet identifying legitimate representatives is challenging. If institutional HPSR is proposed for a political jurisdiction, politically legitimate representatives are appropriate gatekeepers. But in the absence of recognized structures of representation, authorizing informal representatives to approve or veto studies presents complexities.[5]

Incentives, Harm, and Undue Influence

Rattani and Hyder suggest that "the use of incentives creates a unique risk for harm, especially in LMICs, where the socioeconomic effects of poverty may inappropriately influence participation."[6] Incentives to participate in a risky study could in principle produce undue influence by leading participants to misjudge risks, though the reality of that danger is empirically uncertain.[7] But harm from undue influence requires that the *underlying intervention* be risky: incentives cannot make a low-risk intervention into a high-risk one. Meanwhile, though incentives may activate financial motivations, financial motivations do not make participation inappropriate.[8] I worry that the checklist's concerns about incentives may amplify existing misconceptions among research ethics committees that incentives undermine autonomy[9] and motivate disproportionate scrutiny of incentive-based research. It is doubtful that providing an intervention without consent —as institutional-level HPSR often involves —raises fewer concerns than incentivizing its use.

Further, the same "incentives that expand a participant's range of opportunities" may also "entice participants to undergo risks they would not otherwise"[10]: an incentive can expand opportunity while leading participants to assume risks. This is recognized outside research: "in the realm of work it is ethically permissible and not undue influence to offer money as an incentive to get people to perform activities that they would otherwise not."[11] Likewise, workers can accept time-limited incentives (like bonuses) without being harmed by their temporary receipt. This calls into doubt the suggestion that consensual provision of temporary incentives in research is harmful.

The "principlist" (autonomy, beneficence, nonmaleficence, justice) framework familiar in clinical ethics is used to ground the checklist. This framework fits uneasily with research ethics, especially the systems-level ethical issues HPSR presents. For instance, Rattani and Hyder find themselves driven to transmute principlist respect for autonomy to a nonspecific principle of respect. Similarly, it is not clear that beneficence and nonmaleficence should be understood as distinct principles, or separate from justice, in research. Rattani and Hyder understand justice to include improving the well-being of the worst off, which seems like a species of beneficence. Grounding the checklist in ethical frameworks more commonly used in research ethics, and/or frameworks used in public health or population-level bioethics, might enhance the ethical review of HPSR.

Avoiding Research Exceptionalism and Overbroad Mandates

Many HPSR interventions, including conditional cash transfers, could be implemented outside research —either by governments or by employers and philanthropists —without research ethics committee review, and often even without consent. This distinguishes many HPSR interventions from investigational treatments, for which consent is required even outside research. And it raises an important question about research exceptionalism: why should

providing an intervention via HPSR prompt greater ethical review than simply implementing the intervention without research?

While the checklist's goal of improving consistency in HPSR review is laudable, imposing clinical-style REC review on HPSR, or imposing more stringent duties of justice on researchers than non-researchers, creates counterproductive incentives to implement policy changes without research.[12] Clarifying which aspects of the checklist entail mandates as opposed to encouragement could help address this concern. Consent when practicable and not waived (II(2a)), and a reasonable balance of risk and benefit (VII(6)), should be mandatory. By contrast, other aspects of the checklist, such as the details of community engagement and research translation, support encouragement but not mandates.

Excessively aspirational mandates risk either obstructing valuable research or prompting conceptual contortions from research ethics committees and researchers. For instance, while global health research *as an enterprise* should promote health equity and the interests of the worst off, *each* HPSR study in a LMIC need not necessarily to realize those goals. Many low- and middle-income countries are large and economically diverse, and mandating that all HPSR in low- and middle-income countries achieve global justice goals will incentivize overbroad definitions of equity and poverty. It would be better to recognize that just as some HPSR in Boston that neither serves nor harms global justice is acceptable, so is some similar research in Bangalore. Similarly, mandating equipoise in HPSR, as opposed to a reasonable risk/benefit balance, seems dubious given the contested status of equipoise even in medical research.[13]

Mandating "[e]quality in the distribution of power to make decisions, object, or modify various aspects of the study …between researchers and communities"[14] likewise presents concerns. The researcher-community relationship better fits a separation-of-powers model than equal, coextensive power. Typically, participants (whether groups or individuals) have decisive —not merely equal —power to decide whether to enroll or withdraw. But they do not have equal power to modify the design of ongoing studies, and permitting such modification without careful planning can erode the social value and scientific validity needed for research to be ethical. Research ethics should consider how to ensure fairness and prevent harm under conditions of unequal power, rather than imposing a requirement of equal power as a precondition to research.

Selecting the Best Ethical Framework

The "principlist" (autonomy, beneficence, nonmalefi-cence, justice) framework familiar in clinical ethics is used to ground the checklist.[15] This framework fits uneasily with research ethics, especially the systemslevel ethical issues HPSR presents. For instance, Rattani and Hyder find themselves driven to transmute principlist respect for autonomy to a nonspecific principle of respect. Similarly, it is not clear that beneficence and nonmaleficence should be understood as distinct principles,[16] or separate from justice, in research. Rattani and Hyder understand justice to include improving the well-being of the worst off, which seems like a species of beneficence. Grounding the checklist in ethical frameworks more commonly used in research ethics,[17] and/or frameworks used in public health or population-level bioethics,[18] might enhance the ethical review of HPSR.

Note

Professor Persad has received funding from the Greenwall Foundation, compensation from the ASCO Post for column authorship, and consulting fees from WHO.

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DETAIL

Subjek:	Intervention; Research ethics; Bioethics; Human subjects; Consent; Incentives; Medicine; Participation; Exceptionalism; Low income groups; Medical research; Public health; Committees; Design; Ethics; Research; Health care policy
Ketentuan indeks bisnis:	Subjek: Incentives
Pengidentifikasi/kata kunci:	Research Ethics; Systems theory; Research; Health policy; Ethics; Health Policy; Systems Research; Incentives; Global Health
Judul:	Improving the Ethical Review of Health Policy and Systems Research: Some Suggestions

Pengarang:	Persad, Govind
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	123-125
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles: Commentary
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	174 8720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Commentary
DOI:	https://doi.org/10.1017/jme.2021.16
ID dokumen ProQuest:	2730846813
URL Dokumen:	https://www.proquest.com/scholarly-journals/improving-ethical-review-health-policy-systems/docview/2730846813/se-2?accountid=211160
Hak cipta:	
Terakhir diperbarui:	2023-11-28

Soft Law Possibilities in Global Health Law

Sekalala, Sharifah; Haleema Masud

ABSTRAK (ENGLISH)

The COVID-19 crisis has reignited questions about the centrality of law in stemming the spread of infectious diseases. There are questions about whether new laws can enable greater international collaboration, collective action and shared responsibility and accountability for new global health threats. In addressing these global health threats, it will be necessary to look to global health law, reflecting “the study and practice of international law that shapes norms and processes and institutions to create the conditions for people throughout the world to attain the highest possible level of physical and mental health.”1 These sources of global health law have been categorized under international law into hard law (e.g., treaties that bind states) and soft law (e.g., codes of practice negotiated by states).2

This column examines the central importance of soft law in developing and implementing global health law. Beginning by situating the role of hard and soft law in the frameworks of the World Health Organization (WHO), this column illustrates the centrality of soft law in global health law governance. The column then looks to the potential application of soft law in resolving some of the wider questions of infectious disease control in the wake of the COVID-19 crisis, concluding that soft law is complementary to the hard law, as it offers a flexible way to mobilize the consent and commitment of states in a rapidly changing global health environment.

TEKS LENGKAP

Introduction

The COVID-19 crisis has reignited questions about the centrality of law in stemming the spread of infectious diseases. There are questions about whether new laws can enable greater international collaboration, collective action and shared responsibility and accountability for new global health threats. In addressing these global health threats, it will be necessary to look to global health law, reflecting “the study and practice of international law that shapes norms and processes and institutions to create the conditions for people throughout the world to attain the highest possible level of physical and mental health.”[1] These sources of global health law have been categorized under international law into hard law (e.g., treaties that bind states) and soft law (e.g., codes of practice negotiated by states).[2]

This column examines the central importance of soft law in developing and implementing global health law. Beginning by situating the role of hard and soft law in the frameworks of the World Health Organization (WHO), this column illustrates the centrality of soft law in global health law governance. The column then looks to the potential application of soft law in resolving some of the wider questions of infectious disease control in the wake of the COVID-19 crisis, concluding that soft law is complementary to the hard law, as it offers a flexible way to mobilize the consent and commitment of states in a rapidly changing global health environment.

Hard Law and Soft Law in Global Health

Although hard law is binding and soft law is not, the distinction is actually more nuanced. Legal norms are not binary, but are based on graduated normativity, from binding to non-binding.[3] Global health law ranges from binding treaties

and norms (e.g., those encompassed in the right to health and other human rights norms codified under international law) to authoritative yet non-binding normative instruments, such as resolutions, declarations, guidelines, protocols, and recommendations. The implementation of both hard and soft law may rely on policy recommendations which need not have any normative content at all.

The Constitution of the World Health Organization (WHO) grants the World Health Assembly considerable powers to develop global health law.[4] Yet, in its history, the WHO has developed only two treaties: the Framework Convention on Tobacco Control (FCTC) and the International Health Regulations (IHR), and many scholars believe that the WHO should have used its lawmaking authority to agree to more binding law to address global health problems.[5]

The WHO has struggled to fulfill its mandate to develop global health law for three main reasons. Firstly, many global health issues are highly complex and highly interdependent with other international law regimes, such as trade and the environment, which makes it difficult for the WHO to gain international agreement in the World Health Assembly. Secondly, global health outcomes are increasingly determined by non-state actors, such as corporations, which are outside of the direct scope of WHO governance. Thirdly, as seen in the two treaties that the WHO has developed, it is not always easy for the WHO to catalyze state implementation.

The FCTC entered into force in 2005, creating legally binding norms to reduce the demand for and supply of tobacco, with information sharing to achieve tobacco control globally. The FCTC is often viewed as a momentous achievement; however, the treaty took over a decade to negotiate, with a politically contentious process in which states struggled to rein in the power of Big Tobacco, which lobbied state representatives in an effort to prevent FCTC adoption. Despite its success, the treaty has two major weaknesses: First, it contains ambiguous language, which allows countries broad discretion in interpreting treaty provisions, leading to inconsistent implementation. Second, it does not provide resources to low- and middle-income countries to support implementation of the FCTC. Big Tobacco has continued to fight back against the FCTC, bringing cases under multiple international law regimes, such as the World Trade Organization and investment treaties, to prevent states from adopting tobacco-control legislation.[6]

Likewise, the IHR, which aims to prevent, protect, and control the spread of infectious diseases, took ten years to negotiate and has been critiqued for its ambiguity with regards to the notification system, lack of certainty about the circumstances under which diseases are declared a Public Health Emergency of International Concern, and above all for its lack of accountability for violations. For instance, countries have often failed to inform the WHO when facing a disease outbreak, have remained unprepared to respond to public health emergencies in line with their IHR obligations, and have rejected specific WHO advice in the emergency response, instituting additional measures such as border closures in violation of their human rights obligations.[7] Without accountability under global health law, states have not complied with key provisions that are set out by the IHR, thereby leading to the spread of infectious diseases.[8]

The Benefits of Soft Law

Looking beyond these treaties, the WHO has been very successful at using soft law for global health governance: to regulate issues such as unhealthy food and diets, give normative clarification to treaties, set standards, ensure monitoring and accountability, and serve as precursor to hard law, especially when the science is still uncertain or there is a lack of political consensus.

This column examines the central importance of soft law in developing and implementing global health law. Beginning by situating the role of hard and soft law in the frameworks of the World Health Organization (WHO), this column illustrates the centrality of soft law in global health law governance. The column then looks to the potential application of soft law in resolving some of the wider questions of infectious disease control in the wake of the COVID-19 crisis, concluding that soft law is complementary to the hard law, as it offers a flexible way to mobilize the consent and commitment of states in a rapidly changing global health environment.

Soft laws have grown within the WHO framework because they are easy and quick for states to adopt. Their non-binding nature can help achieve consensus in difficult areas where different countries have different interests but also where the commercial interests of private actors are involved. For instance, in the Doha Declaration on the

TRIPS Agreement and Public Health, soft law was used to clarify which norms trumped others when there was a clash between the competing regimes of international trade law and global health law.[9] This soft law agreement allowed countries to prioritize access to medicines as part of the right to health over the rights of intellectual property, thereby ensuring access to generic medicines.

Additionally, soft law can also form a basis for hard law, especially in highly technical areas, or where states need political space for consensus building. The FCTC was agreed in 2003 after a series of 17 non-binding resolutions on tobacco control were passed between 1970 and 1988 by the World Health Assembly, and built upon the 1998 establishment of the WHO Tobacco Free Initiative.

Nevertheless, soft law does have limitations. If not backed by an authoritative body, soft law may lack the binding obligations necessary to motivate states to act. For example, the WHO's Global Code of Practice on the International Recruitment of Health Personnel has had little effect on domestic policies and practices because it has ambiguous provisions without binding obligations to prevent the recruitment of essential health personnel across countries.[10]

Another disadvantage of soft law is that organizations that rely on it may be perceived as weak. For example, if the WHO acts principally through non-binding agreements, while other sectors develop hard law, this may prevent the WHO from being seen as an authoritative international actor,[11] which could cause states to skew their regulatory preferences toward areas in which they may face accountability for non-compliance, causing a regulatory chill in public health regulation.[12] However, there is evidence that states are agreeing to fewer hard law treaties over time, which means that, for the moment, soft law remains the most plausible way to frame global governance.[13]

In strengthening soft law, indicators provide a path to evaluate progress and promote accountability. For instance, the Office of the High Commissioner for Human Rights has developed human rights indicators to monitor human rights structures, processes and outcomes as a way of evaluating human rights implementation across countries.[14] Similarly, UNAIDS uses a series of indicators that arise out of the UN Political Declarations on AIDS in order to measure how countries are responding to the AIDS pandemic.[15] Soft law thus brokers compliance through monitoring and review to facilitate accountability for compliance with international agreements.

Reimagining Soft Law in the Wake of the COVID-19 Crisis

The current COVID-19 pandemic has shown that global health law is critical in responding to infectious diseases, with four specific possibilities for soft law to address the pandemic:

- 1. *Clarification of State Obligations* The WHO could use soft law to clarify and reinforce technical guidance in areas such as contact tracing, testing, treatment, and public health responses. While much of this guidance has been technical, there is scope for this guidance to become normative if it reinforces existing legal norms, facilitating state compliance with the law.

- 2. *Soft Law Amendments to the IHR* Although the WHO has played a critical role in global health governance, there is uncertainty about its role in a post-pandemic world. Scholars have identified a number of weaknesses in the IHR.[16] There have been calls to give the IHR wider-ranging enforcement powers, involve more private sector actors, and expand its core man-date.[17] However, current geopolitical tensions also make it difficult to revise the IHR. Soft law might provide a way forward.[18]

- 3. *Normative Guidance* The WHO could use soft law to further normative guidance in areas such as the relationship between the IHR and human rights. Human rights have a strong textual foundation in the revised IHR (2005), both as a protection against measures that unnecessarily interfere with individual liberties and for interpreting and implementing every aspect of the IHR, notably the right to health.[19] The COVID-19 crisis has highlighted the need for more normative guidance within the context of human rights: for instance, large-scale quarantines, discrimination against vulnerable groups, increased digital surveillance, and access to vaccines. For instance, the existence of the COVAX facility to finance vaccines for people in the developing world could be strengthened if the

WHO gave some normative guidance on international obligations of “solidarity” as part of the essential fulfillment of the right to health.

•4. *Better Enforcement Mechanisms* Previously, the WHO used soft law to enable accountability. For instance, when Indonesia refused to share its samples of the avian flu virus, because it feared that it would not get a fair share of the resulting scientific discoveries, the WHO PIP Framework (a soft law instrument developed under the WHO) was created to incorporate benefit sharing for countries, including both monetary and inkind benefits.[20] There have been several suggestions about how the WHO could use soft law to improve enforcement, including by creating a forum that would try to ease political tensions through sharing and discussing national risk assessments, mediating informally between states, and enabling greater coordination in the response to infectious diseases.[21] The WHO Director General has also proposed a system of universal periodic review, in which countries agree to a regular and transparent review of each nation’s preparedness.[22]

Conclusion

Global health law is largely constituted through soft law, and soft law needs to be viewed as complementary to hard law. An understanding of soft law renews our optimism about what is possible in global health law, as using soft law offers a quick and flexible way to mobilize the consent and commitment of states in a rapidly changing environment with multi-stakeholder involvement.

Note

The authors have no conflicts of interest to declare.

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About This Column

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DETAIL

Subjek:	Agreements; Infectious diseases; Treaties; International law; Global health; Accountability; COVID-19; International; International agreements; Pandemics; Public health; Tobacco; Coronaviruses; Human rights; Disease control; Mental health services; Collective action; State; Threats; Crises

Perusahaan / organisasi:	Nama: World Health Assembly; NAICS: 923120; Nama: World Health Organization; NAICS: 923120
Pengidentifikasi/kata kunci:	Soft Law; International law; Soft law; World Health Organization; COVID-19; Health law; Global Health Law; Global Health Governance; International Health Regulations; COVID-19
Judul:	Soft Law Possibilities in Global Health Law
Pengarang:	Sekalala, Sharifah; Haleema Masud
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	152-15 5
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Columns: Global Health Law
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.20
ID dokumen ProQuest:	2730846743

Regulation of Overlapping Surgery: Progress and Gaps

Kalbfell, Elle L; Schwarze, Margaret L

ABSTRAK (ENGLISH)

Following a highly publicized *Boston Globe Spotlight* report on concurrent and overlapping surgery, the U.S. Senate Finance Committee released patient safety recommendations, strongly advising hospitals to prohibit concurrent surgery and enact policies to regulate overlapping surgery. In this issue of *The Journal of Law, Medicine &Ethics*, Mitchell and colleagues present an exploration of how U.S. hospitals have adopted and implemented policies relative to the Finance Committee recommendations.1 Although their sample is small and difficult to generalize given the sampling strategy and low response rate, the results are important. They found broad agreement about prohibition of concurrent surgery and significant variation in the existence of and details related to policies about overlapping surgery.

TEKS LENGKAP

Following a highly publicized *Boston Globe Spotlight* report on concurrent and overlapping surgery, the U.S. Senate Finance Committee released patient safety recommendations, strongly advising hospitals to prohibit concurrent surgery and enact policies to regulate overlapping surgery. In this issue of *The Journal of Law, Medicine &Ethics*, Mitchell and colleagues present an exploration of how U.S. hospitals have adopted and implemented policies relative to the Finance Committee recommendations.[1] Although their sample is small and difficult to generalize given the sampling strategy and low response rate, the results are important. They found broad agreement about prohibition of concurrent surgery and significant variation in the existence of and details related to policies about overlapping surgery.

Surgery is a Scarce Resource

To the uninitiated, overlapping surgery may seem an unjustified and indefensible procedure. Surgery is depicted in the media as all-encompassing and fast paced, given the need to entertain viewers. The reality of surgery is not

shown. Surgeons spend a lot down time waiting for cases to start and during turnover between cases. It can take up to two hours to get patients onto the operating table and induce anesthesia, particularly for major surgeries that need invasive monitoring or specialized equipment. Surgical expertise is rarely needed to put a dressing on an incision, to witness a patient emerge from anesthesia or to get the patient out of the operating room, yet these procedures can take an additional 30-45 minutes. While policymakers and patients view surgery as an intense undertaking from start to finish, they seem unaware of the non-critical and non-surgical steps that take place in the operating room. For surgeons who spend hours idly waiting, knowing they have many hours of operating to go, the potential to start a case in one room while the previous case is finishing harbors deep promise for efficiency. By reducing unnecessary down time in the operating room, overlapping surgery can recover productivity. It can also reduce long work hours surgeons are accustom to, making for a healthier and more capable surgical workforce.

Moreover, the demand for surgical care is rising. As our population ages and the burden of complex medical conditions grows, more patients develop surgical illnesses.[2] This demand is compounded by the COVID-19 pandemic as cases were put on hold, creating a back log of operations for patients with non-urgent but life impacting surgical needs. Restructuring perioperative care processes can mitigate the consequences of increasing surgical demand due to pre-existing and evolving surgeon shortages.[3] Overlapping surgery, with clearly regulated boundaries to ensure safety, can enhance access to surgical care. Overlapping surgery can increase operative volume during day-time working hours, minimizing the accumulation of delays and downtime that push cases into the night or the following day, and helping patients receive timely care from a well-rested surgical team.

Overlapping surgery also promotes graduated responsibility for trainees, allowing surgical residents and fellows to oversee some aspects of care in the operating room and increase self-confidence. Patients are not left in the hands of an inexperienced clinician; minor portions of an operation can be performed by a trainee with the appropriate level of skill, experience, and supervision to provide safe care. Allowing trainees to mature in a controlled setting benefits future patients by generating a well-trained, competent surgical workforce

Although overlapping surgery is familiar to surgeons and trainees, patients were unaware of this practice and troubled that they had not been told about it. Transparency and disclosure are critical to the formulation of successful therapeutic alliance; if surgeons are viewed as deceitful, patients will not trust them to operate and won't get the care they need. Yet disclosure followed by patient consent cannot denote permissibility. Unsafe treatments or inappropriate interventions are not legitimized through disclosure.

Patient Safety and Transparency

Revelations of undisclosed and self-regulated practices of concurrent and overlapping surgery threatened patient safety largely due to damaging public perceptions of surgical care and generation of mistrust. In response, many institutions without existing prohibition of concurrent surgery, enacted policies banning it due to the obvious threat to patient welfare. Studies of overlapping surgery reveal no impact on surgical outcomes including patient morbidity and mortality and suggest it is likely safe for most patients. However, this research is confounded by variation in the definition of overlapping surgery, which range from "surgeries with >30 min overlapping operating room time" to "two patients under the care of a single surgeon, under anesthesia at the same time for any duration."[4] This variation, also identified in the policies examined by Mitchell et al., makes it difficult to comprehensively assess the risk of overlapping surgery or monitor patient safety. To restore public confidence and ensure surgical safety, additional oversight and recommendations that precisely characterize the limits of overlapping surgery may be needed.

Although overlapping surgery is familiar to surgeons and trainees, patients were unaware of this practice and troubled that they had not been told about it. Transparency and disclosure are critical to the formulation of successful therapeutic alliance; if surgeons are viewed as deceitful, patients will not trust them to operate and won't get the care they need. Yet disclosure followed by patient consent cannot denote permissibility. Unsafe treatments or inappropriate interventions are not legitimized through disclosure. Consider a proposal for sleep-deprived surgeons to disclose their lack of sleep to a patient prior to operating.[5] As sleep-deprivation has been compared to alcohol intoxication, disclosure as a policy solution suggests operating when sleep deprived is acceptable without accounting for safety. We certainly would not permit a surgeon to operate after disclosing their alcohol intoxication.

Concurrent surgery is not safe, and it simply should not be done. We should not rely on surgeon disclosure to a vulnerable preoperative patient to determine acceptability. By contrast, disclosure of overlapping surgery supports patient and public trust, but it must be well-monitored and determined to be safe over time.

Precise and universally applied overlapping surgery policy can foster transparency and safety but cannot manage all competing interests of surgical practice. Every day, surgeons face multiple demands, which are managed through professional judgement and would be difficult to disclose in advance. Surgeons may leave the operating room to use the bathroom, take an emergency call or step out to care for a patient who is struggling in the post-anesthesia care unit; patients are not assured the surgeon's undivided attention just because they are in the operating room. Similar to aspects of overlapping surgery, e.g., leaving a trainee to close the skin, disclosure of the surgeon's other duties may not be salient for the patient. There are limits to regulation and policies about surgical conduct in the operating room. We must trust surgeons and their professional judgment to balance the needs of individual patients against the needs of all patients without requiring undivided attention to one individual based solely on their location in the operating room.

Mitchell and colleagues' study is an important advance of our understanding of policies in place presently to regulate concurrent and overlapping surgery. The variation they characterize reveals inadequacies in both policy development and implementation and suggests there is additional work to be done to ensure safety and access to surgical care.

Note

The authors have no conflicts to disclose.

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DETAIL

Subjek:	Patient safety; Sleep; Disclosure; Surgery; Workforce; Hospitals; Surgical outcomes; Drunkenness; Consent; Congressional committees; Legislatures
Ketentuan indeks bisnis:	Subjek: Disclosure Workforce
Lokasi:	United States--US
Pengidentifikasi/kata kunci:	Overlapping Surgery; Overlap; Policy; Patient safety; Surgery; Concurrent Surgery; Patient Safety; Surgical Policy; Policy Development; Policy Implementation
Judul:	Regulation of Overlapping Surgery: Progress and Gaps
Pengarang:	Kalbfell, Elle L; Schwarze, Margaret L

Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	74-76
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles: Commentary
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Commentary
DOI:	https://doi.org/10.1017/jme.2021.12
ID dokumen ProQuest:	2730846742
URL Dokumen:	https://www.proquest.com/scholarly-journals/regulation-overlapping-surgery-progress-gaps/docview/2730846742/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-28
Basis data:	Public Health Database

The Government and Pharmaceutical Innovation: Looking Back and Looking Ahead

Sampat, Bhaven N

ABSTRAK (ENGLISH)

Current debates about the roles of the public and private sectors in pharmaceutical innovation have a long history. The extent to which, and ways in which, the public sector supports drug innovation has implications for assessments of the returns to public research funding, taxpayer rights in drugs, the argument the high prices are needed to support drug innovation, and the desirability of patenting publicly funded research.

TEKS LENGKAP

1 Background

The concern that taxpayers contribute significant funds to support pharmaceutical innovation, but drug companies then obtain rights to the patents and have free reign on pricing, is once again prominent in health policy debates. From the debates about controlling high drug prices in 2019, to discussions about about Covid-19 therapeutics and vaccines in 2020, there is widespread concern that taxpayers effectively “pay twice” for drugs, once by funding the research, and then again through high prices. If there were evidence that public sector did most of the important work, this could challenge the pharmaceutical industry’s argument that measures to lower prices (limiting patents, increasing competition, negotiation, price controls) would have detrimental effects on drug innovation. If the bulk of the important R&D were being done by the public sector, after all, private sector financial incentives would seem to be less important.

This paper puts the present debates in historical context, summarizes the current state of knowledge on the main arguments, and suggests an agenda for future research. Section 2 traces the history of the debates and discusses what’s at stake. Section 3 reviews empirical evidence on the role of the public sector in drug development. Building on this, Section 4 suggests several questions where additional evidence is needed in order to advance the debate. Section 5 concludes.

2 The History of the Debate

2.1 Roots in World War II

Debates about taxpayer rights in government funded technologies date back to World War II, when the government first started to seriously fund extramural research at firms and universities.[1] During the war, a central question was who should own patents resulting from government funded research? On one side of the debate, Vannevar Bush, the head of the Office of Scientific Research and Development, argued that allowing contractors, rather than the government, to retain patent rights was important for incentivizing participation by firms in the wartime effort and facilitating development of the technologies. Doing so was crucial, since in many fields firms had capabilities, processes, and facilities needed that were lacking in the public sector. A paid-up license for government use during the crisis was viewed as sufficient to protect taxpayer interests. Countering this argument, liberal critics led by Harley Kilgore, a New Deal Democrat from West Virginia, argued that this represented a giveaway of technologies generated through taxpayer dollars, and would promote concentration of economic power during and after the war. During and after the war, the debates on who should control the patents were mainly around balancing private incentives for participation in government research efforts versus the public interest in low prices, competition, and access once a technology is developed. That continues to be one of the key issues in the debate to this day.

Most of this debate was about warfighting technologies, and not about medicine at all. The OSRD's Committee on Medical Research (CMR) had a crucial role in winning the war, supporting research on a range of wartime problems including infectious diseases, trauma, wound treatment, and blood preservation. Unlike OSRD overall, CMR's contracts were mainly awarded to academic institutions, where there were at the time strong norms militating against patenting, particularly strong in the context of medical research.[2] Reflecting this, the CMR typically had contracts giving the government presumptive ownership of any patents that resulted from the funded R&D. During the war, the CMR and other government agencies also directly supported much of the clinical research and development needed to get drugs into use, most prominently in the natural pencillin development and scale-up effort.[3] This weakened the argument (that is prominent today, see below) that private sector control of patents is needed to support these activities.

The question of who retains patent rights from government funded research was also a central one in the famous debates between Bush and Kilgore about the postwar governance of science. Both Bush and Kilgore envisioned a single major funder of research after the war (though differed on what that agency's patent policy should be, political versus scientific governance, funding of basic versus applied research, and other matters). Ironically, while they were debating, a myriad of agencies absorbed wartime R&D contracts. Each would have its own patent policy. CMR contracts were taken over by the NIH, which (through its parent agency) had a general policy of not permitting patents at all, or, when doing so, requiring government ownership of the patents. Again, this may reflect the continuing force of the norm that academic medical research — most of what NIH funded — should not be patented but rather "for the public." Other agencies (including the Department of Defense) had policies allowing funding recipients (which were primarily industrial contractors) to retain patent rights, justified with the same rationale as offered by Bush during the war.

2.2 Kefhauver Hearings

During and after the war, the debates on who should control the patents were mainly around balancing private incentives for participation in government research efforts versus the public interest in low prices, competition, and access once a technology is developed. That continues to be one of the key issues in the debate to this day.

Another issue in today's debates was raised during the "Kefauver" hearings during the late 1950s and early 1960s that eventually would produce the legislation creating the modern FDA. Building on the technological capabilities and opportunities created through the wartime medical research effort, by the 1950s, drug companies became active in research, and also in using patents and other strategies to ward off competition.[4] The resulting high prices attracted scrutiny from antitrust authorities and legislators, including Senator Kefauver. Then as now, representatives of the pharmaceutical industry touted high drug prices as necessary to create research incentives for these valuable drugs. To combat this claim, Senator Kefauver and other critics of the industry marshaled evidence that a large share of drugs were discovered not by pharmaceutical companies, but rather by academic and government laboratories. Economist William Comonor characterized this saga as "the battle of the lists" with different sides in the debate producing different lists of "important" drugs, each with different estimates of the public and private sector contributions.[5]

The Kefauver pricing and patent proposals did not find support in Congress or by the Kennedy administration.[6] Nonetheless, the hearings firmly established one of the key themes in the pharmaceutical policy discussions: if the real source of innovation were the public sector, this would undermine the justification that monopoly prices (and policies that sustain them such as patent protection) are needed.Though the specific patent and pricing provisions that originally motivated the Kevhauver bill were dropped,[7] the aspects of the bill that did survive paradoxically changed the stakes and contours of the debate. Following the thalidomide tragedy in Europe, the impetus grew to add pre-marketing approval and efficacy testing to the FDA's powers. The pre-marketing approval provisions institutionalized a formal clinical trial process, which today accounts for a large share of private sector R&D costs for drugs.[8]

Thus by the 1960s several of the key questions in today's pharmaceutical policy debates had already been well-established. First, is allowing the performers of government R&D to retain patent rights necessary to incentivize

participation and commercialization, or does this effectively mean taxpayers are to “pay twice” for the same technology. Second, does the role of the government in funding R&D, especially for important drugs, undermine drug companies’ claims that high prices and restrictions on competition are essential for innovation?

2.3 Bayh-Dole and Beyond

During the 1960s and 1970s there was considerable policy debate about the lack of “uniformity” of government patent policy across agencies, with some alleging this created confusion for grant and contract recipients, and others countering that different contexts (defense vs. medicine) called for different policies. In the medical research context, several observers and reports raised concerns that the DHEW/NIH’s emphasis on keeping medical research in the public domain may have disincentivized drug companies from collaborating with public sector researchers and thus hindered commercialization of federally funded research.[9]

The argument that patents on government research are needed to promote commercialization, and that “uniformity” of government R&D policy across agencies is an important policy goal, supported the passage of Bayh-Dole in 1980.[10] Bayh-Dole allowed universities and small businesses blanket rights to retain patent rights from federally funded grants and contracts. (The exclusion of large businesses was to alleviate concerns that such a policy would lead to concentration of economic benefits from publicly funded research, though this was dropped by executive order several years later.) As noted, universities had historically avoided active involvement in patenting and licensing, especially in medicine. Bayh-Dole provided cover for doing so, endorsing the idea that this would promote technology transfer and the movement of ideas from lab to marketplace, from bench to bedside. The fact that a number of commercially important biotechnology inventions were bubbling up in university laboratories led academic institutions — desperate for revenues — to support passage of the legislation as well. Under Bayh-Dole, universities could take out patents, and exclusively license them to firms for development. In medicine, the idea was that drug companies would be incentivized to develop embryonic pharmaceuticals, and take them through costly clinical trial processes.

In addition to the original exclusion of large businesses (and limits on university licenses to large businesses), each eventually scrapped, Bayh-Dole included a “march-in” provision allowing the government to circumvent patents on a taxpayer developed invention if the licensee did not achieve practical application, or meet health and safety requirements, among other circumstances.[11] Other provisions (including “recoupment” of profits over a certain level, time limits on exclusive licenses) were considered during the hearings, but not included in the final legislation.[12]

Since Bayh-Dole, NIH funded researchers at universities have patented tens of thousands of inven-tions.[13] These include patents associated with several hundred commercial drugs.[14] Some argue this is prima facie evidence — that allowing universities to retain rights, license exclusively, and let firms charge what the market bears — is basically working.[15] Going back to the pricing of HIV/AIDS drugs in the 1980s, others have argued that the fact that the government is subsidizing much of the work should be accounted for in pricing, and that “march-in” is one way to do so.[16] More generally, echoing some of the arguments during the Kefhauver hearings, critics of high prices in general have argued that the public sector role in drug development undermines the drug industry’s justification that high prices are needed to sustain drug innovation.[17]

3 What We Know: A High-Level Summary

The debate has gone on, along the same lines for the past 75 years. Over this period a considerable body of empirical research has been done, assessing the respective roles of the public and private sector. What does the evidence say?

- One strand of research examines who funds what. The most comprehensive research on funding suggests that the U.S. government, primarily through the National Institutes of Health (NIH), provides about one-third of total U.S. biomedical research funding, pharmaceutical and biotechnology companies about 50 percent, with the medical device industry, state and local governments, and foundations accounting for the rest.[18] However, there is a rough division of labor, with the vast majority of pharmaceutical R&D focused on clinical research, and the majority of NIH funding focused on “basic” research.

- Cross-industry firm surveys consistently suggest stronger linkages between public sector and private sector research activities in pharmaceuticals than in other sectors.[19] In the largest such survey, Cohen and colleagues suggest that in the drug industry 41 percent of R&D projects used research findings from the public sector, 35 percent instruments and techniques from public science, and 12 percent were based on prototypes from public sector research.[20] Overall, the surveys suggest a larger enabling role for the public sector in drugs than other industries, though only 10-15 percent of projects are based directly on public sector research, or build on public sector prototypes.

- Another approach uses detailed case studies of important drugs to assess, through histories and/ or interviews, the role of the public sector.[21] Each of these studies suggests the public sector has a role in the vast majority of important drugs. However, very rarely is the public or private sector solely responsible.

- Analyses of drugs' key patents suggest that the public sector did enough work to obtain a patent associated with the final product (listed on the FDA's Orange Book, see below) for about 20 percent of "important" drugs.[22] This "direct" role of the public sector in principle can be traced through government interest statements which must list any government grants or contracts directly supporting the research on the invention.[23]

- Bibliometric analyses tracing publication inputs for FDA approved drugs[24] and publications cited in the patents on FDA approved drugs[25] suggest that nearly all important drugs have publication links to NIH or other government funded research.

- Econometric analyses relating variation in NIH funding to drug development suggest a statistically significant increase in drugs in trials[26] and approved drugs[27] following increases in NIH funding in the relevant area.

Collectively, the research belies any simple arguments that the public or private sector are primarily responsible for drug innovation. One can squarely reject the argument that the public sector role or the private sector roles are zero; indeed both seem to be qualitatively large, important, and complementary.

What are the implications of this for the longstanding policy debates surveyed earlier? One is that (at least in its extreme) the argument that patents and high prices are not needed for innovation, because the public sector contributes the drug development, seems wrong. Even at the high end of existing estimates, for only 20 percent of drugs does the public sector seems to be involved in enough late stage development to have a key patent on the final product. This is what I have previously called the "direct" role of the public sector. For the other 80 percent of drugs, the private sector appears to be doing important work as well.[28] Other reasonable ways to measure the direct role may yield slightly higher figures,[29] say 30-35 percent, but the basic point remains.

Another reason the direct role is important is that it is for these drugs that Bayh-Dole march-in and other rights resulting from government funding apply. There have been various calls to use these tools to bring down drug prices and promote access in general.[30] However if the numbers on the direct share surveyed above are right, they would only apply to a minority of drugs. March-in is not a comprehensive solution to influencing drug prices, even if it could have an impact in specific, important cases.

Third, even for the ~20 percent of drugs where the government does have a direct role, in the sense of owning a key patent, we cannot just assume that the private sector contribution is negligible. After all, the whole point of Bayh-Dole is that patent exclusivity is needed to facilitate additional investment. For drugs, someone still has to pay for the expensive clinical trials. Seen this way, the important question is what is the right level of exclusivity (or the right

level of prices/profits) needed to incentivize firms to license the public sector technology and invest in the needed additional work. Or, are there other models beyond Bayh-Dole we might use to achieve the same goal? I discuss this and other questions in the next section, where I lay out an agenda for research.

4 What We Don't Know: Data and Research Needs

There have been strong views in this policy debate for the past 75 years, especially in the four decades since Bayh-Dole. Indeed, it is striking how little the debate has changed. This section discusses several types of additional data and analysis that may help advance the debate going forward.

4.1 Better Data on the Direct Role

Even the high-end estimates on the "direct" role suggest that for the vast majority of marketed drugs, there are no Orange Book listed patents with a government interest statement or government ownership. If patents can accurately be linked to drugs (see below) the government interest statements provide fir a full accounting of the direct role of the government in drug development.[31] However, universities and other grant recipients have not always diligently listed government interest statements in the final patents. Perhaps more surprisingly, grantees also do not always report back patents to the funding agency, which they are also required to do under Bayh-Dole.[32] There do appear to be important omissions.[33] Through in-depth qualitative examinations, for a number of important drugs scholars and civil society groups have identified patents that "should have" included government interest statements.[34] Typically, this process involves comparing inventors on drug patents to authors of publications, and looking at publications by the same authors (e.g. in PubMed) that acknowledge government funding or grants to the inventors in similar areas. While this is inherently a subjective process, one promising approach to do this at scale, would be to match patents to "paired" papers[35] using natural language processing and other computational techniques. Alternatively, Congress or the NIH could impose harsher penalties for non-compliance than currently exist, or better enforce existing penalties.[36]

4.2 Patent Landscapes for Biologics

Suppose we had accurate links between NIH grants and patents they funded. The next step to measuring the direct linkages would be to link the patents to drugs. In most contexts, this is hard to do: there is no established method for linking patents to products at scale. In pharmaceuticals, FDA regulations designed to link generic drug approvals to patent status unintentionally created a way to do so. Under the 1984 Hatch-Waxman Act, drug makers are required to list patents covering drug's active ingredients, formulations, or methods of use (for an approved indication) on the Orange Book,[37] to provide notice of potentially binding patents to prospective generic entrants. There are strong incentives to list any relevant patents on the Orange Book, since doing so provides advantages in litigation.[38] While the current version of the Orange Book includes only unexpired patents, numerous sources now include archival versions as well.[39]

Taking the Orange Book patent list as the full set of patents on a drug, one can then assess the share of drugs linked to a government grant or contract, using the approaches outlined in the previous section. One issue that would arise, is which of the several patents on the Orange Book (the average is about 3) is the main patent, and how to attribute a drug where some of the patents result from government funding and others do not.[40] This relates to the cruciality question that will be discussed below.

A more fundamental issue is that biologic drugs approved under Biological License Agreements (BLAs), accounting for a large share of top-selling drugs in recent years,[41] are not subject to Orange Book listing requirements which apply only to drugs approved by New Drug Application (NDA) route. In general, getting patent "landscapes" for biologic drugs is difficult to do at scale, at least with public data. The current "Purple Book" does not require patent listing of relevant patents for biologics, as the Orange Book does for small-molecule drugs. There have been various

legislative initiatives to create more transparency around patents for biologics,[42] mainly as a way to promote biosimilar entry. Such data would also be useful for assessing the public sector role.

It might also be useful to try to use other countries' registers of patents and products, or data on litigated patents for biologic drugs, to assemble patent landscapes for biologics to enable the types of analyses that are now common for small molecule drugs.[43] One could also look at the extended patent for a given drug, plausibly the most important one,[44] using FDA data that is available for biologics as well. There may also be administrative solutions, for example the NIH or other funding agencies requiring notifying the agency when any patent (for small molecule drugs or biologics) is associated with a marketed drug and making this information public.

4.3 Validation of Bibliometric Linkages

The links between grants, patents and products described above would be most useful for understanding the "direct" public sector role. The broader enabling role of the public sector has typically been measured through "bibliometric" measures such as NIH funded publications on a drug, or patents citing NIH-funded publications.[45]

Analyses of publications on a molecule are possible through PubMed,[46] and, as mentioned, have found nearly all approved drugs to have at least one NIH funded publication. Future work might explore the types of publications funded by the NIH versus others, including classifying by timing of publication and MeSH keywords.[47] (Along these lines, Cleary and colleagues show that most of the publications were related to the drug target.[48]) This would allow for assessment of the division of labor between the public and private sector in drug research. One major issue here is that while PubMed does include a flag for whether the article acknowledges U.S. government funding source, articles without this flag do not necessarily come from industry.[49] One might be able to get better data on affiliations of authors on non-NIH funded articles from Web of Science, Microsoft Academic Graph, or other sources. A more important question is cruciality. For most molecules the majority of publications are probably not government funded. In such contexts, we need to better understand whether the public sector contribution was necessary to the development of the drug, i.e. what would have happened absent the NIH research?

Another bibliometric approach involving publications starts with Orange Book patents on drugs (using the techniques discussed in the previous section), but looks not at whether the patent was directly funded by the government but instead whether it cites a publication that was funded by the government. Publications are cited in patents as part of the "prior art" against which a patent application is evaluated. Under U.S. law, if a patent examiner is convinced that an application is "novel" and "non-obvious" relative to the prior art, and meets other criteria, s/he will grant the patent and the patents and publications against which this assessment was made will be listed in the patent. As noted, Sampat and Lichtenberg show the majority of important drugs have an Orange Book listed patent that cites at least one government funded publication, providing support for a large indirect role.[50] However, the same cruciality question raised earlier applies here too. In almost all cases, the drug patents cite non-NIH funded publications as well. How do we divvy up the relative contribution in determining whether a drug counts as a public sector drug? Another issue with this approach is that patent citations to prior art are made for legal reasons (by applicants and examiners). Despite how they are typically used, it is unclear that all cited publications are important for generating the subject patent, or all important publications are cited. This is an area of active research.[51]

4.4 Drug Specific R&D Measures

Another thing we don't know is the level of funding provided by the public and private sector, beyond the very broad aggregates cited in Section 3. On the private sector side, drug specific R&D costs are not typically revealed or reported. The oft-quoted Tufts study cites a figure of $2.6 billion in private investment on average for approved drugs, after accounting for failures and capitalizing investment dollars.[52] This figure has been questioned since it is based on proprietary data provided by industry, and thus not replicable. However, other efforts to estimate the costs

of developing drugs using more public data report similar orders of magnitude.[53] More importantly, the Tufts study ignores in-licensed compounds, so does not tell us the extent of private sector investment in contexts where the public sector has done enough to get the key patent.[54]

We also lack information on public sector (NIH) R&D spending associated with marketed drugs. There are knotty questions here, especially if much of the relevant public sector work is not on the molecule itself, but mechanisms of action, targets, techniques, or basic knowledge. While all NIH grant data are available through RePORTER (together with titles and abstracts) there is a question of how to associate a specific grant with a specific drug. How much of the background research on HIV should count for a given HIV drug, for example? What about cancer research that informed the HIV work? The public sector side raises its own accounting difficulties, including how to deal with indirect costs that account for a quarter of NIH funding.[55] Most importantly, even where we see considerable public sector expenditure, the relevant question from a policy perspective may still be the level of prices/exclusivity needed to incentivize the needed incremental contribution (e.g. clinical trials) from the private sector. Even where the public sector research is necessary (and even a large share of total R&D) is it sufficient? One margin on which we may be able to make more progress, is the public sector role in funding clinical trials. In principle, the pivotal clinical trials for all drugs should be obtainable from FDA review documents[56] and clinicaltrials.gov should indicate funding sources. One could link these data to RePORTER data to look at not just the share of drugs where the government is paying for clinical trials, but also the total amounts of expenditures. In the cases where the government is funding trials as well as one of the main patents, presumably a small share of all drugs, the argument that patents/high prices are needed to stimulate additional private sector spending is obviously weaker.

First, we need evidence on the key empirical parameter in these debates, the sensitivity of commercialization to prices (or to patent protection). The proponents of Bayh-Dole come close to arguing that there would be no commercialization absent academic patents and exclusive licenses.

In most fields, this is unlikely to be true. But in pharmaceuticals, the case is strongest, since, under the current system, we rely on profit oriented firms to take products through expensive clinical trials.

4.5 Broader Questions

Beyond the specific measurement issues raised above, there are two higher level questions too, where more thinking and evidence is needed.

First, we need evidence on the key empirical parameter in these debates, the sensitivity of commercialization to prices (or to patent protection). The proponents of Bayh-Dole come close to arguing that there would be no commercialization absent academic patents and exclusive licenses.[57] In most fields, this is unlikely to be true. But in pharmaceuticals, the case is strongest, since, under the current system, we rely on profit oriented firms to take products through expensive clinical trials. And there is a sixty year empirical legacy in economics suggesting that drug companies' R&D incentives are responsive to the extent of patent protection.[58] To my knowledge this has not been directly examined in the context of publicly funded research: how would the level of licensing of university technology, participation in development, and ultimate commercialization change with more/less patent term or higher/lower expected prices? While there are anecdotes (e.g. the impact of the NIH "reasonable pricing" clauses on participation in CRADA agreements[59]), none are quite on point. Careful, systematic empirical research on this question is needed.

The second question is broader. As I have argued elsewhere[60] one reason this policy debate is hard is that under Bayh-Dole we rely on the private sector to do the expensive clinical trials needed to get a drug to market. They are compensated through the ability to charge monopoly prices during the remaining patent term at time of license. The high prices are baked in and completely unsurprising. An alternative "end to end" approach would be for the

government to directly fund the clinical trials as well, and then distribute the drugs at cost.[61] I could imagine several lines of opposition to this approach, including inability of the government to "pick winners," the lack of government capabilities/incentives to do the trials and development work as efficiently as the pharmaceutical industry does, crowding out of basic research, etc. Against these, it has the major benefit of potentially delinking commercialization incentives from prices. Experimentation along these lines could be useful, as would be careful evaluations of "natural" experiments (including end-to-end approaches the government has employed during crises such as World War II and COVID).

5. Conclusions

Today's policy debates regarding the roles of the public sector in drug innovation have a long history. Many of the themes in the current debate, including whether high prices (sustained by patents) are needed for innovation, and whether taxpayers unnecessarily "pay twice" for drugs developed by the public sector, echo those in previous debates. A large body of empirical evidence suggests both the public and private sector have important roles in drug innovation. Still, it is apparent that more nuanced evidence and thinking is now needed to advance the policy debate.

Note

Parts of this research were supported by the National Science Foundation under Grant No. 1951470.

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DETAIL

Subjek:	Public interest; Laboratories; Drug prices; Research funding; Public sector; Funding; Taxpayers; Private sector; Debates; Medical research; World War II; Patents; Pharmaceutical industry; Drugs; Research &development--R &D; Wage &price controls; Competition
Ketentuan indeks bisnis:	Subjek: Drug prices Taxpayers Private sector Patents Pharmaceutical industry Public sector Wage &price controls
Perusahaan / organisasi:	Nama: Food &Drug Administration--FDA; NAICS: 922190
Pengidentifikasi/kata kunci:	Pharmaceuticals; Patent; Public sector; Innovation; Medication; Private sector; Public policy; Innovation; Drug prices; Patents; NIH
Judul:	The Government and Pharmaceutical Innovation: Looking Back and Looking Ahead
Pengarang:	Sampat, Bhaven N
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	10-18
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Symposium Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences

ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.3
ID dokumen ProQuest:	2730846741
URL Dokumen:	https://www.proquest.com/scholarly-journals/government-pharmaceutical-innovation-looking-back/docview/2730846741/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-28
Basis data:	Public Health Database

Letter to the Editor

Macintosh, Kerry Lynn; Cohen, I Glenn; Sherkow, Jacob S; Adashi, Eli Y

TEKS LENGKAP

Gene Editing Sperm and Eggs for Use in Clinical Trials

In the Fall 2020 issue of the *Journal of Law, Medicine &Ethics*, Professors Cohen, Sherkow, and Adashi (authors) address an annual appropriations rider that bars the U.S. Food and Drug Administration (FDA) from acknowledging receipt of applications for clinical trials in which a human embryo is intentionally created or modified to include a heritable genetic modification.[1] They recognize that the rider affects applications for clinical trials in which human embryos are modified directly and transferred to women to initiate a pregnancy. However, they suggest the rider does not apply to applications for clinical trials in which scientists attempt to get women pregnant with edited sperm and eggs. With due respect, I believe their interpretation is incorrect.

The FDA regulates clinical trials in which drugs or biological products are administered to human sub-jects.[2] In 2001, the Director of its Center for Biologics Evaluation and Research asserted that the FDA has jurisdiction over assisted reproductive technologies in which genetic material is transferred other than by union of gamete nuclei. She gave examples, including “genetic material contained in a genetic vector, transferred into *gametes* or other cells” (emphasis added).[3] As one would expect, the Director did not foresee or address CRISPR/Cas9, base editing, and other current molecular tools specifically. In 2017, however, the National Academies acknowledged that the FDA

has jurisdiction over clinical trials in which scientists attempt to get women pregnant with edited sperm and eggs.[4] The authors do not dispute FDA jurisdiction as such. However, they argue that the rider does not apply if edited gametes are used to create an embryo. In their view, an embryo created via fertilization simply contains the genes of its constituent gametes; thus, it does not include a heritable genetic *modification* as the rider requires.[5]

A common legal maxim holds that all words of a statute should be given effect if possible.[6] The rider applies when a human embryo is intentionally *created or modified* to include a heritable genetic modification. In adopting this language, Congress evidently intended the rider to cover two distinct acts: creation *or* modification. However, the authors write "creation" out of the rider by positing that an embryo constituted with edited gametes can never include a heritable genetic modification.

An alternative interpretation that gives effect to all words of the rider is possible. This column will provide an illustration; but first, some scientific background may be helpful. The reader may have heard of cats that glow green in the dark. These animals result from experiments in which scientists add the green fluorescent protein (GFP) gene to cat eggs before fertilizing them and transferring them to surrogate mothers. The resulting kittens glow green, and so do their own offspring.[7] Thus, the cat eggs include a genetic modification. The embryos created from the eggs also include that genetic modification, which is heritable.

Now, suppose a scientist wishes to conduct a similar experiment with human subjects. She plans to add the GFP gene to human eggs, which then will contain a *genetic modification*. The scientist will fertilize the eggs with sperm —thereby intentionally *creating* human embryos that *include* the original genetic modification —and transfer those embryos to women for gestation. If the experiment succeeds, the end result will be babies who glow in the dark and can pass that trait down to their own offspring. In other words, the genetic modification will be *heritable*. Can the FDA acknowledge receipt of her application to conduct a clinical trial? The answer should be no: the elements of the rider are satisfied. Moreover, although legislative history is sparse, logic supports this outcome. If Congress was worried about heritable genetic modifications, it would attempt to pause all such experiments, whether the genes in question were modified at the gamete or embryo stage.

This is not to say that the rider is a good thing. It serves no legitimate scientific purpose. If Congress eliminated it, the FDA could receive and consider applications for clinical trials in which scientists corrected deadly mutations in gametes or embryos and provided them to women for reproductive purposes. Of course, the FDA would not permit clinical trials to proceed until and unless proponents could demonstrate that the technology was safe and effective for participants, including the children-to-be.[8]

The real purpose of the rider is political. It allows Congress to duck the issue of heritable human genome editing without having to engage the ethical and social questions involved. This act of political cowardice comes at the price of scientific advancement and medical treatments for carriers of genetic mutations and their children.

I share the authors' frustration with the rider. Unfortunately, I do not agree that scientists can sidestep it by working with gametes rather than embryos. Instead, scientists should lobby Congress to eliminate the rider so that the FDA can do its job.

The Authors Respond

Dear Editor,

We thank Prof. Macintosh for her thoughtful reading of our article, but we respectfully disagree with her interpretation of the rider. Prof. Macintosh's interpretation, which centers on giving effect to the words "created or modified," elides the *object* of such actions: "a human embryo." As we explain in our article, an embryo does not exist until it is "conceived" by the union of sperm and eggs, therefore, whatever "heritable genetic modifications" the rider seeks to enjoin must occur *after* this critical moment. For that reason, among others, we believe our interpretation of the rider is correct. We nonetheless share Prof. Macintosh's remaining concerns about the rider and note that while Congress may —or may not —choose to re-establish or clarify this section in its ongoing budget, the technological and interpretive gap we identify remains in place.

DETAIL

Subjek:	Appropriations; Biological research; Embryos; Clinical trials; Artificial insemination; Mutation; Genetic engineering; Biological products; Sperm; Jurisdiction; Pregnancy; Drugs; Genes; Food
Perusahaan / organisasi:	Nama: Congress; NAICS: 921120; Nama: Food &Drug Administration--FDA; NAICS: 922190
Judul:	Letter to the Editor
Pengarang:	Macintosh, Kerry Lynn; Cohen, I Glenn; Sherkow, Jacob S; Adashi, Eli Y
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	156-157
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Letter to the Editor
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Letter To The Editor
DOI:	https://doi.org/10.1017/jme.2021.21
ID dokumen ProQuest:	2730846713

Healthcare Professionals' Experience, Training, and Knowledge Regarding Immigration-Related Law Enforcement in Healthcare Facilities: An Online Survey

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ABSTRAK (ENGLISH)

U.S. immigration policies and enforcement can make immigrants fearful of accessing healthcare. Although current immigration policies restrict enforcement in "sensitive locations" including healthcare facilities, there are reports of enforcement actions in such settings.

TEKS LENGKAP

Background

Undocumented immigrants in the United States live under constant fear of contact with law enforcement and potential deportation by Immigration and Customs Enforcement (ICE).[1] Policies have been in place for decades which facilitate collaboration between ICE and local police departments. Such policies include Section 287(g) of the U.S. Immigration and Nationality Act of 1996,[2] which deputizes police officers to enforce federal immigration laws, and the Secure Communities program, which allows fingerprints from individuals apprehended by police to be cross-referenced with federal immigration enforcement databases.[3] However, in recent years, national anti-immigrant rhetoric has intensified. Former President Trump's executive order signed on January 25, 2017, broadened ICE's focus to most undocumented immigrants in the United States, regardless of criminal record.[4] This represented a striking shift in enforcement priorities from the Obama administration, which prioritized the removal of undocumented immigrants with criminal records or those considered a threat to public safety.[5] Following the executive order, arrests by ICE climbed to a four-year high of more than 158,000 in fiscal year 2018.[6] The Trump administration also fought to expand the definition of "public charge," a policy in which immigrants who legally receive public benefits may be prevented from obtaining legal permanent residence. This expanded "public charge" designation, which newly included the usage of the Supplemental Nutrition Assistance Program (SNAP, formerly known as food stamps) and Medicaid, was instated in February 2020 after a series of legal challenges.[7]

The threat of immigration enforcement affects the health of undocumented immigrants as well as naturalized citizens and US-born members of mixed-status families. Worries about deportation have been associated with greater burden of cardiovascular risk factors among Latina women.[8] Restrictive immigration policies contribute to fear, anxiety, and healthcare avoidance,[9] and have been associated with worse mental health among citizen and non-citizen Latinos.[10] Immigrant communities reported poorer self-rated health and higher rates of low birth weight following immigration raids.[11] Anti-immigrant policies also impact the health of US-born members in mixed-status families; local risk of deportation is associated with a chilling effect including decreased Medicaid and WIC use among citizens in mixed-status families.[12] The health and psychological wellbeing of citizen children of immigrant parents are negatively impacted by fears of parental deportation.[13] Even the lawful presence of federal agents monitoring a detained patient serves to alarm communities and deter immigrant patients from seeking care.[14]
This study aims to evaluate the experience of health professionals with workplace immigration enforcement, their knowledge and training regarding relevant policies, and their beliefs regarding which policies institutions should follow. These findings can help in the development of ethically responsible relevant policies, procedures, and trainings.
Although current immigration policies limit enforcement in “sensitive locations” including healthcare facilities,[15] there are reports of enforcement actions in such settings throughout the United States. These enforcement actions within healthcare workplaces will be defined as “arrests, interviews, searches, and surveillance done for the purposes of immigration enforcement only.”[16] Individuals have been detained while en route to a hospital or leaving a clinic.[17] Others have been questioned or detained at the bedside of their sick children,[18] or forcibly removed from the hospital.[19]
Fears among immigrants about accessing medical care are especially concerning during the global COVID-19 pandemic. In March 2020, ICE announced that it would temporarily limit its enforcement activities to those with criminal charges or who pose a threat to public safety, similar to prior enforcement priorities under the Obama administration.[20] ICE has released individuals and families from detention who may be at high risk of COVID-19 and increased the number of migrants who are turned away at the US-Mexico border, leading to the lowest detained population since 2016.[21] Despite these efforts, advocates fear that immigrants will continue to avoid healthcare settings.[22]
It is essential that the privacy and safety of immigrant residents and their families are protected while accessing health services. Beyond these anecdotal reports, however, it is unclear the extent to which immigration enforcement is occurring in healthcare settings and how prepared healthcare systems and professionals are to address ICE efforts in and around their facilities. While several hospitals and clinics across the country are developing protocols to guide responses to ICE enforcement,[23] these efforts are not widespread and it is unknown how well individual providers understand the policies at their institutions.
This study aims to evaluate the experience of health professionals with workplace immigration enforcement, their knowledge and training regarding relevant policies, and their beliefs regarding which policies institutions should follow. These findings can help in the development of ethically responsible and relevant policies, procedures, and trainings.

Methods

The survey (see Appendix) was distributed nationally via an introductory email and three reminder emails sent from October to November 2018, to the up-to-date Society of General Internal Medicine (SGIM) national online member portal. There are approximately 3,000 SGIM members (including physicians, trainees, researchers, and other healthcare professionals). The online portal, free for all members to access, is the chief means of communication between the society and its members. Recipients of the invitation e-mail were encouraged to forward the survey to other healthcare professionals. Inclusion criteria were defined as any U.S. health professional who provides services to promote health, prevent disease, and deliver healthcare services.[24] All participants met inclusion criteria and no recipients of the questionnaire were excluded from participating. No identifying information was obtained to maintain anonymity. A $5 gift card was offered as incentive to participate. Data were collected anonymously through the

Qualtrics survey tool (Qualtrics: Provo, Utah). The Johns Hopkins Institutional Review Board approved this study (Protocol IRB00126840).

The survey was developed through a process of iterative discussion and improvement within the research group. This process was based on a collective review of the literature and reports of law enforcement interactions with patients or staff in healthcare settings caring for immigrants. The survey was not piloted. It included 20 questions: 4 regarding demographic information; 4 regarding respondents' knowledge about their institutions' relevant policies and training on how to respond to law and immigration enforcement activities in the workplace; 8 regarding respondents' own experience with immigration-related law enforcement activity at or near their workplaces; 3 regarding respondents' perception of institutional preparedness; and 1 allowing respondents to provide additional comments.

Forty-two individuals completed the survey. Data were assessed using descriptive statistics in STATA 15.1 (StataCorp: College Station, TX). Narrative responses were analyzed and coded for themes.

ResultsRespondent Demographics

Most survey respondents were attending physicians (69.1%), with 21.4% listing additional administrative roles such as program director, dean, or division chief (see Table 1). A vast majority worked at academic medical centers (90.5%) and in outpatient settings (83.3%). Most lived in the Northeast (40%) or the Midwest (21.4%). The primary language spoken by a majority of the professionals' patients was English (85.7%), with the remaining 14.3% listing primary languages of "English and Spanish," "Spanish," or "English, Spanish, and Portuguese."

Table 1

Demographics

		N (%), N=42
Q1:	**Job Description**	
	Administrator	9 (21.43)
	Attending	29 (69.05)
	Resident	2 (4.76)
	Other	2 (4.76)
Q2:	**Region**	
	Midwest	9 (21.43)
	Northeast	17 (40.48)
	South	8 (19.05)
	West	8 (19.05)
Q3:	**Academic**	

	Academic	38 (90.48)
	Other (Government, For-Profit, FQHC, Free Clinic)	4 (9.52)
Q3:	**Practice Setting**	
	Inpatient	7 (16.67)
	Outpatient	35 (83.33)
Q4:	**Main Patient Language**	
	English	36 (85.71)
	English &Spanish	4 (11.9)
	Spanish	1 (2.38)

Awareness of Policies and Enforcement

Participants were largely unaware of institutional policies to guide interactions with immigration officials (see Table 2). For instance, 82.5% of respondents were not aware of specific workplace policies regarding immigration-related law enforcement, and 76.2% were unaware of any policies, either general guidance or specific to immigration, that could be referenced in the event of an immigration enforcement action. Professionals who were aware of immigration-specific policies learned about them through working groups, guidance from legal teams, or presentations from external advocacy groups. Known general law enforcement policies included patient confidentiality policies or instructions to contact institutional counsel with any law enforcement activity.

Table 2

Survey Results

	N (%), N=42
Q5: Are you aware of any policies or procedures at your place of work specifically designed to guide a response to immigration-related law enforcement activity? (n=40)	
No	33 (82.50)
Q6: Are you aware of any policies or procedures at your place of work that do not explicitly pertain to immigration-related law enforcement activity but that would be used as default guidance in response to such an activity?	
No	37 (88.10)
Response of “yes” to either **Q5** or **Q6** relating to policy or procedure.	
Yes	10 (23.80)

Q7: Have you received any training specifically designed to guide a response to immigration-related law enforcement activity?	
No	40 (95.24)
Q8: Have you received any training specifically designed to guide a response to law enforcement activity, but not specifically immigration-related law enforcement activity?	
No	38 (90.48)
Response of “yes” to either **Q7** or **Q8** related to training.	
Yes	6 (14.3)
Q9: Are you aware of immigration-related law enforcement activity within or in the vicinity of a clinical setting at your place of work?	
Yes	8 (19.05)
Q17: In what aspects do you feel your facility is prepared to manage any immigration related law enforcement activity within or in the vicinity of a clinical setting at your place of work?[a]	
Not prepared	10 (24.30)
Unsure of preparation level	11 (27.00)
Possibly prepared-general practices	10 (24.30)
Likely prepared-focused response	10 (24.30)
Q18: In what aspects do you feel your facility is not prepared to manage any immigration related law enforcement activity within or in the vicinity of a clinical setting at your place of work?[a]	
Lack of training	15 (35.50)
No known policies	15 (35.50)
Not prepared in any way	8 (19.40)
Concern of deference to immigration law enforcement	4 (9.7)
Lack of awareness of the issue	3 (6.5)
Q19:‘What steps are necessary for your facility to be prepared for immigration related law enforcement?[a]	

Education and training for staff	29 (70.00)
Policies and procedures	24 (56.70)
Leadership engagement	6 (13.30)
Development of response team	3 (6.70)
Provision of additional resources	3 (6.70)
Communication to patients	3 (6.70)
State legislation	1 (3.30)

Only two respondents received training regarding immigration-related law enforcement (4.8%); these trainings were conducted in person or disseminated by e-mail. One respondent had a “public safety” individual come to their clinic to educate staff. The second was a civil surgeon and received updates from U.S. Citizenship and Immigration Services. The impact of these trainings is unclear. Training about law enforcement activity in general was also limited (9.5%). Available training discussed care for patients under police custody or how institutional security personnel would interact with local law enforcement.

Nearly 1 in 5 respondents reported that they were aware of immigration enforcement activities in or near their workplace (19.1%). Of these respondents, a minority were aware of any related policies (37.5%) or received any law enforcement training (25%). Respondents cited cases of detained individuals brought to their hospital by ICE for medical attention or incidents targeting employees at nearby workplaces. Participants listed both physicians and registration staff as employees involved in incident response, and indicated that neither security personnel nor general counsel were contacted when patients in ICE custody were brought for medical care.

Facility Preparedness

The characteristics of a “prepared facility” were not defined for participants in order to elicit their perceptions of what constitutes facility preparedness. Roughly half of participants (51.3%) indicated that their facility was either unprepared to respond to immigrant-related law enforcement (24.3%) or that they were unsure of the level of preparedness (27%). Cited reasons for unpreparedness included lack of training (35.5%), lack of known policies (35.5%), potential deference by staff to immigration law enforcement (9.5%), or lack of awareness of the issue (6.5%).

This is the first study to our knowledge assessing immigration-related law enforcement activity in or near healthcare facilities and the degree to which healthcare facilities and professionals are prepared for that activity. Nearly 20% of surveyed clinicians were aware of immigration enforcement activities at or near their workplace. Despite this, respondents were largely unaware of workplace policies at their institution regarding responses to immigration-related or general law enforcement activity, and most had not received any relevant training. Overall, respondents considered their facility unprepared, or were unsure of the preparation level, to respond to immigration enforcement activity.

In particular, according to respondents, training was lacking in immigrant rights, identifying and responding to ICE agents, filling out ICE paperwork, reviewing what constitutes public space and the purview of immigration enforcement, and caring for undocumented patients. For example, one respondent answered as follows: “I feel general staff may not know whether the person asking for information is an ICE agent. I also think that people are not familiar with how to best protect rights when someone is detained. I also think public space has not been well defined in the walls of our hospital. Is it possible that ICE could legally be in our waiting rooms? Or just outside the hospital at the door.”

Some respondents also connected a lack of policies with a potential deference by staff to immigration law enforcement. As one participant stated, “there is no existing policy and there are not many persons in the clinic or in the overall institution who have knowledge about what is required in these situations. Therefore, I have some concern that there would be a high degree of deferring to immigration authorities.”

About 1 in 4 participants considered their facility possibly prepared based on general characteristics of their organization (24.3%), including communicated values of diversity and inclusion, commitment to patient privacy, and location within a “sanctuary city.” Another quarter of participants indicated that their workplace was likely prepared for an immigration-specific response (24.3%), citing specific training for security personnel, and access to legal counsel or social services organizations as resources in responding.

Participants recommended several measures to improve immigration enforcement preparedness. Most respondents suggested education and training for staff (70%) and/or development of policies or procedures to guide staff action (56.7%). Other recommendations included leadership engagement (13.3%), development of a response team (6.7%), provision of additional resources (6.7%), communication to patients (6.7%), and state legislation (3.3%). Leadership engagement was not well defined by participants, but included hospital/clinic administration communicating values of inclusion and diversity, hosting inservices for staff, and directing appropriate responses to immigration enforcement.

One respondent outlines how to incorporate several of these measures to improve facility-level preparedness: “1) Developing likely scenarios, 2) Generating executive-level consensus on how the organization would respond to each of the likely scenarios, 3) organize/coordinate departments that would have to respond to each scenario, including establish on-call point person, communicating steps each department would take, and providing resources to carry out operations; 4) communicating policies, expectations, and responses to wider audience (patients and staff).”

Discussion

This is the first study to our knowledge assessing immigration-related law enforcement activity in or near healthcare facilities and the degree to which healthcare facilities and professionals are prepared for that activity. Nearly 20% of surveyed clinicians were aware of immigration enforcement activities at or near their workplace. Despite this, respondents were largely unaware of workplace policies at their institution regarding responses to immigration-related or general law enforcement activity, and most had not received any relevant training. Overall, most respondents considered their facility unprepared, or were unsure of the preparation level, to respond to immigration enforcement activity.

The reported extent of immigration enforcement activity in or near healthcare facilities is alarming given that enforcement efforts should be restricted in these “sensitive locations.” However, the findings corroborate reporting of such events in the media. The lack of knowledge of relevant policies and training participation among respondents is also concerning. This is not surprising, given that few protocols addressing this issue are publicly known and national guidelines are lacking. A recent qualitative study highlighted the policies and procedures adopted by 25 healthcare facilities in states with the largest proportion of undocumented immigrants.[26] These facilities are promising examples, but many systems are likely to lack formal or informal policies which protect patients or guide staff response to enforcement events.

This study highlights several areas of opportunity for medical institutions to increase their level of preparedness for immigration-related law enforcement activity in their vicinity. Our findings suggest that institutions should engage their leadership and other key stakeholders, including legal experts, immigrant patients, providers, and local organizations, in order to develop a comprehensive preparedness approach appropriate to their care setting and other contextual factors. Participants highlighted education and training as a key unmet need, as well as clear policies which would protect immigrant patients and guide institutional response to potential enforcement actions. These themes are consistent with recent best practice guidance from the American Civil Liberties Union, National Immigration Law Center, and Physicians for Human Rights, which suggest training staff on “sensitive locations” policies, avoiding documenting immigration status in electronic health records, and educating patients on their rights.

[27] This document also emphasizes the need for specific systems and protocols which regulate staff interaction with law enforcement officials and designate staff to review search or arrest warrants. Similarly, the analysis of institutional policies by Saadi et al. suggest that healthcare facilities should address the risk of immigration enforcement on site, the potential for immigration status disclosure, and the psychological toll on patients and providers.[28] By undertaking a comprehensive set of preparedness efforts, institutions can better ensure that they are ready to offer an appropriate and ethical response to immigration-related law enforcement in the vicinity of their clinical settings.

While institutional policy is critical for protecting immigrant patients, further advocacy is necessary at the state and federal level to ensure protections for undocumented patients seeking medical care. Congressional legislation, such as the Protecting Sensitive Locations Act, would codify and expand the designation of "sensitive locations."[29] For the time being, lawmakers have called upon the administration to end all immigration enforcement in medical facilities during the COVID-19 pandemic.[30] Seeking care for COVID-19 is also currently protected from the public charge rule. However, in September 2020, the U.S. Court of Appeals chose to resume implementation of the expanded Public Charge rule for non-COVID related services.[31] Healthcare workers and their professional organizations should join advocacy efforts to ensure that undocumented immigrants and their families are protected while accessing necessary care including after the COVID-19 pandemic ends.

Limitations

The survey used a convenience sample of members of from the Society of General Internal Medicine professional society. While recipients of the email were invited to send the survey to other interested professionals, this distribution approach appeared to concentrate responses among general outpatient academic internists. Therefore, the results may not reflect perspectives among physicians of other specialties and other healthcare workers or be generalizable to other types of healthcare systems. The sample size of 42 also limited our data analysis and ability to perform meaningful comparative statistics. Accordingly, there is high margin for error in the rates reported in this study. However, for the purposes of this study, the small sample size is suitable for demonstrating that providers are concerned about recent immigrationrelated law activity in or near their institutions and feel unprepared to handle this situation.

The survey instrument itself was also limited. Validity testing was restricted to face validity. Respondent socio-demographic features were not obtained. Institutional policies around immigration enforcement were not publicly available so we were not able to compare whether policies were in place but were not known by the respondent, or whether policies were not in place at all.

Considerations for Further Research

There is significant opportunity to further expand the knowledge base regarding healthcare facility preparedness and response to immigration-related law enforcement activity. The survey respondents were largely physicians coming from academic medical centers. Further research efforts could solicit insight from a broader range of practice settings and professional types and obtain a larger sample size. A qualitative research project would also be useful to probe further into topics such as providers' experiences with trainings, the features of a prepared facility, and the barriers to implementation of immigrant-centered policies. Studies could also be conducted before and after the implementation of educational programs or protective protocols to assess the impact on provider confidence in addressing immigration enforcement efforts at their facility. Surveys of immigrant patients on the features of a safe and welcoming facility would also critically inform the development of institutional policies. As more healthcare facilities implement preparedness initiatives, best practices should be implemented and evaluated for effectiveness.

Appendix

Your completion of the survey or questionnaire will serve as your consent to be in this research study.

Demographic Questions

- 1. What job do you currently hold?

•2. In what state do you currently work?

•3. In what type of facility do you currently work most of the time?

•Academic/teaching hospital - inpatient

•Academic/teaching hospital - outpatient

•Government hospital - inpatient

•Government hospital - outpatient

•Religious hospital - inpatient

•Religious hospital - outpatient

•For-profit hospital - inpatient

•For-profit hospital - outpatient

•Other hospital - inpatient (please describe)

•Other hospital - outpatient (please describe)

•Other (please describe)

•4. What language is spoken by a majority of your patients?

Research Questions

•5. Are you aware of any policies or procedures at your place of work specifically designed to guide a response to immigration-related law enforcement activity?

•No

•Yes (please describe the policies or procedures and explain how you became aware of them)

•6. Are you aware of any policies or procedures at your place of work that do not explicitly pertain to immigration-related law enforcement activity but that would be used as default guidance to respond to such activity?

•No

•Yes (please describe the policies or procedures and explain how you became aware of them)

•7. Have you received any training specifically designed to guide a response to immigration-related law enforcement activity?

•No

•Yes (please describe the training)

•8. Have you received any training designed to guide a response to law enforcement activity, but not specifically immigration-related law enforcement activity?

•No

•Yes (please describe the training)

•9. Are you aware of immigration-related law enforcement activity within or in the vicinity of a clinical setting at your place of work?

•Yes

•No

•10. How many such incidents are you aware of over the last twelve months?
(If answered 1 or more)
We will now ask you several questions about each of these incidents.

•11. Regarding the X incident, to the best of your memory, when did it occur?

•12. Regarding the X incident, who was the focus of the immigration-related law enforcement activity?

•Employee (please specific employee's position)

•Patient

•Patient's family member

•Other (please specify)

•13. In what setting did the X incident occur?

•Inpatient hospital - emergency department

•Inpatient hospital - admitted patient floor (please describe inpatient area)

•Outpatient clinic (please describe outpatient setting)

•School-based clinic (please describe school-based clinic)

•Other (please specify)

•14. Which of the following staff members were involved in some capacity in the response to the X incident?

•Security personnel

•Registration staff

•Nursing staff

•Physicians

•Legal counsel for the health system

•Other (please specify)

•15. To the best of your knowledge, had any of the individual staff members other than you received relevant information or training prior to the X incident?

•No

•Yes (please specify which staff members and what type of preparation occurred)

•16. Please provide a narrative description of the X incident, including sequential actions taken by various members of hospital faculty and staff in response to the initial event and how these actions did or did not adhere to any policies or procedures you are aware.

•17. In what aspects do you feel your facility is prepared to manage any immigration-related law enforcement activity within or in the vicinity of a clinical setting at your place of work?

•18. In what aspects do you feel your facility is not prepared to manage any immigration-related law enforcement activity within or in the vicinity of a clinical setting at your place of work?

•19. What steps would need to be taken for your facility to be fully prepared for future immigration-related law enforcement activity?

•20. Are there any other comments you would like to provide about incidents you have witnessed or your facility's preparation for the possibility of immigration-related law enforcement activity?

Note

The authors have no conflicts to disclose.

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DETAIL

Subjek:	Immigration policy; Patients; Polls &surveys; Fear &phobias; Deportation; Medicaid; Law enforcement; Public safety; Food stamps; Immigrants; Health care; Internet; Medical personnel; Health services; Citizens; Health facilities; Executive orders; Coronaviruses; COVID-19

Ketentuan indeks bisnis:	Subjek: Medicaid
Lokasi:	United States--US
Pengidentifikasi/kata kunci:	Immigrant Health; Health professional; Border control; Immigration; Law enforcement; U.S. Immigration and Customs Enforcement (ICE); Health Policy; Immigration Law; Sensitive Locations
Judul:	Healthcare Professionals' Experience, Training, and Knowledge Regarding Immigration-Related Law Enforcement in Healthcare Facilities: An Online Survey
Pengarang:	Jaime La Charite; Braverman, Derek W; Goplerud, Dana; Norton, Alexandra; Bertram, Amanda; Berger, Zackary D
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	50-58
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.9

Letter From The Editor

Hutchinson, Ted

TEKS LENGKAP

It is with great pleasure that we announce a major change to the publishing program at the American Society of Law, Medicine &Ethics in 2021. Beginning with this issue, we are now co-publishing our two journals, *The Journal of Law, Medicine &Ethics* and *The American Journal of Law &Medicine*, with a new partner: Cambridge University Press. After five years with SAGE publishing, we have made the move to Cambridge because of all the opportunities it offers our two great journals, including greater visibility; better promotion of our work, our authors, and their articles; greater global reach; a more diverse distribution model; and a stronger, more flexible website for the journals that will better serve the needs of our readers. This issue that you hold in your hands is the first of what we hope is long partnership with our colleagues at Cambridge. We hope you enjoy this collaboration as much as we have so far. Please visit *JLME's* new website at www.cambridge.org/core/journals/journal-of-law-medicine-and-ethics.

In the spirit of new beginnings, we wanted to mark the first issue of this partnership with a very special symposium, and I think we found one with "Public Sector and Non-Profit Contributions to Drug Development —Historical Scope, Opportunities, and Challenges," guest-edited by our longtime friend Ameet Sarpatwari. Simply stated, Ameet argues in his introduction that "Particular concern has emerged because some of the new drugs and treatments emerging at high prices in the US, or that have been subject to some of the most substantial price increases over time, have benefitted in their development from critical public sector support." In other words, why are citizens of the United States asked to pay some of the highest drug prices in the world, while it is our tax dollars that support the development of so many of these same medicines? This symposium examines that issue through any number of lenses, including of course how these challenges are shaping our nation's response to the COVID-19 pandemic.

The challenges of the pandemic and the United States government's anemic response is also the topic of every single column in this issue, including incisive thoughts from our longtime column editors Mark Rothstein, James Hodge, and Aaron Kesselheim. As the COVID-19 vaccine is hesitatingly introduced in the United States (as of this writing) we begin to reflect on the many, many profound ways our response to this great tragedy could have been improved. These are questions we will be asking for many years, and it is one that is a fitting introduction to this new era of the *Journal of Law, Medicine &Ethics*.

DETAIL

Subjek:	Medicine; Journals; Ethics; Coronaviruses; Public sector; Publishing; Pandemics; COVID-19
Ketentuan indeks bisnis:	Subjek: Public sector
Lokasi:	United States--US
Judul:	Letter From The Editor
Pengarang:	Hutchinson, Ted
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	1-1
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Letter from the Editor
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik
Bahasa publikasi:	English
Jenis dokumen:	Editorial
DOI:	https://doi.org/10.1017/jme.2021.1

Disruptures in the Dental Ethos: The Birth, Life, &Neoliberal Retirement of Norms in Advertising &Corporatization

Na'eel Cajee

ABSTRAK (ENGLISH)

This paper argues that the trends in advertising and corporatization in dentistry since the 1970s have resulted in processes of de-professionalization and de-regulation, respectively.

TEKS LENGKAP

In the early 20th century, Edgar Randolph Rudolf Parker stood atop circus wagons preaching oral hygiene to the masses and demonstrating painless extractions. He subsequently went on to found the first franchise empire of dental practices called Painless Parker with the proclaimed intent of increasing access to low-cost dental treatment. Painless Parker's legacy is debated, held in esteem and lauded by some, but ridiculed and jeered by others. He is more famously known for his travelling circus in which his painless dental extraction was a regular feature. Most in the dental profession at the time despised this as reckless clinical practice. Parker believed in making dental care pain free by incorporating local anesthetics and distraction techniques, raising awareness about oral hygiene, and helping to lower the cost of dental care. When the Board of Dental Examiners demanded that the name of the dental practice match the name of the owner as a pushback to this commercialization, he took the painless way of just changing his name instead. Edgar Randolph Rudolf Parker became Painless Parker. The board's actions were done in the spirit of restoring professional standards during a time of increased commercialization, a trend that resonates in our current day.

In 1979, a ceremonial meeting of the Board of Dental Examiners in California was called to order to review the revocation of Painless Parker's license nearly a half century earlier in 1932 based on the following two ethical breaches (1) advertising and (2) involving unlicensed persons in the delivery of care. Posthumously, Dr. Painless Parker was exonerated. Not only did this court of dentists dismiss his five-year suspension from the dental profession as excessive, but they also hailed Painless Parker as a pioneer of his time. The decision in 1979 by the mock board unanimously regretted the five year revocation of Painless Parker's license, hailing him as a man

decades ahead of his time. The posthumous decision suggests a shift in values, allowing the public outreach campaign of Painless Parker to trump any concerns of undignified or unprofessional behavior.

Dentistry today is in a similar decision-making position as a community and a profession. Over the past two decades, the rise of corporate models which manage or own dental practices has initiated discussions in the realm of ethics and professionalism as well as law and regulations. The impetus for the corporate model derives from the cost of technology and equipment for new dentists, the cost of dental education, the state of dental insurance, limited access to care for millions, and generational employment preferences. In recent years, important ethical questions have been raised within and beyond the dental community, particularly due to the growth of dental corporations owned by private equity firms. This conversation over the ethics of dental medicine has been limited to actors in the legal system and professional organizations like the American Dental Association, but has extended into the public arena through documentaries and news articles.

Though this conversation has been primarily located in legal contexts, the topics and language used offers a window into the nature and ethical habitus of dental medicine today. There has been a simultaneous trend in dentistry away from coursework in ethics toward coursework in practice management and entrepreneurship. This shift in the ethical framework of professionalism, in general, and dentistry, in particular, raises questions about the mechanisms and processes that shape value systems of communities, whether professional, religious, or both. This project aims to explore the discourse of dental medicine, through the establishment of professional, ethical, and legal norms in the late 19th and early 20th century as well as through prominent legal cases related to the advertising and corporatization of dental medicine.

This paper argues that the trends of deprofessionalization related to advertising and deregulation related to corporatization in the field of dentistry since the 1970s, far from merely an expected outcome, parallels the diffusion of neoliberal logic in terms of the reconceptualization of the profession as a commercial trade and the unraveling of ethical and legal frameworks established and upheld over a century ago.

This paper argues that the trends of de-profes-sionalization related to advertising and deregulation related to corporatization in the field of dentistry since the 1970s, far from merely an expected outcome, parallels the diffusion of neoliberal logic in terms of the reconceptualization of the profession as a commercial trade and the unraveling of ethical and legal frameworks established and upheld over a century ago.

Research Problem

Although the door for learned professionals to advertise opened in the 1970s, the debate over the involvement of unlicensed persons and corporations is ongoing and critically related by the thread of neoliberal logic. In clinics, conferences, and courtrooms across the country, the growth of corporately managed dentistry/dental medicine is currently being discussed and debated. Nearly 10% of dental practices are currently owned by private equity firms, a reality that would have been unconscionable fifty years ago. The trend has raised ethical questions about the nature of dental medicine and the implications of delivering treatment in various models. There are several key events in courts and legislatures across the country which demonstrate divergent approaches in the discourse, ranging from asserting professional values to shifting the boundaries of professional values and practice.

For the sake of clarity, the framing terms of the paper should be laid out carefully. Neoliberalism is an idealistic way of imagining the world whose roots are in both economics and philosophy but extend far beyond the economic realm. Taking the emphasis on maximizing individual freedoms to its logical endpoint, this school of thought seeks to foster competitive speculative environments that are free —in theory —from any state-based interventions. Thought it may appear differently across geographies, it always maintains certain general characteristics, such as an emphasis on individual innovation and open markets as the keys to a better world.[1]

The distinction between neoliberalism and neo-liberalization helps to differentiate between general patterns and particular localized processes. Neoliber-alization refers to the process of practically attempting to shape an environment according to a predetermined “neoliberal” ideal. This process usually involves negotiating with local cultural and political forces to either dismantle or to construct the backdrop in the image of this ideal. These negotiating processes result in hybrid systems in which aspects of an ideal may be described but often are meshed

with state interventions that either support or oppose its idealistic aims. This is applicable to the dental context in as far as the dental profession is situated in a North American neoliberal milieu.

Since a central question of this paper is to attempt to understand the peculiarity of the configuration of discourse occurring at this moment in history, the connection of this neoliberal milieu to the deregulatory outcomes of the discourse are important categories of analysis. Within studies on neoliberalism, attention has been given to processes of deregulation, especially within the roll-back phase of the project.[2] Deregulation, as the prefix "de" suggests, is a negating and reversing process of regulation. The "regulation" in the term refers to the limits, guidelines, laws, and attempts of governing authorities to limit the activities and practices of businesses in protecting the interests of either other businesses, consumers, and/or the environment. As far as it is directed toward ensuring that structures of state authority take a hands-off approach, this may entail dissolving bodies with oversight who observe commercial life or this can involve striking down legislation that specifies rules. While proponents see it as a means to liberate entrepreneurs and businesses to achieve their full potential, critics regard it as a means of facilitating speculation and fraud by repealing protective measures.

Questions

What was the original rationale for the ethical standard that held Painless Parker to account in the 1930s? What has driven changes in ethics of the dental profession previously, and what shapes the prioritization of its values today? Did the neoliberal policies of the 1970s and 1980s influence the changing attitudes toward advertising generally, and by extension advertising within dentistry? What are the primary drivers for the advent of corporate dentistry and what logic sustains its progress?

What facilitates the commodification of dentistry, and is it external or internal to the practice of dentistry? How does neoliberalism exert itself on professions? On future professionals?

The paper begins with an analysis of Painless Parker's trial in 1932, examining the charges against him (advertising and hiring unlicensed persons as managers) and the poetics of this ethico-legal discourse. Next, we will turn our attention to the 1970s and the debates in court that reversed the taboo on advertising professional services within the legal realm and how it eventually enveloped medicine and dentistry. The thread of Painless Parker's posthumous mock trial in 1979 links these processes to the current debate over the involvement of unlicensed corporate management in dental practices.

Literature: Logic of Deregulation

The articles below relate to the "common sense" logic of deregulation how it comes to be formed, and what constitutes its formation.[3] Vinay Kamat, in "Fast, cheap, and out of control? Speculations and ethical concerns in the conduct of outsourced clinical trials in India" questions the ways in which the rationality for welcoming clinical trials by foreign pharmaceuticals is constructed.[4] He finds that it relates to both a reliance on speculation, sacrifice, and deregulation. The Indian government has introduced key legislative measures to foster an environment that creates the "necessary conditions." This undoing of legal checks instituted at an earlier time is motivated by a relentless hope that the financial returns will be disproportionately great. Just as in other neoliberal projects, a vision of future gains justifies sacrificial elements in the present. Kamat, in his interviews with key stakeholders, shares how the desire to "bring something good to the society" is a key intention of many. Under the guise of greater goods, deregulation is understood to be a natural process to clear away the obstacles of success.

Exploring the flattening of ethics into a market analysis, Bernard D'Mello in "Transnational Pharmaceutical Corporations and Neo-Liberal Business Ethics in India" turns to the issue of pharmaceutical corporations coming in India to test their products on people and pay less for clinical trials.[5] He is interested in the reception of this move and how it has been processed in ethical and logistical terms. Ethics is an optics through which valuation takes place. The author argues that the hegemony of neoliberal economics has replaced a diverse set of valuation methods with only a numeric-based market lens. By pointing to potential casualties of this one-dimensionality, he justifies his claim that the pervasive power inherent in market rationality can easily overwhelm and render checks in the system —like ethics committees —into meaningless rubber stamps. D'Mello also emphasizes the role of promotion and advertising when profitability becomes a fundamental and singular value. This in turn drives up

research and development budgets in ways that are ultimately shouldered by patients.

Of the attempts to connect neoliberalism to healthcare, the archival study “Neoliberal pharmaceutical science and the Chicago School of Economics” by Edward Nik-Kah goes beyond a theoretical approach and establishes direct involvement of the neoliberal theorists in shaping pharmaceutical policy and science.[6] It establishes the possibility within other healthcare fields of direct involvement of the Chicago School of Economics. Nik-Kah’s exposits how through a highly influential conference at University of Chicago, there were deliberate efforts to shape the rationality for pushing back against regulations in the law. These regulations —known as the 1962 Kefauver-Harris amendments —that restricted advertisements and established standards for clinical trials were put in place in the wake of the thalidomide debacle in the 1950s. The dismantling of these protections is part of the process of roll-back which is characteristic of the 1970s. This body of material evidence grants another layer of credibility to the effort of removing the veil covering the encroachment of neoliberal rationalities on the healthcare field.

David Sturgeon’s “The business of the NHS: The rise and rise of consumer culture and commodification in the provision of healthcare services” provides a window into the ways an entrepreneurial consumer culture from without and a competitive privatized system from within have changed the NHS.[7] Sturgeon critiques the increasingly common sense notion that patients are consumers by pointing out that healthcare is a necessity of a different order. The “necessity” of consumption is a key factor of why it is an attractive investment for market-oriented entities. Sturgeon connects the narrative of market reforms in the NHS to the broader policies initiated under the Thatcher government in the 1980s.

Literature: De-Professionalization

The formation of personhood in the context of professionalization is a carefully tuned process. As the initiate is trained in a set of skills society has entrusted their profession to serve society with, they are also socialized into the new group and quickly realize that violations of trust because of an individual affect the collective —their colleagues. Starting with the educational process, little has been written about the influence of the healthcare industry in molding medical or dental students at their incipient stage. Kelly Holloway’s “Uneasy subjects: Medical students’ conflicts over the pharmaceutical industry” examines the reactions and attitudes of student toward the ever-presence of the pharmaceutical industry in their training process, from the preclinical years into residency.[8] Her objective is to critique the normalcy of the industry’s presence from the innocent free lunches to the sponsored continuing education programs in later years. Support from the industry makes up more than half the funding for continuing medical education.[9]

Their continued presence compromises the extent of critical evaluation. Beyond the goal of capturing future business from practitioners, the pharmaceutical industry’s increasing presence at educational institutions can also be rationalized as filling the void in funding left by retreating government funding for research.[10]

Juan Irigoyen writing on the “The Restructuring of Medical Profession” tracks organizational structural changes in the profession that he describes as the rise of a “techno-productive model.”[11] The most significant manifestation is the sudden prominence given to management. This new governmentality, according to Irigoyen’s narrative, is a threat to professionalization, and is directly responsible for the “proletarianization” of the profession.[12]

Another study that looks at the medical profession with a keen eye to the results of consumerism is that of Stefan Timmermans and Hyeyoung Oh. In “Continued Social Transformation of the Medical Profession,” they begin by contrasting the pursuits of businessmen with those of physicians.[13] The former’s training emphasized self-interest while the latter’s training stressed reasonable altruism and prioritization of the patient over finanical remuneration.[14] The trust afforded to the healthcare professions fulfilling a unique niche of healing in society was re-conceptualized as a protected market ripe for investment. While the business side encouraged physicians to spend more money, government regulators were concerned about rising costs and suggested rationing and capitation schemes. With “no downside risk” and adequate pressure over time, the rising tide of investment and government intervention may have had a hand in the decline in professional autonomy noted by sociologists. These social scientists noticed three trends in medicine: “proletarianization (the idea that people move from self-employment to wage labor), de-professionalization (the loss of professional characteristics such as autonomous decision-making), and

corporatization."[15]

Studies have used neoliberalism as an analytic lens to uncover and reveal the inner workings of hitherto regimes of common sense. Within the healthcare field, most of the literature has focused on the pharmaceutical industry and the healthcare system on a macroscopic level. What is still neglected are studies that shed light on neoliberalism's influence on the (deformation of professions and the mechanisms that facilitate that process.

This project will hopefully find congruencies between rationalizing trends in neoliberalizing processes, such as roll back and roll out, and accelerating changes in the dental profession, both institutionally and ethically, over the last half century. This will further the project of identifying just how far neoliberalism has encroached into non-economic domains and has crafted a logic in which ethical judgements of the past are hindrances to the future. If the link between the loosening of regulations on advertising turns out to actually be a precursor to the relaxation of regulations on corporate practice ownership, then future studies of neoliberalism and healthcare may benefit from long durée studies that offer perspective on the gradual pace of the roll back.

Part 1: Establishment of Professional Norms

The emergence of the dental profession is in many ways a reaction to what preceded it and what existed alongside it for several decades. Early 19th century Boston hosted dental parlors where prices for procedures were advertised in fanciful ways, no differently from stores selling jewelry. To expose the "arts of quackery" and commodification in dentistry, by 1839, dentists banded together and formed the first professional school and, a year later, the first professional society —the American Society of Dental Surgeons. These professional formations, as well as other legal initiatives in state legislatures, were intent upon protecting the public from "ignorant pretenders."[16] Soon after the American Medical Association published the first code of ethics in 1847, dentists in their professional society founded in 1859 —the National Delegated Association (predecessor of the American Dental Association) followed suit and published the first dental code of ethics in 1866.

These codes of ethics written by and for the medical and dental communities capture the ethical blind spots and concerns of issues they respectively agreed were critical to their professionalization. The 1866 foundational dental code of ethics plainly stated, "it is unprofessional to resort to public advertising, such as cards, hand-bills, posters, or signs calling attention to peculiar styles of work, prices for services, or to claim superiority over neighboring practitioners."[17] In 1868, the Dental Society of New York explicitly prohibited advertising in order "to preserve good feeling and learning among its members."[18]

The original AMA code in 1847 formulated for the first time the prohibition against corporations practicing or influencing the practice of medicine." This appears in later editions in 1912 and 1922 where it was deemed "unprofessional" for health care providers to treat patients under a corporation. The reason cited is due to the fact relations between patient and physician are more intimate than are those between client and attorney. It is impossible for that intimacy of relationship to exist between and [sic] individual and a corporation and if it is against public policy for a corporation to practice law, how much more so must it be for a corporation to practice medicine.[19]

These efforts to articulate an ethical code and a basis for licensure and credentialing would culminate in their approval as law through dental practice acts. The connection between the codes of ethics and legal limits is made clear in the case of *Semler v. Oregon*

Dental Examiners. While the judges admit that the statutes of other states have no "direct bearing" on the case, one cannot be unmindful that legislation "is an adoption of the rules of ethics of the American Dental Association."[20]

The earliest dental practice act appears in Alabama in 1841.[21] Nearly three decades later in 1868, Kentucky, New York, and Ohio eventually established dental practice acts which not only established boards of examiners but also bestowed them with the sole prerogative to issue licenses.[22] Certain aspects of the ethical codes were written into law like the prohibition of advertising. In 1935, Assembly bill 990 legally entrenched the ethical standard. These laws remained in place. In fact, in 1942, in *Valentine v. Christensen*, the first amendment did not protect commercial speech which served no public purpose.[23]

As described earlier in the introduction, Painless Parker's story is useful for helping us to understand the ways in which the ethical and legal codes were interpreted and applied under the legal system's gavel. When Parker started

out in Brooklyn, he hired William Beebe, who had worked in the Big Top of PT Barnum's circus for 45 years, and gave him Barnum's autobiography to read.[24] Beebe told him, "If you used circus methods, you'd soon be a millionaire."[25] Parker's chain of dental clinics became notorious for his alliterative over-the-top signage with slogans like, "Pause, People, Painless Parker is Pronounced a Paragon!"[26]

His methods of advertising and expanding network of dental clinics earned him the ire of the dental community and several lawsuits. On December 7, 1929, the Board of Dental Examiners handed down a five year suspension of his dental license for advertising and the unlicensed practice of dentistry. This case was brought in 1932 before the California Supreme Court, which upheld the Board's judgment with only one dissenting opinion. He was "suspended for unprofessional conduct in aiding and abetting an unlicensed person (a corporation) to practice dentistry in violation of a statute stipulating that any person is practicing dentistry "who manages or conducts as manager, proprietor, conductor, lessor, or otherwise a place where dental operations are performed."[27] This judgement is based on the premise that the "business end" of the practice was inseparable from the actual application of the professional skill."[28] According to their argument, how could a corporation be allowed to do something indirectly which is clearly not allowed directly —treat patients? Referencing the corporate practice of medicine doctrine, the judge underlined the real possibility for "a secondary and divided loyalty to the patient."[29] This would open the door to unprofessional and unethical outcomes such that neither the owner nor the employee dentist could be held responsible. The judge wrote:

The law does not assume to divide the practice of dentistry into such departments. Either one may extend into the domain of the other in respects that would make such a division impractical if not impossible. The subject is treated as a whole. If the contention of [the dentist] be sound, then the proprietor of the business may be guilty of gross misconduct in its management and violate all standards which a licensed dentist would be required to respect and stand immune from any regulatory supervision whatsoever. His employee, the licensed dentist, would also be immune from discipline upon the ground that he was but a mere employee and was not responsible for his employer's misconduct, whether the employer be a corporation or a natural person.[30]

The issue over the possibility of separating dentistry from business was not clearcut for all the judges. Langdon, the dissenting opinion, believed it was unconstitutional for the state to "regulate business as business."[31] However, one fact remained: that a "corporation may not engage in the practice of the law, medicine, or dentistry is a settled question in this state."[32] The court clearly pointed out that its decision went beyond considering only public health; it also sought to preserve "public morals," a broader base away from the one-way "access to care" rhetoric seen in current-day cases of the same type. Instead, there is deference shown to the ethical standards in the dental profession and their origin in "experience" and "investigation and research," to the extent that they have become laws in "many of the countries of the civilized world."[33]

Just as the case in California sets a precedent for the inseparability of business and clinical care, another lawsuit of Parker in Colorado's Supreme Court on March 4, 1929 established that a corporation is not eligible for a license since it cannot take exams or have a diploma.[34] Parker countered this claim of ineligibility by pointing out that it was precisely this impossibility of obtaining a license that made it possible for a corporation to engage in the practice of dentistry.

Part 2 - Disrupture #1:Deprofessionalization through Advertising

The prohibiting language of the Code of Ethics relaxed gradually with subsequent revisions. By 1899, dentists were permitted to use their names outside their practices though the size and nature of the sign were taken into account. Even as late as 1976, the revised code stated that advertising "lowers public esteem for the profession" and an "announcement could only be sent to other professionals or to patients of record."[35] However, the 1970s serve as a critical turning point not just for dentistry, but for its sister professions, law and medicine. In 1977, an Arizona-based law firm was reprimanded by the State Bar for a marketing plan it had developed. *John R Bates &Van O'steen v State Bar of Arizona* went all the way to the Supreme Court where a slim majority ruled in favor of the former based on the first and fourteenth amendments. Whereas previous courts had ruled that commercial speech was no tprotected by the first amendment, the court in 1977 came to a new conclusion and judged that the unethi-cality of

advertising held by the legal profession were unconstitutional restraints on trade.

By bringing the analogy of the learned professions with commerce to its fullest extent, the legal profession, along with the medical and dental professions, were now considered trades subject to the Federal Trade Commission (FTC).[36] This effective demotion changed the terms of the debate. What previously was the domain of a learned profession now became subject to the legal provisions specific to trade and commerce. Two years later, on April 12, 1979, after the FTC charged the American Dental Association and four dental state societies for contravening anti-trust law, the commission settled with the ADA outside of court. They felt that ethical dentists, not the force of the dental board, were the ones responsible for regulating their colleagues. In the wake of this decision, the ethics codes were re-written to reflect the new reality, the new common sense.

However, there were still restrictions on price advertising which were put in place to control the 19th century dental parlor craze. This prohibition too would be overturned in 1999 by the US Supreme Court with the condition that the price was “exact and easily verifiable.”[37]

Part 3 - Disrupture #2: Deregulation

Similar to the case of *John R. Bates &Van O’steen v. State Bar of Arizona*, there were other cases in the 1970s which affirmed the court’s position that antitrust laws applied to the professional domains. In *Goldfarb v. Virginia State Bar*, the Supreme Court terminated the legal profession’s exemption —and by extension other professions’ exemption —from antitrust laws.[38]

In the same manner the ADA was approached by the FTC, the AMA was approached by the same agency due to anti-competitive language in its Principles of Medical Ethics as of the most recent revision in 1971.[39] In 1979, the AMA modified its language in the code of ethics to soften its previously aggressive regulatory stance, and it serves as an important reference in the interpretation and application of law.[40]

However, this was not the expected outcome given the range of cases upholding the precedent of the learned professions’ autonomy. In 1963, the court in *Garvai v. Board of Chiropractic Examiners* held that it was impossible to separate the business side from the clinical side.[41] The case of Painless Parker was cited by a Colorado court in 2000 when two physicians were charged in addition to the professional corporation. In trying to determine if the corporation could be considered responsible, the court cited the precedent for the legislature —and not the professional board —to “lawfully designate by statute those who may practice the healing arts.”[42] For our purposes, this is important because the jurisdiction established by Parker’s case —which prevented a corporation from practicing dentistry —is used ironically to justify the legislature’s right to *approve* a corporation’s ability to practice.

On the other hand, in the same year in California, as a sign of continuity, the precedent of Painless Parker was cited in the case *Steinsmith v. Medical Board* involving a licensed physician who worked in a clinic owned by non-licensed physicians. Steinsmith tried to argue, like Painless Parker, that the owners were solely involved with the business-related aspect of the clinic. However, the court plainly stated that this line of reasoning was rejected in 1932 in *Painless Parker v. Board of Dental Examiners* and could be just as easily applied in medicine as in dentistry.[43]

A key factor in the establishment of the dental profession had been the erection of a state-sponsored dental board by dental practice acts. This board historically defined the licensing requirements and had jurisdiction over professionals in cases of misconduct. Just as the professional societies had been forced by external circumstances to revise ethics codes, professional boards are currently undergoing a new shaping process. After the Board of Examiners in North Carolina threatened non-dentists who were providing teeth whitening services, the case with the Federal Trade Commission went to the Supreme Court. The issues addressed in the case ranged from determining the limits of a dental practice to the fundamental issue of defining the extent of the authority of the board, which claimed state-action immunity. The court ruled against the dental board using the same anti-trust rationale used in the 1970s to open the doors for advertising. This rationale was spelled out clearly in the court records. Far from perceiving the board as being representative of a profession, the court determined that the individuals making up the board were “market participants” and therefore could be self-interested.[44] The profession became a trade in 1979, and professionals became market participants in 2013. Therefore, this reconceptualization opened the door to applying the norms of commerce.

These processes of deregulation are driven by a market logic, one that commodifies a domain previously impervious by the regulatory framework laid down by professional societies beginning in the middle of the 19th century. While the aforementioned case involved the deregulation of a peripheral dental service, the rise of the dental corporation has resurrected the central issue of distinguishing healthcare as a profession and as a business. While the 19th century and early 20th century debates over this distinction resulted in license suspensions and closures, the current debate has shifted the terrain to one of accommodation and adjusted regulations.

The term “corporate dentistry” refers to a relatively recent arrangement of interests between a dental practice and a corporate management company, also called a dental management organization (DMO). Compromising approximately 10% of the dental services market, DMOs are business structures largely owned by private equity firms.[45] They seek to absorb all of the extra-clinical tasks and accompanying costs, from advertising to materials, and allow the dentist to concentrate his or her focus on treating patients. For new dentists graduating with significant debt, a job at a DMO comes with a number of appealing benefits. Dentists as employees can expect to gain exposure to management, further continuing education, and benefit from flexibility in scheduling.[46] The DMO’s control over the business operation, however, and how that affects clinical decision-making and patient treatment continues to come under legal and ethical scrutiny.

The past two decades have witnessed positive changes in access and availability of care, revealing an upward trend in treating more children. While only 21% of children in 1993 reported visiting a dentist in the preceding year, upwards of 40% in 2010 were seen and/or treated by a dentist at least once that year.[47] During the same time period between 1990 and 2010, Medicaid dental expenditures soared from $756.1 million to $7.4 billion.[48] At least 21% of the increase in treatment of children has been attributed to the parallel rise of corporate dental chains.[49] The Children’s Dental Health Project pointed out that the rise of DMO-affiliated practices contributed substantially to the rise in care, while private and safety net providers contributed only modestly.[50]

According to the American College of Dentists, handbook on ethics, the “chief motive [of a dentist is] to benefit mankind, with the dentist’s financial rewards secondary.”[51] In other words, the mandate is to serve others above self. Compare this to the intent and mission of the private equity firm, Friedman Fleischer and Low, which owns Kool Smiles: to produce “attractive returns for our investors.”[52] In this firm’s case, this translates toinvesting in products that enhance cash flow, leading to its investments in Tempur-Pedic, Church’s Chicken, and Speedy Day.

The difference between selling dentistry and other items —memory foam pillows, chicken wings, and payday loans —is the asymmetry of information about the service between the provider and the consumer. A patient wholly relies on the judgment of the clinician for their product, a transaction based on complete trust and respect. Aspen Dental’s CEO Fontana described the motives behind the generous equity pouring into dentistry by saying that private-equity firms want out of a business after about five years, and the key to a big payoff is growth. For a company owned by outside investors and stockholders, there is immense pressure placed on achieving short-term quarterly earnings.

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In 2015, the Attorney General of New York filed a case against Aspen Dental, accusing the corporate dental chain of violating the state’s ban on the corporate practice of medicine. However, the case was settled out of court by imposing a civil penalty of $450,000 and laying down guidelines to achieve a separation between the clinical and the business sides. For the first time since the rise of the DMO/DSO industry, a state agency —and not a dental board, a dentist, or patient —filed a lawsuit with the intent of enforcing the ban on the corporate practice of medicine in a way that “ensures that New Yorkers receive quality dental care.”[53] The lawsuit identified a number of key problematic practices, including the fact that Aspen Dental Management controlled all the financial accounts and took a pre-determined percentage of each dental clinic’s gross profits. This incentive structure amounts to fee-splitting between

a licensed professional and an unlicensed business entity and allows the business entity —with significant decision-making capacity —to benefit directly in proportion to the amount of procedures completed. Although Aspen Dental Management was able to produce licensed dentists as owners on paper evidence showed that, it exerted significant effort to pressure dentists and dental hygien-ists in their clinical work. The lawsuit cites a specific example of how the corporation would communicate directly with clinicians:

I am reviewing Hygiene results and am discouraged to see that we fell further behind budget for the year! (-4.3%) I know that all of you are equally as competitive as me…so you can relate to how I hate losing to dentures (+1.4%) My real frustration comes from knowing that if we deliver good comprehensive care- we will close this gap! The current gap is $52/day per hygienist…less than one Vizilite, less than 2 sites of Arestin, less than one recall patient…you get the idea! Please look at each day's schedule and find the opportunities.[54]

This coercive language suggests to clinicians that there is a goal to meet and ways to fill the discrepancy between the current practice production and the expected practice production. The management company developed a scheduling system that would prioritize lucrative procedures, like crowns and bridges, and limit other more common procedures, like fillings, to only two per day.[55] The settlement demanded that the agreements between the management corporation and the licensed dentists (serving as owners) stipulate that clinic staff could only communicate with the latter.

Much of the recent ethical polemics revolve around the imposition of quotas, with many former employees of corporate-affiliated practices describing production schemes tied to quotas. In smaller practices, there are also target production numbers; however, the practitioner/owner's self-imposed target is conditioned directly by his or her clinical practice. However, in supersized corporate-managed or -owned practices, the clinical and business extensions do not directly inform one another.

It is true that DMOs have sought to infuse their corporate ethic with the professional ethic of service, as challenging as it may seem. However, due to lenient oversight and weaknesses in the model, there is much room for compromising that relationship between the doctor and patient. For example, a state audit found that, between 2007 and 2011, upwards of 90% of Medicaid claims for orthodontic treatment were invalid in a chain of All Smiles orthodontic practices in Texas. The company was previously owned by a dentist but bought over in 2010 by Valor, a private equity firm, who set up a holdings company in Delaware to make the purchase.[56] In her testimony before Congress, the lead auditor Christine Ellis, also an orthodontist, proclaimed:

The flagrancy of the fraud that I have found in the course of auditing for OIG is truly unbelievable. It is highly likely that it was intentional. Quite simply, providers submitted falsified HLD index forms in order to obtain pre-approval for orthodontic care. Providers did not appear to screen prospective orthodontic patients to find the children that Medicaid was designed to help. Not one patient with a craniofacial anomaly or medical compromise was found during the audit.[57]

In this case, what is surprising is that the fraud preceded the arrival of the private equity firm. It demonstrates that there is a need to identify weaknesses within the corporate model, dentist-owned or not, and to design ways to prevent profit-making motives from affecting treatment delivery. In Michigan and California, a number ofdentists grouped together to take their management company, American Dental Partners, to court.[58] A New York based private equity firm JLL Partners bought American Dental, a DMO managing 280 dental clinics in 21 states, for $390 million. The court case revolves around the DMOs' control of materials and equipment. The dentists allege that the company "refused to replace defective anesthesia equipment, used bill-collection policies that led to 'refusal of dental services to patients' and failed to maintain proper staffing levels." As a result, patients were rushed and left unattended, revealing how operations management upstream can directly and indirectly interfere with the *quality* of patient care.[59] These are two examples amongst many which have shed light on the various relationships involved between the government, management companies, dentists, and patients. This web of connections depends on trust and integrity to function, values which have been called into question with recent revelations.

The current private practice of dentistry takes place in three settings: solo practice, group practice, and corporate practice. Often, corporate practice takes the outward form of the solo and group practice, differing only in ownership

and operational methods. Ownership of a practice has significant implications for how a practice is run, which is why legislation is in place to define it. In most states, legislation historically prohibited the ban on non-dentist owned practices for the sake of upholding the independence of the doctor-patient relationship. It sought to prevent corporate business policy or unlicensed persons from interfering in diagnostic and treatment decisions.[60] However, as managed care took off as a cost-containing trend in the eighties and nineties, there was a lobbying push within the medical community to legally permit a professional corporate entity (Professional Limited Liability Corp. PLLC) for the sake of tax privileges. It is challenging to speak legally on behalf of all state codes, but it is safe to share that about twenty-five states in addition to the District of Columbia restrict the ownership of this professional entity to a license-bearing individual.[61] In order to circumvent these legal technicalities, an investment structure was designed through which dental practices are technically owned by dentists but controlled in every other respect by dental management companies from the outside. These dentists are practically “ghost owners” since their ownership is nominal and does not extend completely to the supervision of clinical operations and patient care.[62]

The question of ownership is the basis of the current investigation by Senator Grassley, prompted by reports of abuse, and current class-action cases against the major dental management companies. Theoretically, the government could shut down private equity firm-owned companies involved in the practice of dentistry in a number of states. In order to qualify as a PLLC, the registration and certification process requires a dentist to be an applicant. For a modest monthly stipend, a young dentist may falsely certify that they are the owner.[63] This is the fundamental challenge of the new status quo where the spirit of the law has been reinterpreted. The agreements of the corporation with dentists are often referred to by lawyers scripting the contracts as sham ownerships.

While the question of ownership might be a clear roadblock in states whose legal codes expressly prohibit non-dentist owned practices, the corporate model’s benefits in expanding care have pressured legislators to modify the code.

Corporate dentistry has focused on expanding into areas not cared for by dentists currently, mostly due to the limited acceptance of public insurance. In states like North Carolina, this expanded access to care was a key argument in favor of professionalizing the corporate dental delivery model as opposed to eliminating it. The lobbying face of corporate dentistry in North Carolina was in fact called the “Alliance for Access to Dental Care.”

In Kansas, until recently, the law very clearly stipulated that only a dentist could own and operate a dental clinic. As the state began to realize the limits on access to dental care, legislation regarding both the ownership of dental practices and auxiliary workforce capabilities was liberalized and enhanced. On August 28, 2012, Comfort Dental, a subsidiary brand of the dental conglomerate Interdent, opened its first dental practice in Kansas.[64] Many states are either not enforcing the laws or re-interpreting the meaning and intent of the law to the benefit of the DMO industry.[65] The underlying purpose of the ownership laws was to ensure the clinician’s independent clinical decision-making for the ultimate benefit of the patient. However, due to the mutability of legislation, the debate over the rise in DMOs is ignoring the original intent of the law and shifting to accommodating its delivery of treatment in accordance with the ethics of the profession. Though the issue is being framed as an access to care issue, it is easy to lose sight of the purpose of the legal provisions in place and appreciate the very real concerns at the time of their enactment.

Conclusion

This investigation has explored the deregulation and de-professionalization within dentistry in the context of the processes of establishing the societies, ethical codes, and practice acts. Having traced the formation of the dental profession through societies and boards and the ways in which the courts upheld their jurisdiction in the early 20th century, the trend starting in the 1970s of utilizing antitrust legislation and the accompanying rise of market logic suggests a major shift toward the commercialization of learned professions. While the dental profession became a trade in the 1970s with the Bates case, dentists became “market participants” with the North Carolina Board of Dental Examiners case. Just at about the time the language of commerce becomes commonplace, the argument for increasing access to care and making public insurance programs effective overwhelmingly makes provisions of the past antique. The culmination of the issues presented above has normalized the presence of corporate practices and has brought the issue of regulation to the frontlines of dentistry.

The weaknesses exposed by recent court cases trace back to the evolving relationship between the dentist and the DMO. In the interest of abiding by current state codes and upholding the ethics which preserve the sanctity of the dental profession, legislation is needed to regulate contracts between dentists and management companies. This is already underway in states like North Carolina, which have chosen regulation as the path to resolution, and should be followed through in other states. Existing regulation may take the form of requiring dental ownership or limiting corporate involvement to management alone. Because corporations fall under state law, provisions must be made for dental boards to step in and assess practices according to the ethical values of the profession. The accommodating approach to corporate dentistry that sees a natural separation between business and clinical affairs would be unfathomable a century ago. The layers of insulation between the recent dental school graduate, the sham owners, the dental management company, and the private equity firm blur the lines of responsibility and authority and make change and feedback more challenging. Just as dentists over a century ago rose to the occasion to bring clarity amid change and establish trust, the responsibility to deliberate creatively is upon us now. Our patients deserve it and so do we.

Note

The author has no conflicts to disclose.

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DETAIL

Subjek:	Medicine; Regulation; Oral hygiene; Retirement; Trends; Dentists; Neoliberalism; Values; Debates; Logic; Decision making; Trials; Dentistry; Advertising; Dental care; 20th century; Professional ethics; Deregulation; Professionalization; Medical ethics
Ketentuan indeks bisnis:	Subjek: Advertising Professional ethics Deregulation
Pengidentifikasi/kata kunci:	Dental Ethics; Dentistry; Corporatization; Neoliberalism; Advertising; Dentistry; Advertising; Neoliberalism; Healthcare
Judul:	Disruptures in the Dental Ethos: The Birth, Life, &Neoliberal Retirement of Norms in Advertising &Corporatization
Pengarang:	Na’eel Cajee
Judul publikasi:	The Journal of Law, Medicine &Ethics; Boston
Volume:	49
Edisi:	1
Detail sumber:	Public Sector and Non-Profit Contributions to Drug Development: Historical Scope, Opportunities, and Challenges
Halaman:	77-88
Tahun publikasi:	2021
Tanggal publikasi:	Spring 2021
Bagian:	Independent Articles
Penerbit:	Cambridge University Press
Tempat publikasi:	Boston
Negara publikasi:	United Kingdom, Boston
Subjek publikasi:	Law, Medical Sciences
ISSN:	10731105
e-ISSN:	1748720X
Jenis sumber:	Jurnal Akademik

Bahasa publikasi:	English
Jenis dokumen:	Journal Article
DOI:	https://doi.org/10.1017/jme.2021.13
ID dokumen ProQuest:	2730846674
URL Dokumen:	https://www.proquest.com/scholarly-journals/disruptures-dental-ethos-birth-life-amp/docview/2730846674/se-2?accountid=211160
Hak cipta:	© 2021 The Author(s)
Terakhir diperbarui:	2023-11-27
Basis data:	Public Health Database