



# Regulatory flexibility for COVID-19 research

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## ABSTRACT

Clinical research is critical to combatting COVID-19, but regulatory requirements for human subjects protection may sometimes pose a challenge in pandemic circumstances. Although regulators have offered some helpful guidance for research during the pandemic, we identify further compliance challenges regarding institutional review board (IRB) review and approval, informed consent, emergency research, and research involving incarcerated people. Our proposals for regulatory flexibility in these areas seek to satisfy the goals of protecting participants and promoting the development of high-quality evidence to improve patient care. These recommendations may have relevance beyond the COVID-19 pandemic to enhance the efficiency of research oversight and participant protection more broadly.

**KEYWORDS:** COVID-19, human subjects protection, institutional review board, informed consent, emergency research, prisoners

Clinical research to understand, treat, and prevent COVID-19 is both crucial and highly regulated. Most intervention studies are subject to Food and Drug Administration (FDA) requirements, and federally funded research with human subjects must follow requirements imposed by the Common Rule. Strict regulatory compliance may be

challenging amidst a public health emergency, but participant protection and high-quality science remain essential.<sup>1</sup> In recognition of these considerations, FDA and the Office for Human Research Protections (OHRP) within the Department of Health and Human Services (HHS) have issued guidance on conducting research during the COVID-19 pandemic.<sup>2</sup>

Although this guidance offers a helpful start, gaps remain and additional regulatory flexibility is warranted in some instances. COVID-19 research has been running at a remarkable pace,<sup>3</sup> challenging the capacity of both investigators and institutional review boards (IRBs). To ensure that this research proceeds efficiently and ethically, we offer suggestions to proactively address regulatory compliance challenges regarding IRB review and approval, informed consent, and inclusion of vulnerable populations.

## MECHANISMS OF REGULATORY FLEXIBILITY AND CURRENT COVID-19 GUIDANCE

FDA and OHRP are tasked with interpreting and enforcing statutory and regulatory requirements, but they also possess substantial leeway in doing so. First, regulators sometimes may exercise *enforcement discretion*, deciding not to strictly enforce particular requirements, either as a general matter or on a case-by-case basis.<sup>4</sup> Second, regulatory requirements may sometimes be *waived*. FDA is permitted, under certain conditions, to waive investigational new drug (IND) and investigational device exemption (IDE) requirements, as well as specific IRB oversight requirements.<sup>5</sup> Common Rule department and agency heads also may waive some or all regulatory provisions, so

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- 1 Alex John London & Jonathan Kimmelman, *Against Pandemic Research Exceptionalism*, 368(6490) SCIENCE 476–77 (2020).
  - 2 FDA, *FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency* (July 2, 2020), <https://www.fda.gov/media/136238/download>; OHRP, *OHRP Guidance on COVID-19* (Apr. 8, 2020), <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/ohrp-guidance-on-covid-19/index.html>; OHRP, *Effects of Disasters on Human Research Protections Programs Guidance* (May 14, 2018), <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/effects-of-disasters-on-human-research-protections-programs-guidance/index.html>.
  - 3 See Kristian Thorlund, Louis Dron, Jay Park, Grace Hsu, Jamie I. Forrest & Edward J. Mills, *A Real-Time Dashboard of Clinical Trials for COVID-19*, LANCET DIG. HEALTH (2020), [https://www.thelancet.com/journals/landig/article/PIIS2589-7500\(20\)30086-8/abstract](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30086-8/abstract).
  - 4 See, e.g., Heckler v. Chaney, 470 U.S. 821 (1985). See also OHRP, *Determination of Exception for Certain HHS-Conducted or -Supported Cooperative Research Activities Subject to the 2018 Requirements* (2019), <https://www.hhs.gov/ohrp/regulations-and-policy/single-irb-requirement/114b-exception1/index.html> (“This exception is an exercise of OHRP’s enforcement discretion...”); Rachel E. Barkow, *Overseeing Agency Enforcement*, 84 GEO. WASH. L. REV. 1129, 1131 (2016) (“Most aspects of agency enforcement policy generally escape judicial review.”); Nathan Cortez, *Regulating Disruptive Innovation*, 29 BERKELEY TECH. L.J. 175, 221 (2014) (“agency discretion may reach its apex versus judicial interference in matters of enforcement”); Lars Noah, *The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 902 (2008) (“the FDA enjoys largely unreviewable discretion in deciding whether and how to exercise its enforcement powers”); Gibson Dunn, *FDA Round-Up: Overview of Emergency Actions to Expedite the Availability of Medical Products to Combat COVID-19* (Apr. 13, 2020), <https://www.gibsondunn.com/fda-round-up-overview-of-emergency-actions-to-expedite-the-availability-of-medical-products-to-combat-covid-19/> (providing examples of FDA exercising enforcement discretion for COVID-19 products). But see *Cook v. Food & Drug Admin.*, 733 F.3d 1, 7 (D.C. Cir. 2013) (finding an instance of “clear statutory” language that limited FDA’s enforcement discretion).
  - 5 21 C.F.R. 312.10 (2002); 21 C.F.R. 812.10 (1980); 21 C.F.R. 56.105 (1987).

long as alternative procedures are consistent with ethical principles.<sup>6</sup> Third, in the face of ambiguity, both regulators and IRBs generally have *interpretive flexibility*, meaning they can adopt either more or less restrictive interpretations of particular requirements so long as those interpretations are reasonable.<sup>7</sup>

Thus far, FDA and OHRP have offered only interpretive flexibility for human subjects protection issues relevant to COVID-19 research. As discussed below, one of FDA's most helpful points of guidance in this realm addresses how to conduct the research consent process for COVID-19 patients given infection-control concerns.<sup>8</sup> In addition to guidance to assist sponsors in the clinical development of COVID-19 drugs,<sup>9</sup> other components of FDA's pandemic research guidance address issues that may arise when using remote methods to monitor participants, collect data, and deliver and administer interventions.<sup>10</sup> FDA has also issued guidance permitting certain modified uses of non-invasive remote monitoring devices for clinical management of patients whose care is affected by the public health response to COVID-19, which may have additional relevance for research.<sup>11</sup> HHS's decision to exercise enforcement discretion for certain restrictions on telehealth also may facilitate remote study activities.<sup>12</sup>

OHRP has endorsed FDA's COVID-19 guidance as consistent with Common Rule requirements and drawn attention to prior guidance indicating OHRP's flexibility in disaster circumstances.<sup>13</sup> OHRP's own COVID-19 guidance offers little specific detail, however, beyond clarifying which public health and clinical activities do not require IRB review.<sup>14</sup>

In several key domains, regulators should offer further clarification to facilitate COVID-19 research while maintaining adequate participant protections. If they are not already doing so, IRBs should also exercise the regulatory flexibility currently

6 45 C.F.R. 46.101(i) (2018).

7 See *Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc.*, 467 U.S. 837 (1984). See also *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410, 414 (1945) (“administrative interpretation [] becomes [] controlling weight unless it is plainly erroneous or inconsistent with the regulation”); *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (finding an interpretation of an agency’s “own regulations,” is “controlling unless ‘plainly erroneous or inconsistent with the regulation.’”); *Kisor v. Wilkie*, 139 S. Ct. 2400, (2019) (declining to overturn, but arguably reframing, *Auer* and *Seminole Rock*). Although there have been calls and efforts to overturn these doctrines of deference, they currently remain in place. See, e.g., Jonathan J. Darrow, Erin Fuse Brown & Aaron Kesselheim, *The Regulatory Accountability Act of 2017—Implications for FDA Regulation and Public Health*, 378 N. ENGL. J. MED. 412 (2018); Christopher J. Walker, *Attacking Auer and Chevron Deference: A Literature Review*, 16 GEO. J.L. & PUB. POL’Y 103 (2018); Christopher J. Walker, *What Kisor Means for the Future of Auer Deference: The New Five-Step Kisor Deference Doctrine, Notice & Comment* (June 26, 2019), <https://www.yalejreg.com/nc/what-kisor-means-for-the-future-of-auer-deference-the-new-five-step-kisor-deference-doctrine/>.

8 FDA, *supra* note 2.

9 FDA, *COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (May 2020), <https://www.fda.gov/media/137926/download>.

10 FDA, *supra* note 2.

11 FDA, *Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency* (Revised) (June 2020), <https://www.fda.gov/media/136290/download>.

12 Office for Civil Rights, US Department of Health and Human Services, *Notification of Enforcement Discretion for Telehealth Remote Communications During the COVID-19 Nationwide Public Health Emergency* (2020), <https://www.hhs.gov/hipaa/for-professionals/special-topics/emergency-preparedness/notification-enforcement-discretion-telehealth/index.html>.

13 OHRP, *Effects of Disasters*, *supra* note 2.

14 OHRP, *Guidance on COVID-19*, *supra* note 2.

**Table 1.** Regulatory challenges and proposed flexibility for COVID-19 research.

<i>COVID-19 research challenge</i>	<i>Available flexibility</i>	<i>Recommendations</i>
Heightened workload and personal responsibilities for IRB members	Sites may rely on another IRB of record Sites may create smaller standing IRBs	FDA and OHRP should seek to adjust quorum requirements to permit meeting-specific sub-boards with adequate expertise and representation
Potential for overwhelming consent disclosures	IRBs may exercise discretion regarding disclosure of alternatives and new findings	FDA and OHRP should offer guidance to refrain from specifically listing alternative trials or sharing unreliable reports from outside research FDA should create a central resource of reliable guidance
Community consultation to support EFIC	IRBs may exercise discretion regarding level, type, and approach to consultation	FDA and OHRP should offer guidance on appropriate means and scope for rapid, remote consultation
Satisfying special safeguards for research involving people who are incarcerated	None (leading to exclusion of people who are incarcerated, potentially to their detriment)	OHRP should authorize the inclusion of “prisoners” in certain types of research offering the prospect of direct benefit when enrolled alongside general populations, and should seek to permit such research to proceed based on routine IRB review BOP should also seek to permit such research to proceed with individuals in its custody

Abbreviations: IRB (Institutional Review Board), FDA (Food and Drug Administration), OHRP (Office for Human Research Protections), EFIC (Exception from Informed Consent for Emergency Research), BOP (Bureau of Prisons).

available to them (Table 1). Although the pandemic is changing rapidly, the virus remains a substantial public health threat without adequate therapeutic or prophylactic interventions, suggesting that our recommendations for flexibility will remain relevant for some time. They will also be useful in the face of future pandemics and should be considered for research more broadly.

**Research Review and Approval**

As part of its Coronavirus Treatment Acceleration Program (CTAP),<sup>15</sup> FDA is conducting “ultra-rapid protocol review,” often within 24 hours, for research subject to IND

15 FDA, *Coronavirus Treatment Acceleration Program (CTAP)* (2020), <https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap>.

and IDE requirements.<sup>16</sup> Many IRBs are also taking steps to speed review of COVID-19 protocols, including through disease-specific review boards, prioritization over non-COVID submissions, and more frequent meetings. These approaches can, however, strain board capacity, especially at academic institutions where membership may not be as deep as for commercial boards. Additionally, many members are juggling added professional and personal obligations due to the pandemic.

To address these challenges, research sites should rely on review conducted by other boards with sufficient capacity and expertise whenever possible. This is required for multisite research subject to the Common Rule (unless a site's board has been designated the IRB of record), but is also permitted more broadly.<sup>17</sup> Additionally, FDA and OHRP should consider adjusting quorum requirements through enforcement discretion or regulatory waiver procedures.

Most COVID-19 interventional research will require review at convened IRB meetings. Quorum for such meetings requires a majority of the total board membership, including the presence of at least one member whose primary concerns are in non-scientific areas.<sup>18</sup> Because IRBs must comprise at least five members satisfying certain criteria, the minimum quorum to satisfy regulatory standards is three members.<sup>19</sup> Allowing larger boards to break into meeting-specific sub-boards, each with adequate expertise and representation, would reduce their quorum requirements. This, in turn, would allow the assignment of fewer COVID-19 protocols per reviewer and permit members to attend fewer meetings, easing the burden on each member and allowing more time and attention for rigorous review.

This approach would entail fewer reviewers per protocol than might otherwise be the case, but if additional reviewers lack sufficient time to review all the protocols assigned to them, that tradeoff seems appropriate. Moreover, under this flexible approach, no meeting-specific sub-board would comprise fewer than three participating members, the minimum number of reviewers deemed acceptable by the regulations. Although institutions already have the authority to revise their IRB charters to split larger IRBs into smaller ones, our proposal is more flexible because it would allow IRBs to make membership adjustments meeting-by-meeting as needs change in real time. This may be especially useful as sites re-open to non-COVID research, in addition to their COVID-19 portfolios, thereby further increasing IRBs workloads.

### Informed Consent

As noted above, FDA guidance specifies acceptable procedures to obtain informed consent in the face of isolation requirements for COVID-19 patients and physical distancing requirements that may affect surrogate decisionmakers.<sup>20</sup> In these circumstances, FDA recommends using electronic consent, including via the COVID MyStudies App newly developed by the agency for this purpose. It also describes an alternative process involving a combination of phone or video conferencing, provision of the consent form by someone already entering a patient's room, signed documentation, and either

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16 21 C.F.R. 312.40 (1987); 21 C.F.R. 812.30 (1980).

17 21 C.F.R. 56.114 (1981); 45 C.F.R. 46.114 (2018).

18 21 C.F.R. 56.108(c) (2002); 45 C.F.R. 46.108(b) (2018).

19 21 C.F.R. 56.107 (2013); 45 C.F.R. 46.107 (2018).

20 FDA, *supra* note 2.

a witness attestation of signature or photograph of the signed form for study records. Similar methods may be used for a patient or legally authorized representative unable to travel to the trial site. Investigators are not required to have a signed consent form in hand prior to beginning study-related procedures, but the consenting party must receive the consent form (by email or otherwise), sign, and date it before study-related procedures may begin; if the form cannot be printed remotely, FDA permits the consenting party to sign a blank piece of paper with a written statement of voluntary agreement to participate. This documentation of consent may be confirmed verbally if it is not possible to return the signed documentation immediately.

Although this procedural guidance is helpful, FDA should also take steps to clarify the content of informed consent for COVID-19 research. Relevant regulations require disclosure of “appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subject,” as well as, where appropriate, a commitment to provide “significant new findings developed during the course of the research that may relate to the subject’s willingness to continue participation.”<sup>21</sup> These provisions are likely to be particularly challenging given the rapid pace of research and clinical developments around COVID-19.

Prospective participants may have several alternatives to enrolling in any particular COVID-19 protocol,<sup>22</sup> but disclosing all of these possibilities in detail could substantially lengthen consent materials and risk the appearance of endorsing unproven options. In addition, especially at these still relatively early stages of pandemic response, available alternatives will be in constant flux. Building on existing FDA guidance that “treatment options lacking evidence of therapeutic value do not need to be discussed,”<sup>23</sup> regulators should clarify that COVID-19 research consent need not describe every investigational option currently under consideration for COVID-19,<sup>24</sup> nor list specific alternative trials for which an individual may be eligible. Instead, risks and benefits of research participation should be discussed in relation to what could reasonably be expected outside the trial (i.e., local standard of care, which may depend on access to scarce resources<sup>25</sup>), and consent materials should broadly disclose that individuals may choose to pursue clinical alternatives or other research studies. To the extent that participating in a particular study might foreclose eligibility to enroll in other studies simultaneously or in the future, or preclude the use of other medical interventions available outside trials, that should also be disclosed. Prospective participants should be directed to their treating clinicians for further guidance, although investigators should be prepared to have context-appropriate discussions with individual patients and families.

21 21 C.F.R. 50.25 (2011); 45 C.F.R. 46.116 (2018).

22 See Holly Fernandez Lynch, Alison Bateman-House, Arthur L. Caplan, ‘Panic Prescribing’ Untested Coronavirus Treatments: A Danger To Patients Today and Tomorrow, HEALTH AFFAIRS BLOG (2020), <https://www.healthaffairs.org/doi/10.1377/hblog20200330.265604/full/>.

23 FDA, *Draft Guidance: Informed Consent Information Sheet* (2014), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent>.

24 See David C. Fajgenbaum et al., *Treatments Administered to the First 9152 Reported Cases of COVID-19: A Systematic Review*, INFECT. DIS. & THER. (2020), <https://link.springer.com/article/10.1007/s40121-020-00303-8>.

25 See Lev Facher, *Trump Administration Announces Plan to Distribute Covid-19 Drug Amid Concerns Over Allocation*, STAT NEWS (May 9, 2020), <https://www.statnews.com/2020/05/09/trump-administration-announces-plan-to-distribute-covid-19-drug-amid-concerns-over-allocation/>.

Because consent is an ongoing process, participants must receive information that could influence a decision to withdraw as it becomes available. Existing FDA guidance emphasizes the need to provide new risk information, such as adverse events that are unexpected or found to occur at a greater frequency or severity than previously disclosed.<sup>26</sup> However, the regulatory language extends further to new findings both within and outside a particular protocol. In the context of COVID-19, IRBs and investigators will likely struggle with how to respond to the constant barrage of research data, especially given disputes about what conclusions are reasonably drawn from those data.<sup>27</sup> Regulators should therefore clarify the standard for disclosure, including which disclosures require re-consent and amended forms versus other mechanisms of information sharing. At a minimum, participants should be informed of new agency warnings (e.g., recent FDA statements and actions regarding hydroxychloroquine),<sup>28</sup> government treatment recommendations,<sup>29</sup> and new product approvals or emergency use authorizations relevant to trial participation decisions.<sup>30</sup> In contrast, the disclosure standard should exclude new information gleaned from outside reports based on preprints without peer-review or interim findings from incomplete research, which may be more misleading than informative. In addition, rather than expecting each IRB and investigator to engage in the difficult and potentially duplicative work of parsing new COVID-19 data for trial participants, FDA's CTAP could maintain an up-to-date website to serve as a source of reliable guidance relevant to COVID-19 study participation.

### Emergency Research

Because COVID-19 can entail rapid development of severe, acute respiratory failure and other acute, life-threatening conditions, some protocols may need to be conducted under regulations for emergency research that allow subjects to be enrolled under an exception from informed consent (EFIC).<sup>31</sup> The primary challenge for COVID-19

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26 FDA, *supra* note 23.

27 See, e.g., Matthias Blamont, Alistair Smout, Emilio Parodi, *EU Governments Ban Malaria Drug for COVID-19, Trial Paused as Safety Fears Grow*, REUTERS (May 27, 2020), <https://www.reuters.com/article/health-coronavirus-hydroxychloroquine-fr/eu-governments-ban-malaria-drug-for-covid-19-trial-paused-as-safety-fears-grow-idUSKBN2340A6>; *COVID-19 Study on Hydroxychloroquine Use Questioned by 120 Researchers and Medical Professionals*, THE GUARDIAN (May 29, 2020), <https://www.theguardian.com/world/2020/may/29/covid-19-surgisphere-hydroxychloroquine-study-lancet-coronavirus-who-questioned-by-researchers-medical-professionals>.

28 FDA, *FDA Cautions Against Use of Hydroxychloroquine or Chloroquine for COVID-19 Outside of the Hospital Setting or a Clinical Trial Due to Risk of Heart Rhythm Problems* (Apr. 24, 2020), <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>; Letter from Denise M. Hinton, FDA, to Gary L. Disbrow, Biomedical Advanced Research and Development Authority (BARDA), Revocation of Emergency Use Authorization for chloroquine phosphate and hydroxychloroquine sulfate distributed from the Strategic National Stockpile (June 15, 2020), <https://www.fda.gov/media/138945/download>.

29 Centers for Disease Control and Prevention, *Coronavirus Disease 2019 (COVID-19): Therapeutic Options* (2020), <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>.

30 FDA, *Remdesivir Emergency Use Authorization Letter* (2020), <https://www.fda.gov/media/137564/download>.

31 21 C.F.R. 50.24 (1996); Department of Health and Human Services, *Waiver of Informed Consent Requirements in Certain Emergency Research*, 61(192) Fed. Reg. 51531-3 (1996), <https://wayback.archive-it.org/3929/20160209155859/http://archive.hhs.gov/ohrp/documents/100296.pdf>.

EFIC research is that the regulations require, prior to IRB approval, consultation with individuals from communities “in which the research will be conducted and from which the subjects will be drawn.”<sup>32</sup> This has traditionally been a lengthy process, often involving face-to-face contact with stakeholders, which will be difficult for COVID-19 research given urgency and the likely need to continue physical distancing for some time. Regulators should therefore encourage IRBs to focus on rapid identification of high-priority community concerns from key stakeholders. Appropriate stakeholders will be site and condition-specific; they may include community advocates and advisory boards, religious and cultural leaders, and government leaders. Involvement of patients and family members at high risk for COVID-19 or who have experienced related conditions are also critical, as is attention to the views and concerns of minority groups and socioeconomically disadvantaged individuals disproportionately affected by this disease. Regulators and IRBs should recognize that these efforts may need to be more focused than in other contexts and that researchers will predominantly need to rely on remote consultation methods, including webinars, online surveys, and telephone calls. However, it is critical that genuine efforts to solicit community views not be abandoned.

### Research Involving Incarcerated People

In light of open questions about how best to treat COVID-19, clinical care for patients suffering from moderate to severe disease often involves trial participation. This makes it important to consider including people who are incarcerated,<sup>33</sup> given the substantial risk of infection associated with their confinement.<sup>34</sup> Yet, as a vulnerable population, the inclusion of incarcerated people in research is subject to additional regulatory safeguards.

Biomedical research funded by HHS may involve “prisoners” as subjects when the research examines practices that have “the intent and reasonable probability of improving the health or well-being of the subject,” among other circumstances.<sup>35</sup> This determination must be made by OHRP and is not left up to IRBs.<sup>36</sup> Moreover, when this research requires assignment to control groups that may not benefit from participation, OHRP is required to consult with experts in penology medicine and ethics, as well as to publish public notice of intent to allow such research.<sup>37</sup> In addition to these authorizations, HHS-funded research involving “prisoners” may only be approved by an IRB that has a “prisoner representative” amongst its membership,

32 Id.

33 Consistent with recommendations to avoid stigmatizing and dehumanizing language, we use the terms “people who are incarcerated” or “incarcerated people,” except where directly quoting regulations that use the term “prisoners.” See, e.g., Health in Justice Action Lab at Northeastern University School of Law, *Justice-Involved People, Changing the Narrative*, <https://www.changingthenarrative.news/justice-involved-people>; Prison Studies Project, Language, <http://prisonstudiesproject.org/language/>.

34 Laura Hawks, Steffie Woolhandler, Danny McCormick, *COVID-19 in Prisons and Jails in the United States*, JAMA INTERN. MED. (2020), <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2765271>; Matthew J. Akiyama, Anne C. Spaulding, Josiah D. Rich, *Flattening the Curve for Incarcerated Populations—Covid-19 in Jails and Prisons*, 382 NEW ENG. J. MED. 2075–77 (2020).

35 45 C.F.R. 46.306(a)(2)(iv) (1978).

36 OHRP, *Prisoner Research FAQs*, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/prisoner-research/index.html>.

37 Id.; *supra* note 35.



which would be unusual for a hospital-based board that does not traditionally review research involving incarcerated people.<sup>38</sup> Federal Bureau of Prisons (BOP) regulations go further than HHS rules, requiring that research projects involving individuals in its custody “must not involve medical experimentation . . . or pharmaceutical testing.”<sup>39</sup> Notably, FDA does not have any specific requirements for research involving people who are incarcerated.

Ethical concerns are reduced when incarcerated people are not specifically targeted for COVID-19 research, but rather are included alongside members of the general population. This helps to ensure that incarcerated people are not unfairly exposed to research-related risks as a matter of convenience. However, when incarcerated participants are not scientifically necessary for inclusion, researchers are unlikely to pursue the time-consuming and burdensome regulatory steps required for their enrollment, especially given the myriad other pressures arising in pandemic circumstances. As a result, this population may be excluded from COVID-19 research that offers a prospect of direct benefit, a perverse result of regulatory safeguards intended to protect them.

We therefore recommend that OHRP rapidly consult with relevant experts and, if appropriate, publish a broad determination that potentially beneficial COVID-19 trials that only incidentally enroll incarcerated people in non-prison settings can meet the requirements for their acceptable inclusion. This might apply, for example, to incarcerated people receiving care at outside hospitals who happen to be eligible for trials enrolling broadly from that site’s patient population without any specific intention to include them. In addition, OHRP should pursue waiver of the requirement that such research be reviewed by a specially constituted IRB, given that the inclusion of people who are incarcerated may not have been contemplated at the time of study approval and the difficulty of securing timely special review once an eligible patient presents for enrollment. BOP should also seek a waiver to permit those in its custody to participate in these potentially beneficial studies. To the extent that state and local rules limit the research participation of incarcerated people, adjustments to those rules may be necessary as well. When people who are incarcerated are not specifically targeted for research, relying on traditional IRB approval standards and consent requirements should offer sufficient protection while also facilitating their access to possible research benefits.

## CONCLUSION

The COVID-19 pandemic should not be viewed as an opening to opportunistically reduce participant protections. Yet, it presents an invitation to revisit regulatory requirements and their conventional interpretations to evaluate which are truly necessary and which may constitute unjustified barriers to research. In that regard, we must acknowledge that while human subjects research regulations and guidance are often important means of participant protection, existing approaches are not evidence-based and therefore should not be presumed to be more effective than or otherwise preferable

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38 45 C.F.R. 46.304 (1978).

39 28 C.F.R. 512.11 (1997).

to less burdensome alternatives.<sup>40</sup> Thus, it is critical to rigorously examine opportunities for regulatory flexibility with the goal of identifying the most parsimonious ways to protect participants while facilitating the efficient conduct of ethical research. This should be a high priority for regulators and IRBs in the time of COVID-19, with continued attention after the pandemic has passed. We therefore urge regulators and IRBs to implement the flexible approaches we recommend for COVID-19 research and then to consider their relevance to the full spectrum of biomedical research.

#### DISCLOSURES

Holly Fernandez Lynch receives research funding from the Greenwall Foundation. She is the founder and co-chair of the Advancing Effective Research Ethics Oversight Consortium (AEREO), a member of a subcommittee of the U.S. Department of Health and Human Services Secretary's Advisory Committee for Human Research Protections, a board member of Public Responsibility in Medicine and Research (PRIM&R) and the American Society of Law, Medicine, and Ethics, and a member of the NYU Working Group on Compassionate Use and Preapproval Access. She received travel costs and honorarium for a lecture to WCG Clinical in 2017 and consulting fees from Hueston Hennigan in 2019 on matters related to research compliance.

Neal W. Dickert receives research funding from NIH, AHRQ, and the Greenwall Foundation.

Patricia J. Zettler reports serving as an expert witness retained by the Direct Purchaser Class Plaintiffs in *In re Suboxone Antitrust Litigation*, No. 2:13-MD-2445 (E.D. Pa), as an expert witness retained by the Direct Purchaser Class, End Payor Class, and Retailer Plaintiffs in *In re Opana Antitrust Litigation*, No. 14cv-10150 (N.D. Ill.), and as a consultant to Georgia State University on tobacco and nicotine research funded by FDA and NIH.

Steven Joffe receives research funding from Pfizer through the Perelman School of Medicine.

Emily A. Largent has no disclosures.

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40 Stuart G. Nicholls, *Revisions to the Common Rule: A Proposal in Search of Evidence*, 13(2) RESEARCH ETHICS 92–6 (2017).