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SPECIAL ARTICLE

Ethical Challenges in COVID-19 Biospecimen Research: Perspectives From Institutional Review Board Members and Bioethicists

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Abstract

Biospecimen research is a prominent investigative strategy that aims to provide novel insights into coronavirus disease 2019 (COVID-19), inform clinical trials, and develop effective, life-saving treatments. However, COVID-19 biospecimen research raises accompanying ethical concerns and practical challenges for investigators and participants. In this special article, we discuss the ethical issues that are associated with autonomy, beneficence, and justice in COVID-19 biospecimen research and describe strategies to manage the practical challenges, with an emphasis on protecting the rights and welfare of human research participants during a pandemic response. Appropriate institutional review board oversight and bioethics guidance for COVID-19 biospecimen research must maintain their focus on protecting the rights and welfare of research participants, despite the urgent need for more knowledge about the virus and the threat it poses to communities and nations.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the newly identified virus that causes coronavirus disease 2019 (COVID-19). As of September 28, 2020, SARS-CoV-2 has infected more than 33.2 million individuals worldwide and has been associated with 999,298 deaths.[1] It is imperative to find an intervention that successfully prevents or mitigates morbidity and mortality, especially to avoid overwhelming of critical health care infrastructure. Although clinical trials are ongoing to investigate therapeutic options and preventive strategies for COVID-19, biospecimen research has become a prominent investigative strategy to further understand the disease, improve testing, and inform clinical trials that are assessing treatment and prevention strategies, including a vaccine.

Biospecimen research encompasses the practices of collecting, storing, and using biological specimens (eg, tissue, blood, urine, and body fluids) and clinical data for research purposes. Biospecimen research is essential in the COVID-19 era because these studies can help provide novel insights into viral infectivity, generation of and duration of immune response, and effect of treatments on viral load, thereby providing a deeper understanding of the disease for the benefit of public health. In contrast to clinical trials, one advantage of such research is minimal risk; after collection it can proceed without imposing any additional risk of SARS-CoV-2 exposure on donors.

Although biospecimens research may contribute to discoveries which ultimately can lead to life-saving results, pandemic biospecimens research is associated with some important and unique ethical issues. Ongoing discourse in the biorepository and biospecimens literature captures a variety of ethical and regulatory concerns distinct to pandemic biospecimens research including: donor vulnerability at the time of collection, potential disruption of already overwhelmed clinical institutions, laboratory

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biosafety, the need for large and harmonized data specimen collection and data sharing, and the sustainability of use once the pandemic subsides.[2-5] In this article, we emphasize how ethical and practical challenges of COVID-19 biospecimen research appear from the perspective of those involved in human subjects research protection, and we consider strategies to manage these challenges for those involved in biorepository oversight.

The 1978 Belmont Report[6] established the foundation for research oversight, and articulates three ethical principles. These provide a default theoretical framework that institutional review board (IRB) professionals and members often turn to when dealing with novel questions not addressed more directly by regulations. These principles include: 1) Respect for Persons: "Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection." 2) Beneficence: "Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms." And 3) Justice: This principle is most often implemented in relation to subject selection: "the selection of research subjects needs to be scrutinized in order to determine whether some classes (eg, welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied."

RESPECT FOR PERSONS

The basic ethical principle of respect for persons, otherwise known as respect for an individual's autonomy, is to ensure that individuals are truly informed about their research participation. This principle is divided into two moral requirements: 1) the requirement to acknowledge autonomy, and 2) the requirement to protect those with diminished autonomy.[6-8] Thus, autonomy refers to the right of a person to decide freely and independently whether they wish to participate in research, and this decision is informed by the accurate and relevant information that is provided to them.

Different models of informed consent in biospecimen research have been proposed with various supporting and opposing arguments. These models range from broad consent to study-specific (traditional) consent to hybrid models.[9] The adequacy of broad consent authorizations in biospecimen research is intensely debated because it involves giving consent to the future use of samples, uses that are unknown at the time of the initial consent. In addition, anonymous or de-identified biospecimens can be used for research, and although this practice is common (and established long before the current novel COVID-19 pandemic), it was among the most debated topics during the recent revisions to human subjects research protections (the Common Rule).[10] In the revised Common Rule, "broad consent" is a new type of regulatory consent that permits collection, storage, and secondary use of data for future unspecified research. The National Institutes of Health provides guidance on consent for future research use and broad sharing of genomic research data.[11] However, it is not mandatory, and the significant changes in systems and processes that are needed to use broad consent have presented implementation barriers to institutions. Moreover, available data on patient opinions are mixed because biospecimen contributors have expressed support for various consent models and positions on using de-identified clinical biospecimens for research.[12-14]

Concerns about several aspects of biospecimen research were already being discussed because of events that occurred before the current pandemic. Biospecimens have been used by researchers in ways that were not within the scope of the participants' initial consent, as noted in the well-publicized case involving Arizona State University researchers and the Havasupai tribe.[15] Such actions have undermined the

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public's trust that research partnerships prioritize community health needs. Additionally, the Henrietta Lacks case has shown that a foundational premise of biospecimen research, which is the assurance that future generations will benefit from the knowledge gained, may not be true for marginalized populations if they are denied access to clinical care or have other health disparities.[16] Nevertheless, most patients are willing to contribute biospecimens for use in research and view those contributions as essential for helping others, even though some ethical concerns about the body and identity, privacy and confidentiality, and commercial use persist.[17-19]

It is against this complex background of ethical considerations that COVID-19 biospecimen research has emerged, and the urgency of this public health crisis has compounded the challenges of regulatory oversight that are noted above. Practically speaking, COVID-19 biospecimen research faces several issues that complicate its ethical oversight. First, the high-risk patients are frequently older, have multiple medical comorbidities, and often are hospitalized and critically ill.[20] Other vulnerable groups in the United States, including racial and ethnic minorities, children, those who are socioeconomically disadvantaged, or the incarcerated are also disproportionately affected by COVID-19.[21-23] These individuals may temporarily or permanently lack the capacity to give informed consent. The heightened anxiety faced by surrogates or legally authorized representatives (LARs) who may be approached for consent can result in delays in obtaining consent, particularly as these surrogate decision-makers think through the questions about ongoing clinical care plus the choices associated with research participation. Second, isolation precautions and personal protective equipment and masking procedures may preclude the traditional face-to-face consent discussions, thereby limiting the ability of research recruiters to use conventional in-person methods of obtaining participant consent. Study team members then must rely on methods of obtaining consent that may not be ideal in noisy and highly fatiguing inpatient settings. Notably, such methods likely lack the richness of human interaction and communication and can impact the ability to understand nonverbal cues and create opportunities for participants to ask questions about aspects of research participation that may be unclear. Third, because of visitor restrictions, patients hospitalized with COVID-19 are socially isolated from persons they may typically rely on for assistance in making health care decisions. Additionally, family members may not have access to technology that could allow them to communicate with the research team, receive digital consent forms and study documents, and return digitally signed documents.

Institutional review board oversight of COVID-19 biospecimen research must account for these multiple obstacles to obtaining informed consent from patients or their LARs. In designing recruitment strategies, investigators and IRBs must balance issues of justice and respect for persons with the approved methods of discussing informed consent. In the recruitment of human participants for COVID-19 biospecimen research, investigators should be sensitive to the medical issues of post—COVID-19 with prolonged recovery times, to ensure that recruitment strategies are not coercive or heavy handed. The consent strategies must ensure that proper means of informed consent are used, bias and discrimination in selecting and recruiting participants are minimized, and ensuring that participants agree to participate willingly and free from coercion, especially vulnerable persons. No population should be overly burdened by research and no population should overly benefit from research. This commitment is clearly articulated in the Belmont Report and other influential statements of research ethics.[24]

Under the revised Common Rule,[1] prospective collection of research biospecimens before obtaining informed consent is no longer allowed. However, an IRB can waive consent for the initial collection if the procedure meets the criteria in the Common Rule: 1) no more than minimal risk to participants; 2) no adverse effects on the rights and welfare of participants; 3)

impracticability of conducting research without the IRB consent waiver; and 4) provision of additional information after participation. Institutional review board consideration of consent waivers depends on all these conditions being met, but impracticability is a factor that is especially relevant during public health emergencies. From an infection control perspective, rapid collection and timely analysis of COVID-19 biospecimens is critical to improve and expand testing. The mental and/or physical state of the participants may preclude them from being approached for consent. There may be issues regarding optimized infection control which makes obtaining written informed consent impracticable. However, researchers must go beyond this positive justification and also provide a rationale that explains why individual consent is not merely difficult to obtain but genuinely impracticable in a pandemic setting. These justifications and rationales can still be developed within the framework of constraints described above.

The Office of Human Research Protection, part of the US Department of Health and Human Services, has provided guidance on COVID-19.[25] This guidance encourages the research community to prioritize public health safety, given the current circumstances, and assure flexibility in its decision-making as investigators and institutions take necessary actions to protect the public and research participants. In addition, the US Food and Drug Administration has provided guidance on alternative methods of obtaining and documenting informed consent during the COVID-19 pandemic consistent with the regulations from the Code of Federal Regulations of 45 CFR 46.[26] When traditional paper or electronic methods are not possible, alternative methods include transmittal of a photographic image of the signed and dated consent form by facsimile, text message, or e-mail to the investigator; return of signed consent form by mail or at a future in-person study visit; use of a witness to sign and date an attestation that a participant has agreed to participate; or use of the US Food and Drug Administration's MyStudies app.[26,27]

Institutional review board approval of studies involving an initial waiver of consent requires investigators to develop a robust plan for locating, contacting, and obtaining consent from the participants or their LARs before using the samples.[28,29] If a participant or their LAR cannot be located, the sample should be destroyed. However, in the current situation, when blood samples from patients with COVID-19 are vitally important for improving scientific understanding of the virus and its consequences, investigators may reasonably explore alternatives to destroying samples when consent cannot be readily obtained. One strategy may be to de-identify samples, which then can be used in a narrower range of future research studies in which identifiers cannot be used to track individual patient serologic responses over time or changes in various parameters due to interventions in the individual. This approach still allows samples collected to be used for research purposes, despite not being linked to an identifiable individual, thereby promoting scientific discovery and greater understanding of the global health pandemic while mitigating any potential risks to the patients from whom these biospecimens were collected. The benefits of this approach must be weighed carefully, however, against potential concerns about dignitary harms (defined as "those incurred when individuals are not treated as persons with their own values, preferences, and commitments, but rather as mere means, not deserving of respect")[30] to sample contributors and other harms to disadvantaged populations. Although de-identified information is not considered protected health information under Office of Human Research Protection guidance, the same information may not necessarily be de-identified for Health Insurance Portability and Accountability Act Privacy Rule purposes.[31] Institutional leaders and IRB chairs may benefit from meeting with a research ethics consultation service[32,33] and other specialists in bioethics when considering alternatives to de-identification or sample destruction.

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Using biospecimens without explicit consent raises multiple concerns about patient autonomy because consent is neither implied nor documented at the time of collection. Moreover, the delayed consent process seems contradictory because it offers no real choice to patients if their de-identified samples will still be used for research. A compromise may be to create a hybrid consent model in which individuals could withdraw the right for researchers to use their biospecimens in an identified or de-identified way. No matter how dire the situation, researchers do not have an unrestricted right to access human biospecimens in the absence of permission.[34] Indeed, even after such permission, biospecimen use can always be revoked if a patient so indicates.

Institutional review boards, scientists, and bioethicists must continue to reflect upon the appropriate use of biospecimens collected from patients with COVID-19. These decisions are substantially easier when patients grant informed consent for such use. These decisions require more complex thought and review when research is authorized for de-identified biospecimens that were obtained during situations in which patients were not consulted or were not available to authorize the use of their biospecimens for research. Substantial time is required to review and discuss the regulatory requirements, the bioethical principles that must be met, and the relative merit of the impact of the discovery as a trade-off for reduced autonomy. We recommend that IRBs work closely with research ethics consultation services to ensure preservation of autonomy and respect for persons as guiding and overarching principles, and IRBs must remain flexible as they face new and emerging situations that may challenge these principles in the course of scientific innovation.

BENEFICENCE AND ITS COROLLARY, NONMALEFICENCE

Beneficence is an ethical principle in research that requires protection of research participants from harm and exploitation, as well as maximizing possible benefits from participating in research.[6] Given that COVID-19 biospecimen research typically requires biospecimen collection as the only research intervention, oftentimes with medical record review, it may be designated as minimal risk research. However, if collection of biospecimens is established without proper disclosure or consent, biospecimen research may not be as low risk as it initially appears. Autonomy is a compelling but not overriding principle. Informed consent (or the lack thereof) is only one layer of protection, and autonomy alone can never provide sufficient protection for potential participants.[35] There are risks which accompany biospecimen research and it is important to focus on them briefly.

What Are the Risks of Biospecimen Research?

Violation of participant privacy and breach of confidentiality are major risks in biospecimen research. Health records are private and patients expect their confidentiality will be maintained.[36] However, patient records can be inadvertently compromised by any research effort, including biospecimen research. It is unclear whether current privacy protections are sufficient for patients who donate biospecimens because biobank samples and results can be shared locally or globally.[37] A recent large survey of potential biobank participants reported that 90% of respondents were concerned about privacy.[38]

A second potential risk is that of exploitation of protected and vulnerable groups. It can be argued that COVID-19 biospecimen research is for public or population health benefit. While true, it is also conceivable that public stigmatization for those considered "infectious with COVID-19" might occur. It is well-established that biospecimen research participation does not offer individual participants any prospect of direct benefit. However, these concerns may be outweighed by the urgent need for better testing to detect the infection and for further understanding of antibody response and resistance. In addition, biospecimen research can facilitate recognition of new mechanisms

and candidates for novel treatments, vaccines, and other forms of prevention.

The potential of COVID-19 research being on an accelerated translational pathway offers the hope that participants would receive the social benefits of advancements within a relatively short period. Certainly, the proponents of COVID-19 research anticipate that their work will have a high and timely impact on mitigating the disease or altering its course. These expectations are likely more aspirational in nature and not strongly rooted in history or reality as the timing and benefit of scientific inquiry cannot be predicted a priori. These scenarios, in which benefits are realized at a population or community level, may imply some reciprocity for participants. As such, they do not fit well within current regulatory schemes, which focus more on the direct benefits to individual participants and rarely consider the potential social value of projects.

Institutional review board oversight of COVID-19 biospecimen research requires adherence to a maximum level of privacy and confidentiality for participants, and minimizes risks of exploitation of protected and vulnerable groups. Institutional review boards must review biospecimen research protocols for data protection strategies that ensure protection of identity of participants and reduce risk of re-identification, such as proper consenting procedures, data use agreements, technology security, compliance with regulatory guidelines (such as the Health Insurance Portability and Accountability Act), and processes for establishing ownership or custodianship of biospecimens guided by regulations or best practices.[3,15,39-43] The need to minimize risks of exploitation of protected and vulnerable groups who are disproportionately affected by COVID-19 does not mean excluding these groups from COVID-19 biospecimen research. Coronavirus disease 2019 has impacted minority and economically disadvantaged communities to a greater extent than more affluent and/or White communities. It is important that research findings be generalizable to all populations, and there has been increased focus on minority subject recruitment. However, IRBs must guard against exploitation of disadvantaged communities by researchers who might offer exculpatory inducements and/or promises for research participation or over promise the potential benefit of rapid translation of findings into benefits for any given group of participants. Institutional review boards must ensure that a study has equitable selection of subjects, appropriate consent processes, effective and clear cultural and multilingual communications, community engagement, and mechanisms in place to identify and address stigmatization.[39,41,43] As with the Havasupai case, it became evident that community engagement is critical in building trust and understanding a study population's perspective. Similar models of community and participant engagement have been used in other areas of biobanking research, including research with American Indian and Alaska Native communities.[15,40]

JUSTICE

Every pandemic evokes new questions about what justice requires, even as the pandemic also potentially worsens existing inequalities. In applying the principle of justice as conceived in the Belmont Report, IRBs have traditionally focused on the equitable selection of subjects. The Belmont Report also points out that the benefits of publicly funded research ought to be fairly available to all; however, there is no specific guidance on how to actually make the benefits of research available to all within the report.[6] Expediting pandemic-related research and allowing waivers of informed consent for the initial biospecimen collection procedures relies on social arguments about the responsibility to participate in research that likely yields collective benefits, especially when that research can occur only during an active pandemic or other emergency.[21] The acceptability of allowing a waiver of consent for initial biospecimen collection depends on an IRB's ongoing commitment to support the just distribution of research-related benefits. We suggest that IRBs prioritize

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research along lines that the scientific review process believes will yield the greater public good most quickly, and advocate publicly that sponsors and researchers ensure their discoveries are available in an equitable manner to all.

Institutional review boards must consider how to meet the demands of justice in the initial review of COVID-19 biospecimen research protocols and when reviewing subsequent requests for access to biospecimens. Initially, the protocol review must focus on equitable recruitment and inclusion so that the benefits and burdens of research are fairly allocated. With this framework, IRBs should consider how researchers will recruit a diverse population of participants and also consider ways in which certain groups are particularly vulnerable in a pandemic.[44] Beyond reviewing the initial COVID-19 biospecimen research protocols, IRBs have an ongoing obligation to ensure fair access to the therapeutic benefits of research, as well as to promote the inclusion of historically disadvantaged populations in future pandemic planning efforts. Additionally, IRBs should engage vulnerable populations in the post—COVID-19 era to assess whether the public agrees with a waiver of consent and what types of research they are willing to engage in without giving explicit informed consent. The current pandemic will not be the last time IRBs and scientists engage these questions.

RECOMMENDATIONS FOR IRB MEMBERS AND BIOETHICISTS

Specialists in human subject protections, such as IRB members, should work collaboratively with bioethicists and investigators to ensure that the principles of respect for persons, beneficence, and justice are met prior to research approval. Formal institutional policies and study-specific approaches must strive to balance the need to conduct biomedical research with the need to preserve the rights and autonomy of research participants. These strategies should include consideration of creative methods for discussing study involvement and obtaining informed consent from participants or their LARs in a manner that preserves patient autonomy, honors respect for persons, and advances our understanding of this dangerous new virus while minimizing risks to participants. In the extreme context of a pandemic response, situations may arise in which prospective participant consent is waived until the public health crisis subsides and consent authorizations are retroactively sought (ie, after biospecimen collection). However, research use of such biospecimens should not occur until patient consent (or LAR authorization) is documented.

When creating institutional guidelines, bioethicists and IRBs must also consider the health risks to staff from obtaining in-person written consent when participants have a highly contagious and potentially fatal illness. Bioethicists and IRBs must also consider how to weigh empirical evidence about public attitudes. For example, some researchers involved in pandemic planning have solicited public opinion on how research could be conducted during pandemics, including assessing the public's willingness to accept simplified study enrollment or delayed consent for biospecimen research.[45] Although such findings are valuable when shaping IRB policy, public attitudes about hypothetical issues can diverge substantially from real-life preferences, especially when individuals are influenced by their illness experience.[46,47]

CONCLUSION

Ethical concerns about autonomy, beneficence, and justice are evident in COVID-19 biospecimen research. Appropriate IRB oversight and bioethics guidance must center on protecting the rights and welfare of research participants, despite the urgent need for more knowledge about the virus and its impact. Institutional review boards must continue their essential role in protecting human research participants, especially those who are now more vulnerable because of the impact of COVID-19—related disease and the social isolation necessary for its management. In serving this role, IRBs must also be flexible with regard to the specific policies that they adopt for the purpose

of protecting human research participants so that scientific innovation and discovery can proceed and guide future care. Institutional review board decisions should ensure that COVID-19 biospecimen research is conducted ethically and in compliance with regulatory requirements, while simultaneously advancing the goal of benefiting the public.

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Abbreviations and Acronyms: **COVID-19** = coronavirus disease 2019; **IRB** = Institutional Review Board; **LAR** = legally authorized representative; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2

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