Respect for Persons and the Dilemma of Control in Informed Consent for Organoid Research

A Research Paper submitted to the Department of Engineering and Society

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

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Spring 2025

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

Henrietta Lacks was an African-American woman whose cells were collected and distributed across the research world without her knowledge (Beskow, 2016). Since Lacks's cells were collected in 1951, federal regulations for research with human biospecimens have been enacted, regulating the use of biological materials from humans. The initial donation and research with biospecimens requires informed consent, but secondary research (i.e., research after the initial use for which they were donated) may be conducted without consent as long as the specimens are deidentified. After the publication of *The Immortal Life of Henrietta Lacks* (Skloot, 2010), protections for biospecimens research became a prominent topic of debate (Beskow, 2016), leading to proposed updates in the procedures for informed consent and secondary research. The changes ultimately failed, but they still represent the unmet public concern for transparent use of human biospecimens.

Biospecimens regulation is also not updating alongside advances in biomedical research that present new concerns. This is evident in the case of organoids. These three-dimensional biological models are derived from stem cells or tissue samples and grow to mimic organs or other biological tissues, on a miniature scale. Organoids are an increasingly popular tool for researching disease and personalized medicine given their greater biological accuracy compared to other models (Tang et al., 2022). Although organoids are regulated the same as other biospecimens, their complexity raises ethical concerns and uncertainties that have not been addressed (de Jongh et al., 2022). Failing to update biospecimen regulation to recognize public concerns and the changing landscape of organoids is intrinsically problematic in that it limits autonomy for human subjects in research. It also risks creating a distrusting relationship between researchers and the public that will hinder research participation.

I aim to understand the necessary steps for implementing informed consent that respects participants and prepares for a future of organoid research. I begin by outlining the current informed consent regulation for human subjects and assessing these regulations using the Deontological idea of respecting persons (Kant, 1785). Then, I discuss the argument for organoids specifically, using the Collingridge Dilemma, which explains the difficulty in controlling technologies at different stages of development (Collingridge, 1980). I first look at organoids as a new technology, arguing why they are especially important in the informed consent discussion, and how we can mediate their sociotechnical development by analyzing the values in human-organoid relationships. Finally, I discuss organoids and biospecimens as a well-established technology, exploring different consent models and how these could be implemented despite resistance.

Human Subjects Protection in Biospecimen Research

Human subject protections in the United States were developed in response to ethical violations by researchers. The Tuskegee Syphilis Studies saw hundreds of rural Black men studied for untreated syphilis over 40 years. The participants were convinced to participate through free medical treatment. Even after Penicillin was found to treat syphilis, participants received placebos or invasive diagnostic shots disguised as treatment (Tobin, 2022). Publicization of this study resulted in numerous changes to human studies research, including the writing of the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (NCPHSBBR), 1979). This federal report laid a framework for the ethical study of human subjects and later guided the creation of human subjects regulation, known as the Common Rule. Within this framework are three key ethical principles: respect for persons, beneficence, and justice.

Informed consent is connected to respect for persons, which reflects the deontological views of Immanuel Kant (Pritchard, 2021). According to Kant (1785), people have the right to freely reason and exercise autonomy, and have a duty to respect that right for others. The Belmont Report emphasizes the necessity of informed consent, that is, allowing persons to choose how they shall participate in research, given sufficient information, comprehension, and voluntariness. Yet, this principle does not provide an unwavering guideline for ethical research. A fellow principle of the Belmont Report, beneficence follows a more utilitarian approach (Mill, 1861; Pritchard, 2021). Beneficence focuses on avoiding harm for the specific subjects of a study while also maximizing benefits for society as a whole (NCPHSBBR*,* 1979.).

The discourse surrounding the Common Rule highlights the sometimes incompatible nature of respect for persons and beneficence. Biospecimens research has incredible potential for beneficence and low risk to donors, especially when anonymized (Beskow, 2016)**.** However, it presents blurred lines on what is a human subject, and therefore uncertainty on who respect is owed to. The Common Rule requires informed consent for human subjects research, but the secondary use of a biospecimen is not considered a human subject as long as the specimen is not identifiable.

Increasing public attention surrounding *The Immortal Life of Henrietta Lacks* (Skloot, 2010) contributed to the notice of proposed rulemaking (NPRM) by the federal government in 2015 (Beskow, 2016). The NPRM suggested changes to the Common Rule, including redefining a human subject to include all biospecimens, thereby requiring consent on all biospecimens. It also proposed regulatory broad consent as an alternative means to secondary research, which would explain possible future uses, with the donor agreeing to all future research under these terms (Lynch et al., 2019).

Despite an effort to respect persons and public concerns, the NPRM was strongly opposed. The Council on Government Relations (COGR), an association of research institutions focusing on research policy, collected opinions and comments on the NPRM. They found that opposition primarily came from researchers and patients, with over 90% of each group opposing the redefinition of human subjects (*COGR, 2016*). Researchers highlighted how critical biospecimens are for biomedical innovation and contested the feasibility of broad consent infrastructure. Meanwhile, patients and loved ones emphasized the urgency of research with biospecimens. Ultimately, the redefinition of a human subject was removed from the revisions (Lynch et al., 2019). The overwhelming opposition to the changes in the NPRM support that it would sacrifice too much beneficence. Yet, the concerns which elicited the NPRM are not without merit, and further compromises should be sought. Doing so is necessary to satisfy the respect that human subjects are entitled to. Additionally, it serves to build trust in research institutions, creating greater willingness to participate.

It is important to understand why the current regulation raises public concern, even when deidentified biospecimens have minimal risk of privacy invasion or other tangible harm. According to Lynch et al. (2019), subjects may think that broad consent limits their ability to make future decisions about their biospecimens, not realizing the existing possibility of them being used without consent, via deidentification. Once informed about this possibility, they may favor broad consent for its transparency, but lose trust in research institutions. This underscores the failures of the current model. If reframing the model for consent would make participants aware and upset about existing possibilities for using their specimens, is this really the respect for persons and *informed* consent that the Belmont Report sought to protect?

The comments in opposition to the NPRM are easy to empathize with, but, when addressing supporters of the NPRM, place too much emphasis on privacy without recognizing underlying concerns for trust and autonomy. One patient's comment reads, "[p]lease don't put the remote chance of invading the privacy of some patients ahead of the lives of others" (*COGR, 2016,* Patients and Patient Representatives p.1). Privacy is important, as one study found 94% of respondents expected careful protection of their privacy. That said, 93% were still willing to donate specimens (Peppercorn et al., 2020). Willingness to participate in research does not reflect that participants are unconcerned with privacy, but rather that they have trust in researchers to protect patients, as did 76% of respondents. When presented with the possibility of their tissue being used without their consent, for example using deidentified residual tissue from surgery, 49% of participants were less willing to donate as this trust would be violated. Thus, the main reason for changing regulation is not simply privacy. It is to earn the trust of participants, who are owed this if they are to make an autonomous decision.

Diverse experiences also create different levels of willingness to participate in research, and failures in medical research have created barriers to participation for minority groups in the U.S. For example, the Havasupai Tribe in Arizona had blood samples unknowingly used for secondary research that resulted in stigmatization surrounding mental illness (Lynch et al., 2019). Unsurprisingly, 100% of comments to the NPRM from tribal nations supported redefining human subjects and opposed broad consent, preferring to limit secondary study without direct consent. In another case, Kraft et al. (2018) conducted focus groups with diverse participants, discussing hesitations towards research participation. Once again, trust was a key factor, and historical discrimination, such as the Tuskegee Syphilis Study or the story of Henrietta Lacks, played a large role in this level of trust. Trust was also related to day-to-day occurrences such as

poorly translated medical forms or lack of representation in medical staff. These concerns lead to lower research participation for many minority groups, making it harder to make medical discoveries that represent these groups (Kim & Milliken, 2019). The third principle of the Belmont Report, justice, discusses fairness in who should bear the burden of research and who should receive its benefits (NCPHSBBR, 1979.). If history has created additional concerns that prevent specific groups of people from participating in and benefiting from research, failing to address these is not only a violation of respect, but also justice.

These accounts show that current standards for informed consent do not meet the standards of the Belmont Report. Many are excited by the prospects of biospecimens research and want to participate (*COGR*, 2016; Peppercorn et al., 2020). That said, donors deserve a route to participating as much as they want to, or else their autonomy is violated. The changes presented by the NPRM limited the beneficence of scientific research, and the content of future changes should be reconsidered. However, taking steps towards more transparent use of biospecimens will earn a greater body of participation and is necessary to provide respect.

Human Subjects Protections in Organoid Research

Organoids as a New Technology: Understanding Donor Concerns

Defining the scope for secondary use of biospecimens presents challenges as new scientific discoveries are made. Biobanks may store specimens indefinitely, for use years after donation (Annaratone et al., 2021). Informed consent that does not anticipate new developments during this time may allow for the use of a donor's sample, regardless of whether it aligns with their values. Informed consent for biospecimens research must be able to accommodate new developments in a way that respects donors' values, especially for rapidly developing technologies

One example of a rapidly developing technology is organoids. Using PubMed (2025) search results to demonstrate relevance, a traditional biospecimen such as “cell line(s)” showed consistent growth from the 1960s, before slowing in the 2010s. These are well-established technologies and have been thoroughly explored for uses and consequences. On the contrary, organoids were not established until 2009 (Sato et al., 2009). Searching for “organoid(s)” first returns over 100 results in 2015 and shows increasing relevance every year after that (Appendix: Figure 1). Organoid research involves the pursuit of currently unattainable techniques, for example larger or more complex organoids that could serve as organ replacements (Shariati et al., 2021). Without knowing where organoid research is heading, it is difficult to provide transparency when discussing informed consent (de Jongh et al., 2022).

The framework I will use to discuss this problem is the Collingridge Dilemma (Collingridge, 1980), which describes the difficulty in controlling a technology. In the early stages of a technology’s development, little is known about its social consequences. Once it is well-established, there is greater resistance to implementing control. I first explore organoids as a new technology that warrants consideration beyond other forms of biospecimens. I do this using a method suggested by Kudina and Verbeek (2019), called technological mediation. This method, in an attempt to balance speculation and concurrent observation, studies the interactions of human values with a developing technology. Comments and themes from interviews with patients and donors about organoids provide insight into concerns of people, regardless of the exact future of organoids. Understanding these concerns now is important, as it will only become more difficult to update informed consent regulation in the future.

One emerging theme echoes the attitude towards biospecimens in general: the importance of trusting relationships. Several respondents felt comfortable with organoids being used by

public researchers or in hospitals, but not by commercial entities, such as pharmaceutical companies. They feared benefits being limited to the wealthy and were distrustful of commercial parties acting in their best interest (Boers et al., 2018; Bollinger et al., 2021). Furthermore, some respondents indicated that they preferred research in the hands of the original group they were donated to (MacDuffie et al., 2023). Finally, many participants preferred to be notified with the results of studies (Boers et al., 2018; Bollinger et al., 2021; MacDuffie et al., 2023). These views highlight that donated organoids are sensitive materials and a personal investment.

Other concerns related to the complexity of organoids. The most common topic was brain organoids. Participants supported brain organoid research, but showed worry when consciousness was discussed. One parent said, "I would hate to think of any part of [my daughter] to be in pain" (MacDuffie et al., 2023, p. 1391). Another patient thought that as you come closer to fully functional "brains," it becomes harder to distinguish personhood (Bollinger et al., 2021). Many felt an ambiguous personal connection with organoids and noted that future increases in size or complexity may make this relationship closer (Boers et al., 2018). In other cases, participants alluded to the uncertainty of the field, referencing science-fiction themes such as Frankenstein's monster or immortality, worrying that organoids may be used for the sake of pushing the boundaries of science (Bollinger et al., 2021). Although these applications may not seem realistic, they reflect that advances in science affect the level of value sharing between donors and organoids, and as such, it is important to inform donors of new uses for organoids. Additionally, they emphasize that donors care about whose hands the organoids end up in, so as to avoid research that doesn't align with their values.

These accounts demonstrate what the public is concerned about with organoid research, and what oversights in informed consent may leave them feeling disrespected or untrusting.

Ongoing communication and personal involvement was important to respondents for a variety of reasons, indicating that a one-off broad consent would not be suitable. It is also important to note that the studies contained mostly White participants, which may contribute to more favorable opinion of medical institutions as these participants have likely experienced less medical discrimination. Additionally, most participants had some significant medical diagnosis, indicating established relationships with clinicians or researchers and possibly a greater investment in medical research. Further investigation with diverse groups of prospective donors should be done to uncover more important values surrounding organoid research.

Organoids as an Established Technology: Enacting New Consent Models

Thus far, several models of informed consent for organoid use have been proposed, one of which is consent for governance. Consent for governance focuses on the obligations that researchers have towards donors. Boers and Bredenoord (2018) suggest such a model where the initial consent procedure includes terms for privacy, donor engagement, commercialization, and ethical oversight, in addition to foreseeable research uses. Rather than try to predict and eliminate public concerns such as commercialization or specific research activities, consent for governance sets a framework for responsibly addressing future developments and relies on transparency to garner donor trust.

Consent for governance aims to do right by donors beyond the initial consent, but some argue that is insufficient. Lewis and Holm (2022) suggest that the focus should be on autonomy rather than consent. Autonomy, they argue, ensures that participation is a reflection of one's true values, and not a binary decision based on what others think is in their best interests. For example, Boers and Bredenoord (2018) do not address which researchers or doctors may use the sample as a part of consent for governance. Yet, this is important for many participants,

especially among minority groups (Kraft et al., 2018). Lewis and Holm say that prospective participants should receive value-specific information before agreeing to donate. This would ensure that a donor has their concerns addressed and additionally are not coerced into participating due to information overload.

Regardless of the model, implementing new informed consent regulation will face resistance, representing the later stage of the Collingridge Dilemma (Collingridge, 1980). Organoids are regulated under the Common Rule with all biospecimens, many of which (e.g., cell lines) have been well-established for decades. Therefore, changes to protocol, such as the NPRM, are met with great opposition (Lynch et al., 2019). Genus and Stirling (2018) discuss the factors of the Collingridge Dilemma that limit responsiveness to change, and strategies for improving responsiveness. Two strategies that are applicable to organoid informed consent include addressing dogmatism and making incremental decisions.

Countering dogmatic ideas, that is ideas that are presented as indisputably true, will help to recognize the value of informed consent regulation and mitigate concerns around heightened regulation. First, many opposed to changes see them as providing little benefit, with one researcher stating, "[t]he subjects who participate in our trials are not asking for this excessive regulation … given that the specimens are already de-identified and that we are all already held to high ethical standards…" (*COGR, 2016,* Researchers and Practitioners p. 3) Yet, there are people asking for more, who may feel excluded from research activities, and their concerns do not end with privacy and deidentification (*COGR, 2016*; Kraft et al., 2018). Another dogmatic idea is that more regulation means fewer participants. Thorough initial consent does present more opportunities for a participant to say no (Lynch et al., 2019). That said, thoroughly informing a participant of future possibilities also instills trust, potentially reassuring the donor

that future ethical dilemmas will be handled responsibly. For ongoing consent models, another worry is unresponsiveness. However, using a value-based model such as that proposed by Lewis and Holm (2022), those who do not want to continually respond can define that. Meanwhile, those who otherwise would have felt excluded can participate and ensure that their values are respected.

Another way to address the concerns about reduced research ability is to adopt incremental changes. The changes proposed by the NPRM applied to nearly all samples and research settings, and required infrastructural changes for handling broad consent with an estimated cost of $1.2 billion annually. These costs would disproportionately affect smaller research settings or clinics (*COGR, 2016*). Yet, these smaller settings have the most trust among diverse groups of patients (Kraft et al., 2018). It would be better if more comprehensive consent procedures are first enforced (or voluntarily enacted) with larger entities such as commercial biobanks. These settings likely have stronger infrastructural resources and are greater sources of concern among donors. This has several benefits: it introduces change towards greater respect for human subjects, offers an opportunity to learn how implementing new consent models affects research participation and timeliness, and displays intent to address public sentiments. Another fear about the NPRM was the loss of existing deidentified biospecimens. Ideally, all specimens would garner the same protections, but critics are correct that having to either track down the original donors or remove the biospecimen would be infeasible and damaging to studies that save lives. Thus, we could gear regulation towards future donations. Even then, it will take time and resources to adapt to new systems. It may then be beneficial to prioritize sensitive donations, for example those with commercial implications, from disadvantaged backgrounds, or with potential for complex and ethically ambiguous uses. Ultimately, all donors and biospecimens should be

given the same improved protections, but making incremental changes is the most feasible way to work towards this and demonstrate an interest in public concerns.

It is difficult to request more of research institutions which are currently under attack, making the already significant administrative burdens of increased regulation seem insurmountable. Yet, these changes, which may seem like trivial barriers, could serve as a bridge to garner support for the scientific community. Shown in the frustrations of one supporter of the NPRM, the current regulations make human subjects protections seem like an "inconvenience [to] researchers who would rather not be bothered," (*COGR, 2016,* General Public p. 3), reflecting an at-times combative relationship. Researchers study disease to help people, but must recognize their concerns as legitimate, whether or not they are shared. Based on the strategies for responsiveness, increased protection for human subjects may not be as detrimental to research as commonly thought. Beginning to make gradual changes will exhibit attention to the public, and transparent communication of these changes and intentions will instill greater trust and support for the research community. With stronger public backing, it may then be possible to propel research even further, while giving human subjects the protection they are owed.

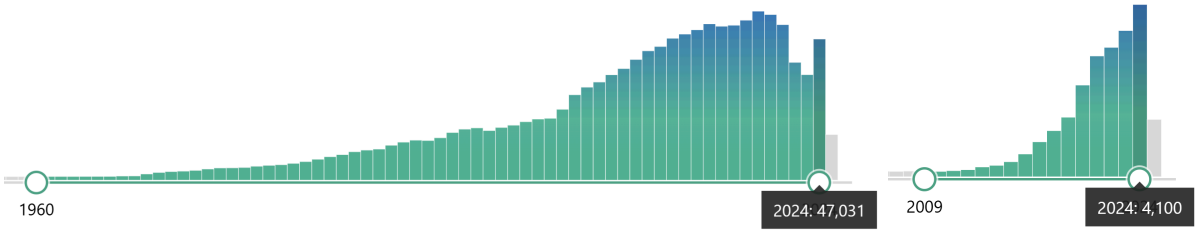
Conclusion

Current regulations for informed consent in the use of biospecimens are not sufficient for respecting persons. For organoids specifically, there should be more active engagement than initial consent. Failing to respect persons through sufficient informed consent is intrinsically wrong as donors seek to advance science with the expectation that they can trust researchers. While certain groups are enthusiastic and trusting already, diverse perspectives lead to different values, levels of trust, and possible concerns that should be respected. Failing to do so will ultimately decrease public engagement with research. For organoids, a common concern is about

increasing complexity and the unknown possibilities of future uses. Therefore, if regulation for secondary use of specimens is not enhanced, donations may be used for projects that go against donor values. When it comes to implementing enhanced regulation, the administrative concerns posed are valid but not unconquerable. To accomplish this, we must change the perception of consent from being a burden to something that can foster a strong relationship between researchers and the public, and find incremental steps that build this relationship. Perspectives on organoid use are limited, so we should continue to use technological mediation to understand concerns about organoids from more diverse perspectives. Finally, implementing further protections for human subjects will likely be a gradual process. It is important that as more comprehensive informed consent procedures are implemented, we continue to learn from participants and observe what changes make them feel most protected.

Appendix

Figure 1



PubMed (2025) by-year search results for “cell line(s)” (left) and “organoid(s)” (right).

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