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Rescuing human fetal tissue research in the United States: A call for additional regulatory reform

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SUMMARY

Research using human fetal tissue has saved millions of lives through vaccines and other advances, but was markedly restricted by federal regulations in 2019. Although the restrictions were partially reversed in 2021, additional regulatory changes are needed to prevent further damage to essential research programs while preserving protection for human subjects.

Human fetal tissue (HFT) has played a pivotal role in many areas of biomedical research. Vaccines developed using HFT have saved millions of lives worldwide. HFT is also an essential tool for investigating human-specific aspects of disease, including HIV and other infections, immune dysfunction, diabetes, transplantation biology, and cancer. Furthermore, HFT is required for studying developmental and disease processes that are not fully recapitulated in animal, cell-based, or organoid model systems (McCune and Weissman 2019).

Research using HFT (hereafter HFT research) has also been a focus of social and ethical debate, as the tissues are generally donated by women who have chosen to end a pregnancy. Anti-abortion advocates and politicians have repeatedly targeted HFT research, as demonstrated most recently by the Trump administration's efforts in 2019 to effectively halt federally funded HFT research in the US by restricting extramural and intramural NIH funding. In April of this year, the Biden administration reversed some, but not all, of the Trump-era regulations. We gathered input from HFT investigators on the impacts of Trump-era regulations and argue that the changes made so far by the Biden administration have not gone far enough to establish effective policies that support the ethical use of HFT in research and repair the damage sustained to US-based HFT research.

Ethical precedent for HFT donation

Current practices for HFT donation in the US were first delineated in 1975 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The topic received renewed debate during the Reagan administration, when the 1988 Fetal Tissue Transplantation Panel was convened to evaluate the possibility that HFT donation could influence a woman's decision to end a pregnancy. Finding no evidence that this occurs, the panel concluded that HFT research is ethical and should be allowed to proceed (Childress 1991). Nevertheless, to protect against the possibility of influence, the panel issued recommendations (made into law in 1993) requiring that consent for termination be obtained before introducing the option of tissue donation. Subsequent research has indicated that the method of HFT disposition after termination has little influence on reproductive decisions (Myers et al., 2015). Instead, the most commonly reported reasons for ending a pregnancy include concerns about financial and emotional ability to care for a child, lack of a supportive partner, and the need to focus on existing children (Biggs et al., 2013).

Regulation of publicly funded HFT research under the Trump administration

The last 2.5 years have seen considerable changes to the regulatory landscape for HFT research in the US. In June and July 2019, the Department of Health and Human Services (HHS)—citing the Trump administration's priority of "promoting the dignity of human life from conception to natural death")—announced new regulations prohibiting NIH training grants and fellowships from proposing the use of HFT, and precluding intramural NIH scientists from conducting research that entails new

tissue acquisition (HHS, 2019; National Institutes of Health, 2019). Extramural investigators were also required to use limited space in the research strategy section of their grant proposals to provide detailed scientific justification for HFT use and detailed descriptions of processes for HFT collection and disposal.

Finally, and most significantly, grants proposing the use of HFT that were favorably reviewed for scientific merit by the NIH study section and approved for funding by the NIH Council were required to undergo additional review by an Ethics Advisory Board, appointed by the HHS Secretary. The Advisory Board was tasked with assessing the scientific justification for HFT use, ensuring compliance with the regulations, and reviewing the consent process—including reviewing IRB-approved consent documents used for tissue donation, even if the application did not propose new tissue collection.

On July 31, 2020, the Board convened for the first time. The 15 member Board, which was only disclosed that morning, included 10 members who had publicly expressed opposition to abortion and/or HFT research (Goldstein 2020). In its final report released 3 weeks later, the Board recommended that the HHS Secretary withhold funding from all but 1 of the 14 applications reviewed. Denials were based on the Board's judgments of insufficient scientific justification for HFT use versus potential alternatives, and inadequate detail in the IRB-approved consent forms used for donation (National Institutes of Health, 2020). In fact, one Board member called into question whether consent for tissue donation "could ever be valid given the vulnerability inherently present within the context." This statement directly contradicts the findings of the 1988 panel review, and invokes ideas of vulnerability and over-protection during pregnancy that have negatively impacted women's health (Ballantyne, 2019). The only proposal the Board recommended for funding did not propose new acquisition of HFT (although at least two other proposals using preexisting tissue were rejected). Importantly, the decisions made by the Board were not unanimous, and the report included a dissenting opinion from two members: "This board was clearly constituted … so as to include a large majority of members who are on the public record as being opposed to human fetal tissue research of any type. This was clearly an attempt to block funding of as many contracts and grants as possible" (National Institutes of Health, 2020).

On April 16, 2021, 3 weeks after Xavier Becerra was sworn in as the new HHS Secretary, the NIH announced a reversal of the requirement for Ethics Advisory Board review (NIH, 2021). On April 26, 2021 the office of intramural research website was updated to reflect that intramural investigators may now acquire, use, and store HFT for intramural research. However, contrary to some reports in the popular press (Mandavilli 2021) all other aspects of the 2019 regulations remain in place, including the additional justification text requirement and the stipulation that training grants may not propose use of HFT.

Gathering HFT investigator input

It will take years and extensive research to measure the effects of the 2019 HFT regulations on US biomedical research productivity based on publications, grant funding, and scientific advances. In an attempt to better understand the precarious situation for HFT research and guide future policy, we developed a set of questions to elicit a qualitative snapshot of attitudes from a sample of investigators using HFT (HFT investigators). Our intent was to gather timely and exploratory data on the subjective experience of investigators working with HFT in the year following the 2019 NIH regulations.

Invitations to participate were distributed by email to three groups:

1. Recent recipients (past 5 years) of HFT through the Birth Defects Research Laboratory (BDRL) at the University of Washington (n = 57).
2. All past recipients (~15 years) of HFT through the MRC-Wellcome Trust Human Development Biology Resource in the UK (n = 321).
3. An email listserve of directors of Stem Cell Institutes in the US (n = 45). Directors were asked to forward the invitation to investigators in their institutes working with HFT. Stem Cell Directors were not specifically asked to fill out the questions themselves, unless they worked with HFT.

Between 20 July and 24 August 2020, we received 41 responses from US investigators. Given our focus on US research policy, only data from investigators working in US-based laboratories are included in this article. The respondents work in 11 states, with the majority located in California and Washington (Table 1). Most investigators responded immediately after the initial invitations and after reminder emails sent midway through the response period. Twenty-one responses were received before the NIH Ethics Advisory Board meeting on 31 July, 2020, 18 responses were received (following reminders) between the date of the EAB meeting and release of the report on 18 August, 2020, and 2 responses were received on/after the date of the EAB report.

We used a combination of Likert-style and yes/no response items to query investigator attitudes, including optional free text fields to allow for open-ended comments. We also asked respondents to select the component of NIH regulations that had most impacted their research (Figure 1). All questions were intended to be exploratory, rather than providing a definitive measurement of research regulation impacts. Binary yes/no response

Table 1. Sample characteristics

	Sample of US HFT investigators	
Total N	41	
Gender		
Female	39%	
Male	59%	
Prefer not to answer	2%	
Age (years)		
25 to 34	5%	
35 to 44	27%	
45 to 54	32%	
55 to 64	17%	
65 to 74	12%	
75+	2%	
Respondent role		
Principal investigator	88%	
Research scientist	5%	
Trainee	7%	
Respondent state	California	32%
	Washington	26%
	Alabama, Connecticut, Indiana, Massachusetts, Michigan, Missouri, New York, Oregon, Pennsylvania	42%

Totals may not equal 100% due to missing responses on some items.

frequencies (Table S1) and open-ended responses (Table S2) are provided in the supplement. We conducted thematic analysis of open-ended responses to distill three major themes that informed our recommendations.

Preliminary evidence of impacts on HFT investigators in the US

First, the investigators we queried appeared to understand the need to balance the ethical sensitivity of HFT research with the substantial benefits to biomedical research and human health. Investigators emphasized the importance of voluntary informed consent by donors, and validated the utility of centralized tissue banks which strictly adhere to ethical consent procedures and thus serve as trusted sources of HFT. Investigators reported that HFT is essential for their research in a variety of areas including mechanisms of human brain development, gene expression during typical and atypical development, infectious disease pathogenesis, vaccine research, recovery from central nervous system trauma, and validation of stem cell and organoid models. Multiple investigators described the lack of suitable HFT alternatives (e.g., "I'd prefer if iPSCs worked well—but currently they don't"), citing uniquely human aspects of disease and development that cannot be modeled in rodents or non-human primates, as well as the need to validate organoid and other stem cell-based models against HFT (e.g., "We can't model what we don't know").

Second, our results suggested that, in a single year, the NIH regulations had already substantially impacted investigators' research activities and future directions. Respondents reported feeling discouraged by the poor prospects for current HFT research funding and uncertainty about future funding. One investigator reported halting their HFT research "because of funding and legal uncertainties as regulations evolve on a shorter time horizon than projects can be completed." Investigators also noted that regulations interfered with their ability to forge and maintain collaborations out of fear that inclusion of HFT in a joint proposal would "kill funding possibilities for the entire grant." While the EAB was cited as the most impactful component of the new regulations (e.g., "The extra layers of review amount to a de facto ban"), investigators also described difficulties with fitting newly required justification text within the existing page limits: "Applying for federal grants requires research plan space to be used to defend the source/use of HFT even though all regulatory requirements have been met and documented."

Finally, specific impacts on trainees emerged as a clear barrier for future progress. Investigators reported that their trainees were "anxious" and "worried" about working with HFT, and cited direct impacts from the ban on the use of NIH training funds for HFT research—e.g., sudden stoppage of work in progress and associated career disruption. As noted by one investigator, "[trainees] cannot complete the projects they were midcourse in accomplishing." Impacts on overall lab funding were also cited for their effects on hiring and retaining trainees. Investigators described difficulties hiring trainees due to sudden changes in lab funding,

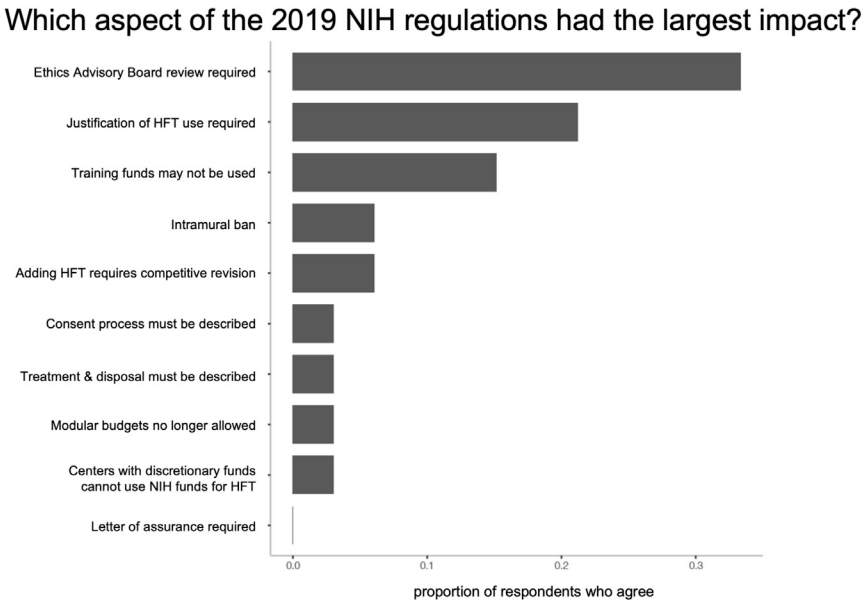

Figure 1. Component of NIH regulations with largest self-reported impact on research

HFT investigators selected the component of the 2019 regulations that had most impacted their research. While the Ethics Advisory Board no longer presents a barrier, the second and third most endorsed barriers (justification of HFT use required in research plan, training funds unable to be used) remain in place.

and the impact of additional review time imposed by the once-per-year EAB meetings: "Given the career trajectory of many of my trainees, it is a complete ban."

These exploratory data have clear limitations. The investigators we queried do not necessarily represent the full community of US-based scientists who use HFT based on the sampling requirements for this difficult-to-access population. It is certainly possible that investigators with specific attitudes about the regulations might have been more or less likely to respond to our invitation, introducing a self-selection bias that could have skewed our findings. Data were collected anonymously to protect the respondents given the risk of harassment and physical harm from anti-abortion advocates; therefore, we are not able to link responses directly to the ascertainment strategies to calculate response rates. Finally, these data were collected during the summer of 2020, when the 2019 regulations were still in place. A survey conducted now could reveal different attitudes given the partial reversal of the 2019 regulations this year.

Recommendations for additional regulatory reform

The Biden administration now has an opportunity to reevaluate the regulatory landscape for HFT research in the US. We base the recommendations below on the previously established ethical and regulatory frameworks, feedback collected from HFT investigators described above, and prior letters to the Trump administration from expert consortium groups including the ISSCR (ISSCR 2019).

(1) Free up space in research strategy section of NIH grant applications: responsible stewardship of HFT is essential, and it is appropriate to include justification for the amount of HFT used and plans for disposal in grant proposals; however, requiring these elements within the page limits of the research strategy is unnecessary and takes space away from substantive content needed for justifying the scientific merit of proposals. HFT regulatory elements could easily be included in a supplemental section, similar to those required for human subjects, vertebrate animals, and human embryonic stem cell research that do not contribute to the research strategy page limits.

(2) Remove trainee restrictions: trainees on NIH-funded training grants should not be restricted from participating in HFT research. This restriction not only harms the career trajectories of current trainees (as indicated by our survey respondents), but also threatens the long-term future of HFT research by creating a pipeline problem in which future investigators lack the training to work appropriately with HFT. Furthermore, restricting training undermines the stated HHS goal of finding alternatives to HFT, which need to be validated using HFT to determine how accurately they recapitulate human development, function, and disease. Without HFT research skills, the next generation of scientists will be unable to validate new models such as organoids, risking inaccurate results, and wasting valuable resources.

(3) Establish standard informed consent language for HFT donation to ward off future challenges: HFT research remains vulnerable to restrictive regulation by future administrations with anti-abortion agendas. Biomedical innovation requires a stable regulatory foundation shaped by long-term evidence of risks and benefits, rather than short-term swings of the political pendulum. Now is the time to establish standards for the ethical conduct of HFT research that can ensure balanced regulations based on sound scientific and ethical reasoning. We see opportunities for bioethicists, scientists, and policy makers to work together to: (1) gain a better understanding of the decisional context in which women elect or decline to

donate HFT by engaging the perspectives of those seeking pregnancy termination and their providers, (2) identify the key factors required for appropriate consent in this context, and (3) establish standard informed consent language that ensures ethical tissue collection and protects research participants. Together, these steps should defend against future attempts to challenge the validity of informed consent for HFT donation as a politically motivated means of denying NIH funding for otherwise meritorious HFT research.

HFT research has been saving lives and promoting human health for decades; the path to federal funding must be fully restored so we can confront the spectrum of current and future health challenges with every tool in our biomedical research toolset.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2021.10.016.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, formal analysis, visualization, writing – original draft preparation, K.E.M.; conceptualization, methodology, writing – reviewing & editing, I.H.; data curation, writing – reviewing & editing, M.M.K.; methodology, writing – reviewing & editing, J.C.D.; writing – reviewing & editing, resources, C.E.M.; methodology, writing – reviewing & editing, resources, A.J.C.; conceptualization, methodology, writing – reviewing & editing, resources, I.A.G.; conceptualization, methodology, writing – reviewing & editing, resources, supervision, D.D.

CONFLICT OF INTERESTS

C.E.M. is an employee and equity holder in Sana Biotechnology. The other authors declare no competing interests.

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