Overview

The National Human Genome Research Institute (NHGRI) Ethical, Legal and Social Implications (ELSI) Research Program frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let excerpts of their ELSI grant applications be posted online.

Acknowledgement

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application), where applicable. We do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., budgets, biographical sketches, letters of recommendation or letters of support). NIH grant formats or rules may have changed since these applications were prepared; therefore, applicants should always follow the application format instructions included in the funding announcement.

Copyright Information

The text of the grant applications is copyrighted. Text from these applications can only be used for nonprofit, educational purposes. When using text from these applications for nonprofit, educational purposes, the text cannot be changed and the respective Principal Investigator, institution, and NHGRI must be appropriately cited and credited.

PI: **Cwik, Bryan**	Title: Intergenerational Monitoring in Clinical Trials of Germline Gene Editing: Ethical, Legal, and Social Issues	
Received: 02/15/2018	FOA: PA17-445 Clinical Trial:Not Allowed	Council: 08/2018
Competition ID: FORMS-E	FOA Title: Ethical, Legal, and Social Implications (ELSI) of Genomics Small Research Grant Program (R03)	
1 R03 HG010417-01	Dual:	Accession Number: 4140720
IPF: 6297008	Organization: PORTLAND STATE UNIVERSITY	
Former Number:	Department: Philosophy & University Studie	
IRG/SRG: ZRG1 SEIR-B (80)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 50,000 Year 2: 50,000	Animals: N Humans: N Clinical Trial: N Current HS Code: Evaluative Info HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Bryan Cwik	PORTLAND STATE UNIVERSITY	PD/PI

OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*
❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

2. DATE SUBMITTED 2018-02-16

Application Identifier

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:** 0522268000000

Legal Name*: PORTLAND STATE UNIVERSITY
Department:
Division:
Street1*: BOX 751
Street2:
City*: PORTLAND
County:
State*: OR: Oregon
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 972070751

Person to be contacted on matters involving this application
Prefix: First Name*: Jennifer Middle Name: Last Name*: Ward Suffix:
Position/Title:
Street1*: BOX 751
Street2:
City*: Portland
County:
State*: OR: Oregon
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 972070751
Phone Number*: 503-725-9900 Fax Number: Email: awards@pdx.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 36-4776757

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Intergenerational Monitoring in Clinical Trials of Germline Gene Editing: Ethical, Legal, and Social Issues

12. PROPOSED PROJECT
Start Date* 09/01/2018
Ending Date* 08/31/2020

13. CONGRESSIONAL DISTRICTS OF APPLICANT
OR-003

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Bryan Middle Name: Last Name*: Cwik Suffix:
Position/Title: Assistant Professor
Organization Name*: PORTLAND STATE UNIVERSITY
Department: Philosophy & University Studie
Division:
Street1*: PO Box 751
Street2:
City*: Portland
County:
State*: OR: Oregon
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 97207-0751
Phone Number*: 503-725-3565 Fax Number: Email*: bcwik@pdx.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$148,500.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$148,500.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Corey Middle Name: Last Name*: Smitke Suffix:
Position/Title*: Grants & Agreements Analyst
Organization Name*: Portland State University
Department:
Division:
Street1*: PO Box 751 (SPA)
Street2:
City*: Portland
County:
State*: OR: Oregon
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 97207-0751
Phone Number*: 503-725-2242 Fax Number: Email*: spablack@pdx.edu

Signature of Authorized Representative*
Corey Smitke

Date Signed*
02/15/2018

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	PORTLAND STATE UNIVERSITY
Duns Number:	0522268000000
Street1*:	BOX 751
Street2:	
City*:	PORTLAND
County:	
State*:	OR: Oregon
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	972070751
Project/Performance Site Congressional District*:	OR-003

Additional Location(s) File Name:

Funding Opportunity Number: PA-17-445. Received Date: 2018-02-15T15:45:32.000-05:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ○ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ○ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ○ **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary_Final_Corrected.pdf
8. Project Narrative*	Project_Narrative_FInal.pdf
9. Bibliography & References Cited	References_Final.pdf
10.Facilities & Other Resources	Cwik_Facilities_BC_edits_2.14.pdf
11.Equipment	Cwik_Equipment.pdf

Funding Opportunity Number: PA-17-445. Received Date: 2018-02-15T15:45:32.000-05:00

Project Summary

The breakneck pace of development towards potential uses of germline gene editing (GGE) in medicine raises some very crucial ethical questions. Though much research still needs to be done before GGE will be safe for use on humans, the technology has progressed very rapidly over the past few years. Among the most pressing of the ethical issues raised by GGE are those concerning human subjects research. Future clinical trials will confront novel ethical conundrums that are difficult to resolve given current guidelines. The most difficult of these conundrums are those concerning *intergenerational monitoring* – long-term follow-up study not just of the original subjects, but also of their children and grandchildren. Numerous scientists, advisory panels, and professional associations have stated that such study will be necessary. There is currently little precedent in research ethics for the kind of intergenerational monitoring required here, and no precedent for the specific challenges posed by GGE. If future clinical trials are going to meet requirements of ethical research, the difficult issues raised by intergenerational monitoring must be resolved.

This project will make an initial start on designing intergenerational monitoring protocols for future clinical trials of GGE. Drawing on prior work in clinical research ethics and the broader literature on the ethical, social, legal, and philosophical dimensions of GGE, the project will examine this unique set of ethical issues and apply these insights to the design of future clinical trials. The ultimate aim of the project will be to help advance research into the uses of GGE in medicine by dealing with a set of crucial barriers to future applications. In so doing, this project will contribute to the role of NHGRI and the ELSI program in providing leadership and guidance on the ethics of GGE in medicine, and on the potential use of this technology for the treatment of disease and improvement of human life.

Project Narrative

This project will examine ethical issues raised by the need for intergenerational monitoring in future clinical trials of germline gene editing in humans. This is a crucial barrier to applications of this technology in medicine, and so the project aims will aid in the possible adoption of gene editing for the treatment of disease and improvement of human health. The project will also contribute to the broader conversation on the ethics of gene editing in humans.

FACILITIES AND OTHER RESOURCES

Laboratory: None

Animal: None

Clinical: None

Computer:
The PI is equipped with an office computer with sufficient power and storage to meet the needs of this project, and has access to software through their university sufficient for the project

Office:
The PI has a ~150 sq. ft. office with a MacBook Pro computer and all software required to do the analysis.

Data Storage:
The PI's has access to a cloud-based drive through their University, as well as ample space to store data on their office computer. There are no data security requirements for this project; this data storage capacity is sufficient for the project.

Equipment

None

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

Personnel Justification

Bryan Cwik, PhD, Principal Investigator. Dr. Cwik will serve as Principal Investigator on this project. He will devote EFFORT each academic year and EFFORT months in year 1 and EFFORT months in year two to leading this project. During this time Dr. Cwik will conduct original research into the ethics of intergenerational monitoring as it relates to germline gene editing, and will write academic articles on the results of this research.

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	Specific_Aims_Final_-_replace.pdf
3. Research Strategy*	Research_Strategy_Final_Re-corrected_2.14.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	Cwik_Letters_of_Support.pdf
10. Resource Sharing Plan(s)	Resource_Sharing_Plan.pdf
11. Authentication of Key Biological and/or Chemical Resources	
Appendix	
12. Appendix	

Funding Opportunity Number: PA-17-445. Received Date: 2018-02-15T15:45:32.000-05:00

Specific Aims

The breakneck pace of development towards potential clinical application of germline gene editing (GGE) has made ethical issues about clinical trials, use, and future regulation of the technology extremely urgent. Though there is still much research needed to determine if GGE can be done safely and with acceptable risks, the technology has progressed very rapidly since the first experiments with GGE on human embryos in 2015. Among the most pressing issues are those concerning human subjects research. Future clinical trials will confront novel ethical conundrums that are difficult to resolve given current guidelines. At the top of this list are issues about *intergenerational monitoring* – long-term follow-up study not just of the original subjects, but also of their children and grandchildren. Numerous scientists, advisory panels, and professional associations have stated that such study will be necessary. Though long-term follow-up of individuals and families in other areas is not uncommon, there is currently little precedent in research ethics for the kind of intergenerational monitoring required here, and no precedent for the specific challenges posed by GGE. If future clinical trials are going to meet requirements of ethical research, protocols for intergenerational monitoring of subjects will need to be in place, and the ethical issues will have to be resolved.

This project will make an initial start on designing intergenerational monitoring protocols for future clinical trials of GGE. Drawing on prior work on gene editing and the broader literature on the ethical, social, legal, and philosophical dimensions of GGE and human subjects research, the project will examine this unique set of ethical issues and apply these insights to the design of future clinical trials. The ultimate aim of the project will be to inform the development of elements of a protocol for ethical intergenerational monitoring, which can be incorporated into future study design and policy frameworks. This project will tackle a crucial requirement for future clinical trials and clinical application of GGE. It will also help shed light on ethical issues in adjacent areas of research, such as ethical issues in somatic gene editing. In so doing, the project will contribute to the role of NHGRI and the ELSI program in providing leadership on the application of gene editing technology to different areas of medicine, and on the potential use of this technology for the treatment of disease and improvement of human life, as outlined in the recent NIH Notice of Interest (NOT-LM-17-001).

Specifically, the project will:

1. Identify ethical issues involving intergenerational monitoring for GGE. This analysis will draw on the existing literature on GGE (and gene editing in general) and the bioethics literature on human subjects research, and build off the work of advisory panels such as the National Academies of Science, Engineering, and Medicine (NASEM) and the Nuffeld Council, as well as the numerous policy statements and platforms issued by professional societies such as the American Society of Gene and Cell Therapy (ASGCT).
2. Examine ethical issues in light of existing research ethics protocols. Protocols for long-term follow-up of individuals and families exist for certain kinds of research (for instance, in the social sciences and public health) and for related bioethical issues (such as biobanking, access to/use of genetic information, and disclosure of incidental findings). The investigator will consider the special challenges of intergenerational monitoring for GGE in light of existing protocols, and apply insights from related areas. Further, this ensures other bioethicists can replicate the findings of the project, by examining the results of the project in light of accepted practice in human subjects research.
3. Develop a framework for intergenerational monitoring in future clinical trials. The investigator will consider what would be required to conduct intergenerational monitoring ethically in future clinical trials, and will identify rules, norms, guidelines, and design features for intergenerational monitoring that can ensure such research meets requirements of ethical human subjects research.
4. Apply the framework to design of protocols for intergenerational monitoring. The investigator will apply findings from Specific Aims 2 and 3 to the issues identified and examined in Specific Aim 1 and consider possible elements of a protocol for future clinical trials of GGE. The investigator will model work towards this specific aim on similar work done in other parts of bioethics, such as the extensive work done on protocols for release of incidental findings.
5. Disseminate results of the project to researchers, policymakers and bioethicists. The investigator will publish results in professional journals and present them at professional meetings. Because of the practical goals of Specific Aim 5, dissemination will focus not only on other academic bioethicists but also on medical researchers and health policy analysts.

Research Strategy

Significance

Potential clinical applications of germline gene editing (GGE) offer enormous therapeutic potential, especially to individuals and families dealing with inherited genetic disorders. For individuals with family histories of diseases such as Huntington's, Tay Sachs, sickle cell anemia, or hypertrophic cardiomyopathy, GGE holds the possibility not just of treating and preventing disease in individual offspring, but removing them from family lines permanently (Lander 2015). As such it is an improvement over the use of pre-implantation genetic screening or potential treatment with somatic gene editing (better known as gene therapy), both of which will treat or prevent disease only in a single individual. As the technology progresses, it may become possible to use GGE on more complicated inherited disorders. However, the possibility of making permanent, heritable genetic changes to individuals raises a rather large set of serious ethical issues. Because of the current lack of clarity on these issues, different groups of scientists, ethicists, policy analysts, and other experts in genetics and medicine have called for a moratorium on use of GGE in human beings pending further research on potential risks and a better understanding of the ethical situation (Wade 2015). As one of these groups put it, there is "an urgent need for open discussion of the merits and risks of human genome modification" (Baltimore et al 2015).

This urgency is underscored by the rapid (and seemingly accelerating) pace of development of gene editing technology. Systems that use engineered nucleases such as zinc finger nucleases (ZFNs), transcriptor activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR) allow for fast, efficient, and accurate gene editing in complex organisms (Mei et al 2016). Because of its efficiency, CRISPR has received the lion's share of both public attention and use by researchers. Results of the first experiment on human embryos with CRISPR were published in 2015 by a team of researchers in China who used the technique on the *HBB* gene, a gene that is mutated in individuals with the inherited blood disorder beta thalassemia (Liang et al 2015). Though the use of the technique was effective in cleaving the *HBB* gene, most of the edited embryos were genetic mosaics and there were a large number of off-target effects (unintended changes in the genome). The experiment was an important 'proof of concept'; it showed that CRISPR could be used to make directed edits in human embryos, but also showed that there was still a long way to go before the technique was safe enough for potential clinical use. In August of 2017, results of another experiment using CRISPR on human embryos were published, this one to correct a mutation in the *MYBPC3* gene that leads to hypertrophic cardiomyopathy, a serious cardiovascular disease. Using a different technique from the Chinese team, rates of off-target effects were drastically reduced, and most of the resulting embryos were free of the mutation (Ma et al 2017). This dramatic improvement in two short years shows how quickly research on the use of GGE in humans is progressing, and how pressing the need for ethical deliberation on its potential uses really is (Cwik 2017).

There is a large literature in biomedical ethics on GGE, most of which addresses issues such as the possible use of GGE to enhance human physical or cognitive characteristics (Buchanan 2013; Savulescu and Bostrom eds. 2011). To the extent that the topic has been treated seriously by biomedical ethicists, the discussion has focused mostly on questions about whether GGE should or should not be done at all, and on questions about uses to enhance human characteristics that are, at best, a lot of research away from becoming technologically feasible. Though discussion of these issues is interesting and important, there is a whole set of more 'ground floor' ethical issues, such as questions about use of embryos in GGE research, design of future clinical trials, and rules for initial clinical use in reproductive medicine, that are becoming more and more pressing as research and development of the technology progresses. Should we decide, through democratic processes (as several panels and advisory bodies have recommended), to permit GGE in humans, these issues will need to be addressed and resolved, in order for research, clinical trials, and eventual clinical use to meet ethical standards. Furthermore, lack of clarity on these issues could serve as a barrier to the use in medicine of GGE, slowing down the spread of benefits from the research (Pinker 2015). In a potential worst case scenario, intense pressure to conduct clinical trials and start introducing GGE into medicine could prompt its use in humans to go forward even if there is no clarity on ethical issues about, for instance, clinical trial design, resulting in future incidents of research misconduct.

One of the most pressing and difficult problems in this set of 'ground floor' ethical issues about GGE in humans concerns *intergenerational monitoring* of research subjects. Changes to the genome at the germline, unlike in

somatic gene editing, are heritable. Any changes made in the process of GGE will not only result in genetic changes in a single individual but thus in all of their descendants. GGE thus introduces risks not just to specific individuals whose parents have chosen to create a pregnancy with an edited embryo, but also to their future descendants, and have the potential to spread throughout a population. The nature of the risk depends on the techniques used. In applications of GGE that involve the removal of a single mutated gene and replacement with a 'wild type' of the gene (meaning, a version of the gene already present and widespread in the population), as in the study on *MYCB3* (Ma et al 2017), the risks are likely to be lower than other forms of gene editing, since the procedure results in the replacement of a faulty gene with a non-mutated version present in many other humans. With other techniques, such as those that depend on homologous recombination directed repair of a cleaved cite, the risks are – as the initial 2015 experiment showed – different and potentially higher (Liang et al 2015). Different techniques could carry their own sets of risks; risks will increase and be compounded with multiple edits (since in that case interaction between genes during development, and not just changes in the function of single genes, will be effected). The nature of the risks will also depend on what kinds of genes are edited, increasing as the complexity of the function of the targeted genes increases. There is also serious worry about whether unknown risks to individuals as the result of the editing process will only manifest later in life, as was the case with the uptick in risk for diseases such as Prader-Willi Syndrome because of the effects on DNA methylation in development for individuals who were conceived through in vitro fertilization (IVF) (Menezo et al 2017; Chiba et al 2013). There could also be subtle effects on gene expression that manifest later in life, after an individual has reached reproductive age and passed on the risks to children. For these reasons, many advisory panels and professional associations of scientists have called for long-term follow-up monitoring not just of the original subjects, but also of their children and grandchildren (National Academies of Science, Engineering, and Medicine 2017; Friedmann et al 2015).

There is little precedent for how such intergenerational monitoring could be done ethically. The closest analogues are in long-term follow-up of individuals to assess risks from assisted reproductive technologies (ARTs) (Lu et al 2013), though these are focused only on the original subjects, and in epidemiological studies such as the Framingham studies of cardiovascular disease (Splansky et al 2007). In the Framingham studies, however, researchers were studying risks that already existed in the population; in the case of multiple generations of a family from an edited subject, researchers will have induced these risks by editing the original subjects. This is a crucial difference, as it means that researchers could have responsibilities (such as responsibilities to communicate adverse findings or to provide medical care) that were not present in the Framingham study. Further, intergenerational monitoring in trials of GGE will involve genetic information and touch on areas such as reproductive health, which are not only extremely sensitive but also already subject to different regulation and ethical scrutiny.

Intergenerational monitoring will confront a number of challenges that are, in terms of existing practice and knowledge in clinical research ethics, extremely difficult to resolve. The most straightforward path to recruit subjects into monitoring will be for their parents to make the decision to enroll the initial subjects and then to rely on families to 'socialize' their children (and eventually grandchildren) into participation. This is the only ethical way to enroll subjects; as the National Academies of Science, Engineering, and Medicine (NASEM) report stated, individuals can be "encouraged" to participate, but not coerced (National Academies of Science, Engineering, and Medicine 2017). This has proved effective in the past (for instance, in the Framingham study), but it is possible that not every family will want to participate, and so that there will be descendants of subjects that are not, at some future time, being monitored. If researchers discover a serious health impact on edited subjects and their descendants, there is a real question about the proper way to contact them and disclose this information. Doing so comes with many complications; it may require revealing information that individuals do not know (such as information about their real parentage). Stigma about 'genetically modified humans' may develop, and informing individuals that they are descended from an edited subject may expose them to psychological and social harms. If the information impacts their reproductive decisions, this adds an additional layer of complication (Cwik 2017). Follow up study will involve research on children, which carries a large set of ethical baggage in and of itself.

Intergenerational monitoring also requires storage, access, and use of genetic information. As the UK's Nuffeld Council stated in a report on GGE, researchers may need to keep genetic information about subjects in a central database for several decades, and whole generations of researchers that are working on the project

will need to have access to it (Nuffeld Council 2016). Rules about privacy, proper use, privileges of access, and a suite of other issues will need to be worked out in advance. Most of these sorts of issues do not arise for other individuals; future generations, if they are descendants from edited subjects, will thus be subject to a different set of rules from the rest of us regarding their interactions with doctors and researchers because of their unique biology, which is problematic.

The intersection of all of these different strands of moral complication result in, to borrow a metaphor from the applied ethicist Stephen Gardiner, a 'perfect moral storm' (Gardiner 2011). The aim of this project is to address these issues by conducting research into the 'perfect moral storm' of intergenerational monitoring for GGE, publish results of this research, and make a start on building a literature to address this set of problems. Work on this issue is crucial and uniquely urgent within the broader discussion of the ethics of GGE for two reasons. First, as argued above, there is little precedent for how intergenerational monitoring could ethically be done. Other aspects of research into GGE (for instance, issues about embryo use and solicitation of gamete donations for research) have well-covered analogues in other parts of biomedical ethics, but intergenerational monitoring has received little attention. Second, until a protocol for intergenerational monitoring of subjects and their descendants is worked out, clinical trials of GGE in humans cannot be (ethically) done. The lack of work on this issue is thus a significant barrier to moving forward with what could be one of the most significant advances in clinical medicine of our time. Should we, through a broader societal conversation, decide that GGE should be permissible, it cannot be done on humans unless and until a protocol for intergenerational monitoring is in place. This project will thus contribute towards removal of a significant barrier to future clinical use of GGE.

The principal investigator (PI) will be assisted by a project advisory committee of scientists, biomedical ethicists, and philosophers of science with expertise on genomics, life sciences research, and the ethical, legal, and social aspects of GGE. The following individuals have agreed to regularly consult with, discuss ideas, and review research conducted by the PI as part of this project:

- **Dr. Arthur L. Caplan**, PhD, Drs. William F. and Virginia Connoly Mitty Professor of Biomedical Ethics, Department of Population Health, and founding head of the Division of Medical Ethics, NYU School of Medicine
- **Dr. Shoukhrat Mitalipov**, PhD, director of the Center for Embryonic, Cell, and Gene Therapy, Senior Scientist, Division of Reproductive and Developmental Sciences, Oregon National Primate Research Center, and Professor of Biomedical Engineering, Obstetrics, Gynecology, and Pediatrics, and Molecular and Medical Genetics, Oregon Health and Science University
- **Dr. Craig Callender**, PhD, Professor of Philosophy and co-director of the Institute for Practical Ethics, University of California, San Diego
- **Dr. Mark Bedau**, PhD, Professor of Philosophy and Humanities, Reed College, and Adjunct Professor of Systems Science, Portland State University
- **Dr. Lisa Weasel**, PhD, Associate Professor of Women, Gender, and Sexuality Studies, Portland State University
- **Dr. Jay Odenbaugh**, PhD, Associate Professor of Philosophy, Lewis and Clark College
- **Dr. Ashley Graham Kennedy**, PhD, Assistant Professor of Philosophy and Assistant Professor of Clinical Biomedical Science in the Medical College, Florida Atlantic University

Innovation

The project will produce new research into the topic of intergenerational monitoring of research subjects in clinical trials of GGE, which is currently underexplored in the biomedical ethics literature on GGE. As there is currently no protocol for design of future clinical trials of GGE, the research from this project will thus be the first to directly address a key ethical issue in the creation of such protocols. As such, it will take a novel step towards future clinical use of GGE in medicine, toward removing barriers to eventual clinical use, and will provide clarity on ethical issues relating to the introduction of this novel medical technology. The project will also bridge several existing literatures that currently are relatively isolated from each other: literatures on clinical research, assisted reproductive technologies and reproductive medicine, biobanking and use of genetic information, research on children, and GGE. The research produced will thus also be relevant to future issues at the intersection of these families of ethical concern. The project will also aim to stimulate a new area in the biomedical ethics research into GGE, about the ethical requirements of clinical trials of GGE.

Approach

This project will use the methodology of ethical analysis common in biomedical ethics (Beauchamp and Childress 2012) and in clinical research ethics (Emanuel et al eds. 2011). It will include an extensive review of multiple literatures, consultation with members of the advisory committee, review of existing regulations and protocols for design of clinical trials involving human subjects, and the production of new research on the key ethical questions. Preliminary findings will be discussed with the advisory committee.

The project will be divided into five phases:

1. Identify Ethical Issues Involving Intergenerational Monitoring for GGE

The PI will conduct an extensive review of the existing literature in biomedical ethics and clinical research ethics on GGE. This review will also include the work of advisory panels such as the recent NASEM report, statements and platforms of professional organizations of scientists and researchers in cognate areas, and the broader philosophical and social literature on GGE. Because there is so little precedent for intergenerational monitoring of the kind that would be necessary with GGE, the full moral geography here is underexplored. A crucial step forward would be to get a (relatively) complete map of the ethical terrain. Of special interest here would be those issues that are unique to GGE; a premise of the project is that GGE raises problems here not just because clinical trials may require intergenerational monitoring, but also because the nature of the monitoring required by GGE is itself problematic. In this the PI will consult with members of the advisory panel who have direct experience with scientific research and who have served on advisory panels.

2. Examine Ethical Issues in Light of Existing Research Ethics Protocols

Though there is, as argued above, little precedent for the sort of intergenerational monitoring required for GGE, long term follow-up study is an established part of the testing of new medical technologies (such as ARTs, or new medical devices), and many of the issues specific to intergenerational monitoring have (loose) analogues in other areas of research ethics. A good example is the discussion about and literature on the communication of incidental findings (such as research that reveals adverse health effects) in medical research and in research utilizing biobanks (Wolf et al 2012). Review of research into these issues, and existing active or proposed research ethics protocols, is thus a very helpful starting point for work on intergenerational monitoring for GGE. The second phase of the project will involve examining the ethical issues identified in phase 1 in light of existing work in research ethics. There are three research questions that the PI will explore in this phase:

- What aspects of a future protocol for intergenerational monitoring can be subsumed under existing ethical guidelines for other forms of human subjects research?
- What aspects go beyond current established practices, existing or proposed guidelines, and ethical opinion?
- Are there ethical issues involving intergenerational monitoring that challenge ethical commitments (for instance, about what constitutes an invasion of privacy with regard to someone's genetic information), and so may prove either intractable or require a rethinking, in light of the potential benefits of GGE, of the status quo?

The second and third questions are of particular interest and concern, and particularly important for biomedical ethicists. A public conversation about whether GGE should be permissible, as called for by numerous advisory panels, requires clarity about what aspects of human subjects research into GGE challenge our existing (and maybe even deeply held) beliefs about how research should be done. Clarity on these questions, and so clarity on just what the moral stakes are, is thus a prerequisite of such a discussion. As with the first phase of the project, phase 2 will also involve an extensive review of literature and existing codes and protocols in clinical research ethics, as well as consultation with members of the advisory committee. Dr. Shoukhrat Mitalipov, who actively conducts research into applications of GGE and was a key researcher and one of the directors of the recent experiment to edit mutated *MYC3B* genes, will be a particular help to the PI during this phase, and has agreed to consult with the PI and discuss ideas.

For phases 1 and 2, the PI will conduct a part of the work at the Institute for Practical Ethics at the University of California, San Diego, as a visiting fellow. The Institute is an interdisciplinary research center with close ties to several units at UC San Diego as well as medical researchers in the greater San Diego area. The co-director of the Institute, Dr. Craig Callender, is a member of the advisory committee for this proposal, and has extended an invitation to the PI to conduct research there as a visitor should the project be funded. This will allow the PI

access to an extensive set of resources and to a community of researchers working on GGE and emerging medical technologies from multiple angles, as well as facilitate consultation with a key member of the advisory committee.

3. Develop a Framework for Intergenerational Monitoring in Future Clinical Trials

With the results of phases 1 and 2, the project can move on to considering what would have to be done, and how it could be done, in order to conduct intergenerational monitoring of subjects and their descendants in future clinical trials of GGE. This will involve a combination of extending and transposing existing protocols and guidelines from current codes of research ethics, considering new guidelines, and considering what commitments would have to be interrogated if GGE on humans is permitted. Preliminary work on these issues has identified five areas that are likely to be of particular concern in this phase of the project:

- *Recruitment of subjects*. For the initial subjects, their parents will be able to choose to have them monitored up until the age of consent. After that time the individuals will have to agree to proceed. Past experience has shown that this is likely to be (relatively) successful (Lu et al 2013). Beyond the first generation the situation becomes much murkier. It may be important to the experiment to contact children of initial subjects who opted out at some point in the future and encourage them to participate; how subjects can be identified and contacted in such situations requires strict guidelines to preserve their privacy. What constitutes informed consent, and what an informed consent instrument would need to be here, are important in recruiting subjects. Finally, because the process will stretch over several decades, monitoring of future generations will need to be handed off from the initial team of scientists to future researchers who take their place. Protocol will need to be in place (here past experience, in studies such as the Framingham study, will be very useful). This will require passing on identifiable genetic information and extensive medical records; rules for handling this information will need to be worked out in advance.
- *Ancillary obligations of researchers*. Because future generations will be exposed to some possible harms through the decisions of the initial subjects' parent(s), and because monitoring will expose them to some hardships (in the form of minimally invasive medical procedures), it is likely that researchers will need to provide them with some form of ancillary benefit as compensation. A reasonable starting point is the provision of medical care, and counseling on important parts of their health related to the study (reproductive health and genetic counseling, for instance), to descendants of the initial subjects as part of monitoring. This could place extensive cost on researchers, however, so the nature of the obligations and risks at play need to be carefully considered. The line between inducements to participate in monitoring and what researchers may owe future generations regardless of whether they consent to be monitored must be fixed and guidelines for adhering to it must be in place. Special care will need to be taken here with subjects from vulnerable populations.
- *Communication of findings*. It is very possible that some health impacts on future generations will only manifest themselves or become known to researchers after the initial subjects have reached reproductive age. Researchers could be in a position here to be forced to communicate these findings to individuals who may not be monitored and may not know they are the descendants of an edited subject. Three further situations could complicate this: (a) contacting these individuals may reveal information about their parentage they do not know; it is quite possible that some subjects not only may not know that they had an edited parent or grandparent, but didn't know the edited individual was in fact their parent or grandparent; (b) contacting these individuals may reveal sensitive information about them and their genetics they did not know; in the case, for example, of clinical trials to remove genes for genetic disorders heavily associated in the popular mind (rightly or wrongly) with a particular race, ethnicity, or religion (such as Tay Sachs or sickle cell anemia) researchers will be divulging sensitive information that may have profound psychological and social effects on individuals; and (c) in a (not implausible) future scenario where a stigma has been attached to edited individuals (as was the case with the furor over "test tube babies" with the first children conceived through IVF), researchers may be divulging information that could carry significant psychological and social harms. Care will have to be taken at all stages, protocols and guidelines for handling these and other delicate situations will have to be in place, and given that the information communicated is likely to touch on sensitive and intimate parts of individuals' lives (such as decisions about reproduction), provision of care and counseling will likely need to be on the table.
- *Biobanking*. Intergenerational monitoring will require the maintenance of a database with identifiable genetic information on initial subjects and their descendants, accessible to researchers, for several decades (Nuffeld Council 2016). Beyond the obvious need for strict rules about access, use, and maintenance of privacy, this goes beyond, or at the very least stretches, existing laws and guidelines about

the storage and use of identifiable genetic information (such as those in the US Genetic Information Nondisclosure Act). These will have to be revisited in light of the requirements for intergenerational monitoring here. There is some existing experience with biobanks of genetic information of this scope: a private company, deCODE, has been assembling and maintaining a database of information on Icelanders for several years, and has used information stored in the database to conduct research (Árnason 2004). Using databases of genetic information to conduct research, such as genome-wide association studies (GWAS) is now common practice, and there is an existing literature on the ethics of this (Caulfield et al 2008). There are crucial differences between this research and the kind of biobanking in play with intergenerational monitoring in clinical trials of GGE. In the latter, researchers will need to know the identity of the individuals involved (at least in some cases), and the stored information will need to be identifiable.

- *Exploitation*. Many of the above-discussed complications for intergenerational monitoring result because subjects and their descendants will have to be treated differently from other individuals. For instance, should a doctor find out some genetic information about an individual that impacts their health by examining someone's biological father, there is no question about whether it is in their discretion to contact them. This may not be the case with the descendant of an edited subject. At a fundamental level, subjects and their descendants of the first clinical trials of GGE in humans will be placed into a different category because of their unique biology. There is great potential for exploiting their unique status by doctors and researchers, and this potential is magnified if the individuals are from a vulnerable population. Care will have to be taken in structuring relationships between researchers and subjects because of this.

4. Apply the Framework to Design of Protocols for Intergenerational Monitoring

Design of a full protocol for monitoring is not within the purview of the project and is a big task for one researcher; however, an aim of the study will be to make some initial steps here that could be of use by considering application of the results of step 3 to action-guiding principles for the design of future protocols. For example, this phase of the project could include consideration of what sorts of guidelines should be in place for contacting descendants of subjects and communicating findings to them. A possible candidate here could be a rule that requires an extensive weighing of harms and benefits (such as harms to individuals of divulging information about their parentage vs. harms to them and their future descendants of not communicating information) by an ethics review board before researchers take the step of contacting individuals. Research on these sorts of action-guiding principles could inform the design of future protocols for clinical trials of GGE and even be incorporated directly into future codes. A parallel here is the extensive discussion over incidental findings in genetics research, which included not just research into the ethical issues but also research into protocols, and which eventually resulted in several candidate protocols and codes for communication of incidental findings in genetics (Green et al 2013; Cho 2008). The aim of this phase of the project will be to make a start along a similar path by doing initial research applying the results of phase 3 to some potential protocols for future clinical trials.

5. Disseminate Results of the Project

In the final phase of the project, the PI will write academic papers and communications for scientific journals reporting the results of the project. The PI will also attend academic conferences and meetings of professional societies and give presentations of the results. The ultimate goal of the project is to produce new research on this topic and also to stimulate work by other biomedical ethicists on the issues. This will require not just publication and presentation in journals and at meetings for other bioethicists, but also in venues that will reach scientists working on GGE as well. The advisory committee, especially those with past experience writing for broad audiences, will consult with the PI and aid in choosing the right venues to publish and present, as well as look at drafts of publications before they are submitted.

Preliminary Findings

The PI has conducted preliminary research into this set of issues (and into the ethics of GGE more generally) over the last several years. This research was summarized in an article published in November 2017 (Cwik 2017). Preliminary research identified the gaps in the literature and broader discussions of GGE the PI is seeking to address, as well as the urgent need to address these issues. The PI will build on this preliminary research (especially in phase 1) to produce new research over the life of the project.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	○ Yes ● No
Is the Project Exempt from Federal regulations?	○ Yes ○ No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Does the proposed research involve human specimens and/or data	○ Yes ● No
Other Requested information	

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Resource Sharing Plan

Data generated from this project will be shared by:

1) Publication in peer-reviewed journals that ensure all conditions of NIH Public Access Policy.
2) Presentation of unpublished data at scientific meetings.
3) Making unpublished data freely available to other investigators.