SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **07/05/2018**
Revised Date:

Application Number: **1 R03 HG010417-01**

Principal Investigator

CWIK, BRYAN

Applicant Organization: PORTLAND STATE UNIVERSITY

Review Group: **ZRG1 SEIR-B (80)**
Center for Scientific Review Special Emphasis Panel
Societal and Ethical Issues in Research

Meeting Date: **06/21/2018**
Council: **OCT 2018**
Requested Start: **09/01/2018**

RFA/PA: **PA17-445**
PCC: **X5NL**

Project Title: **Intergenerational Monitoring in Clinical Trials of Germline Gene Editing: Ethical, Legal, and Social Issues**

SRG Action: Priority Score **Percentile** Percentile

Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**

Human Subjects:
Animal Subjects: Evaluative Info

Project Year	Direct Costs Requested	Estimated Total Cost
1	50,000	Estimated Costs
2	50,000	
TOTAL	100,000	

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R03HG010417-01 Cwik, Bryan

RESUME AND SUMMARY OF DISCUSSION: This project will evaluate the ethical issues that may occur in future clinical trials of germline editing of humans that will involve intergenerational monitoring. The project is significant and innovative as the topic of how such monitoring will take place in an ethical manner has not been studied. The investigator demonstrates considerable knowledge in gene editing and has gathered a strong interdisciplinary advisory group. The project will evaluate current protocols that involve long-term follow-up of subjects and the project lists specific areas of inquiry that will be important to consider in intergenerational monitoring. The project includes an impressive advisory committee but a minor concern is that not all the members provided letters of commitment. After discussion, the reviewers all agreed that this is an interesting and significant conceptual project that has a high likelihood for developing an ethical framework on intergenerational monitoring for future clinical studies.

DESCRIPTION (provided by applicant): 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.

PUBLIC HEALTH RELEVANCE: 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.

CRITIQUE 1

Significance: 1
Investigator(s): 1
Innovation: 5
Approach: 2
Environment: 1

Overall Impact: Determining the safety and efficacy of human germ line gene editing will require intergenerational monitoring. This conceptual study will consider how such monitoring might be

accomplished in an ethical manner. Determining the safety and efficacy of human germ line gene editing will require intergenerational monitoring. While commentators recognize the challenges, there has been little consideration of how such monitoring might take place or whether it would comport with ethical principles. This conceptual study will consider how such monitoring might be accomplished in an ethical manner. Issues to be addressed include recruitment of subjects and informed consent, obligations of researchers to future generations, ethical and practical issues related to communication of findings to descendants and relatives, management of genomic specimens and data over extended time periods, power imbalances between subjects and researchers, and the potential need for ancillary resources for descendants, such as health care and counseling. The investigator is a junior scholar with past experience in climate change and intellectual property research, but who has published an article on the subject of this project in NEJM in 2017. The application evidences considerable knowledge of gene editing science. There is an advisory committee, although with one exception they are not “usual suspects” but collaborators or acquaintances of the investigator. The investigator will examine existing protocols for long-term follow-up of subjects, such as for the Framingham Study, but acknowledges important differences between them and germ line gene editing follow-up (23). The application cites the debate over incidental findings as an example of how similar ethical issues have been addressed (25, 27). The application includes appropriate dissemination methods.

1. Significance:
Strengths

- Determining the safety and efficacy of human germ line gene editing will require intergenerational monitoring. While commentators recognize the challenges, there has been little consideration of how such monitoring might take place or whether it would comport with ethical principles. This conceptual study will consider how such monitoring might be accomplished in an ethical manner.

Weaknesses

- None.

2. Investigator(s):
Strengths

- The PI is knowledgeable about genetic science.
- The PI has completed preliminary research that has been published in the NEJM.
- The project has a group of advisors with interdisciplinary expertise.

Weaknesses

- There are letters of support from only two of the seven members of advisory committee.

3. Innovation:
Strengths

- None.

Weaknesses

- The methodology is not innovative.

4. Approach:
Strengths

- The application identifies appropriate issues to be addressed.
- The investigator will examine existing protocols for long-term follow-up of subjects, such as for the Framingham Study, but acknowledges important differences between them and germ line gene editing follow-up (23).
- The application cites the debate over incidental findings as an example of how similar ethical issues have been addressed (25, 27).

- The application includes appropriate dissemination methods.

Weaknesses

- It is important for the PI to obtain input from his advisory committee, but 5 of the 7 named advisors have not provided letters of support, and it is unclear from the 2 letters submitted if they accept the significant advisory role the PI envisions.

5. Environment:

Strengths

- The study site at Portland State University has the necessary facilities for the project.
- Four of the seven members of the advisory committee are located near the PI.

Weaknesses

- None.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Not applicable
- Race/Ethnicity: Not applicable
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Not applicable

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

- Data will be shared vis dissemination of results.

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

- The project may not need [redacted] of effort to complete, in which case it may be more suitable for [redacted].

CRITIQUE 2

Significance: 2
Investigator(s): 2
Innovation: 1
Approach: 3
Environment: 2

Overall Impact: This R03 proposes to investigate ethical issues related to future clinical trials involving germline gene editing (GEE), specifically, challenges in intergenerational monitoring within families of individuals who have undergone GEE. There appears to be a lack of literature on this topic, and the PI, Dr. Cwik, will undertake a literature review and examination of unique ethical issues raised by GEE, framed against existing models for conducting intergenerational monitoring in other research contexts. The research question is innovative and the products from this work will likely fill a gap in the literature. There are questions as to how the excellent expertise from the assembled advisory committee will be utilized, as letters of support from several are not provided. More detail regarding what steps will be taken to assure that the proposed research is of sufficient rigor, and regarding the specific methods to be used, would strengthen the application.

1. Significance:
Strengths

- This proposal focuses on a provocative and understudied topic related to the emerging technology of germline gene editing (GGE). Specifically, the proposed study will address ethical challenges in conducting intergenerational monitoring following the completion of GGE. The proposal describes a sound scientific premise for the proposed research, noting the unique ethical challenges posed in conducting intergenerational monitoring studies, and the similarities and gaps in current research practice and the literature.
- The primary contribution of the proposed research will be the completion of a literature review and identification of ethical issues in regard to intergenerational monitoring studies, which will contribute to the development of an ethical framework for conducting intergenerational monitoring in clinical trials focused on 5 primary areas. While the proposal mentions design of protocols for such monitoring in future research, it is stated that that is outside of the current scope of work for this study. Instead, Aim 4 may contribute new knowledge on action-guiding principles that could be applied to future research protocols. The potential outcomes of this aim were compared to early efforts to define ethical guidance on communication of incidental findings in germline genetic testing.
- Given that this topic appears to have received limited attention in the ethics literature, a significant contribution of this work is expected to be new knowledge on intergenerational monitoring research for GEE, and potentially stimulating work and discussion by other bioethicists on this topic.

Weaknesses

- The timeframe for moving GEE into clinical human studies is uncertain, and the ultimate- and potentially long-term- relevance of expected findings from this study is uncertain. However, this is a minimal concern.

2. Investigator(s):
Strengths

- Dr. Cwik is an assistant professor of philosophy at Portland State University with prior research experience related to climate change policy. He collaborated on the development of a tool to integrate community members' data into the process of making climate change resiliency plans. His prior work on intellectual property has included the development of a framework for considering ethics of intellectual property, which may involve an approach similar to what is proposed in the current study. Dr. Cwik published a paper on GEE in the NEJM in 2017.
- Dr. Cwik notes an impressive team of scientists who will serve in an advisory capacity for this study. The group includes Dr. Shoukrat Mitalipov who has been actively involved in early research on GEE.
- Dr. Cwik will conduct part of the work as part of a visiting scientist fellowship at UCSD, presumably in collaboration with Dr. Callendar, also on the advisory board.

Weaknesses

- Letters of support are provided from only two potential advisory board members.

3. Innovation:
Strengths

- It appears that ethical issues and considerations in conducting intergenerational monitoring in future clinical trials of GEE have not been addressed in the literature to date. This appears to be a very innovative study.

Weaknesses

- Methods do not appear to be innovative but nonetheless appear to be appropriate for the proposed study.

4. Approach:
Strengths

- Within the approach described for each specific aim, the proposal does a good job of listing specific areas of inquiry, particularly regarding the examination of ethical issues in light of current knowledge, areas to focus on regarding the development of a framework for considering intergenerational monitoring in clinical trials, and suggesting how results might be applied to future protocols.

Weaknesses

- The proposal does not explicitly describe what steps will be undertaken to assure rigor and reproducibility in the proposed research. The Approach described general guidance for undertaking steps in addressing the specific aims, but lacks some detail as to how the actual work will be accomplished.
- Reference to seeking input from the advisory board is mentioned, but specific steps for engaging them, along what timeline, whether they will be compensated, and what input is expected are not clearly explained.

5. Environment:
Strengths
Weaknesses

- The Facilities and Resources are described in limited detail. It is assumed that Dr. Cwik has resources necessary to conduct the proposed research e.g., library facilities, online databases.

Study Timeline
Strengths

- Not relevant, no clinical trial proposed.

Weaknesses

- None noted

Protections for Human Subjects:
Not Applicable (No Human Subjects)
Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):
Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Not applicable
- Race/Ethnicity: Not applicable
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Not applicable

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:
Not Applicable (No Biohazards)

Budget and Period of Support:
Recommend as Requested

CRITIQUE 3

Significance: 3
Investigator(s): 3
Innovation: 3
Approach: 4
Environment: 3

Overall Impact: This is an interesting project that has a lot of potential. Creating tools and getting ethical approval is important, but underlying legal and social issues will arise as well. Furthermore, relying on an advisory panel to help out is limitative. Members who have accepted to participate in the committee are likely to be very busy and only provide pinpointed comments or advice.

1. Significance:
Strengths

- 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 is a timely topic.

Weaknesses

- Without a strong review of ethical and legal issues, it is hard to see how the tool that will be prepared can efficiently be adopted. These inherent issues do not need to be the main aims of the study, but including them would have been beneficial for future implementation.

2. Investigator(s):
Strengths

- The investigator has published on the topic of research (one paper).

Weaknesses

- The PI does not seem to have a lot of experience in the field.

3. Innovation:
Strengths

- Includes a diversity of approaches in the fields of ethics.

Weaknesses

- The approaches suggested (which include building on existing literature and consulting with an advisory committee) are not innovative.

4. Approach:
Strengths

- Includes a diversity of approaches.

Weaknesses

- Unfortunately, it is unclear how that diversity can truly be the groundwork for important impact in the field.
- Unsure how the advisory committee (who are listed as part of the approaches used in this research) will have meaningful impact in the overall research. When reading some of the letters of support, the role they will play is quite limited.

5. Environment:
Strengths

- The PI will benefit from being hosted at the Institute for Practical Ethics at the University of California, San Diego, as a visiting fellow.

Weaknesses

- None noted

Protections for Human Subjects:
Not Applicable (No Human Subjects)
Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):
Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender:
- Race/Ethnicity:
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18:

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)

Biohazards:
Not Applicable (No Biohazards)

Budget and Period of Support:
Recommended budget modifications or possible overlap identified:

- Very difficult to understand how the budget will be utilized and for what phase of the project. The budget justification was very short and not detailed enough.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R03 HG010417-01; PI Name: Cwik, Bryan

Ad hoc or special section application percentiled against "Total CSR" base.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by

averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.