Notice of Award

RESEARCH
Department of Health and Human Services
National Institutes of Health

Federal Award Date: 11/05/2018

NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Grant Number: 1R01HG010168-01 REVISED
FAIN: R01HG010168

Principal Investigator(s):
Insoo Hyun
Josephine Marguerite Johnston (contact), MBHL
Karen Joann Maschke, PHD

Project Title: Actionable Ethics Oversight for Human-Animal Chimera Research

Wood-Nutter, Carol
Director of Grants Management
21 Malcolm Gordon Road
Garrison, NY 105244125

Award e-mailed to: nutterc@thehastingscenter.org

Period Of Performance:
Budget Period: 09/12/2018 – 06/30/2019
Project Period: 09/12/2018 – 06/30/2021

Dear Business Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to HASTINGS CENTER, INC. in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Human Genome Research Institute of the National Institutes of Health under Award Number R01HG010168. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

Lisa A. Oken
Grants Management Officer
NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Additional information follows

SECTION I – AWARD DATA – 1R01HG010168-01 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$109,533
Fringe Benefits	$30,668
Personnel Costs (Subtotal)	$140,201
Travel	$2,942
Other	$1,000
Subawards/Consortium/Contractual Costs	$182,710
Federal Direct Costs	$326,853
Federal F&A Costs	$105,884
Approved Budget	$432,737
Total Amount of Federal Funds Obligated (Federal Share)	$432,737
TOTAL FEDERAL AWARD AMOUNT	$432,737
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$432,737	$432,737
2	$527,906	$527,906
3	$516,736	$516,736

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Human Genome Research
CFDA Number:	93.172
EIN:	1132662222A1
Document Number:	RHG010168A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2018

IC	CAN	2018	2019	2020
HG	8472561	$432,737	$527,906	$516,736

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: X5JB / **OC**: 414A / **Released**: eRA Commons 11/02/2018
Award Processed: 11/04/2018 11:03:20 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1R01HG010168-01 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1R01HG010168-01 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget

period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

An unobligated balance may be carried over into the next budget period without Grants Management Officer prior approval.

This grant is subject to Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) R01HG010168. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

Revision #1

Restriction Release
This revised award reflects the Office for Human Research Protections' (OHRP) approval of Assurance(s) of Compliance with 45 CFR 46 the awardee organization and removes the special condition on the award issued on 9/12/18. Accordingly, the special condition prohibiting research involving human subjects is removed, effective as of the date of Institutional Review Board approval.

Restriction Release
This revised award reflects the NIH awarding component's acceptance of the certification of Institutional Review Board (IRB) approval for the awardee organization and releases the restriction on the Notice Grant Award issued on 9/12/18. Accordingly, the special condition prohibiting research involving human subjects is removed, effective as of the date of IRB approval.

The human subjects code for this award is changed from non-exempt human subjects (code 30) to exemption 2 human subjects (code E2) in accordance with the IRB determination and Program Official concurrence.

Awardees are reminded that terms from the previous award that are not changed by this revision remain in effect.

Supersedes Notice of Award 9/12/18

_____

Information
This award is subject to PA-17-444 entitled, Ethical, Legal, and Social Implications (ELSI) of Genomics Research Project Grant Program, posted on August 1, 2017, which is hereby incorporated by reference as special terms and conditions of this award.

Copies of this announcement may be accessed at the following Internet address: https://grants.nih.gov/grants/guide/pa-files/PA-17-444.html or obtained from the Grants Management Contact referenced in the award.

Information
Although the budget period end date for this award is 6/30/19, this award includes funds for 12 months of support. Future year budget periods will cycle on July 1st. Research Performance Progress Reports are due 45 days prior to this date.

Information
Inflationary increases are not allowable and have been removed from future year commitment(s) per the NIH Guide Notice NOT-OD-12-036 at http://grants.nih.gov/grants/guide/notice-files/NOTOD-12-036.html.

Human Subjects
This award reflects the National Human Genome Research Institute's acceptance of the certification that all key personnel have completed education on the protection of human subjects, in accordance with NIH policy, "Required Education in the Protection of Human Research Participants, " as announced in the June 5, 2000 NIH GUIDE (revised August 25, 2000) (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html).

Any individual involved in the design and conduct of the study who is not included in the certification must satisfy this requirement prior to participation in the project. Failure to comply can result in the suspension and/or termination of this award, withholding of support of the continuation award, audit disallowances, and/or other appropriate action.

Consortium
This award includes funds awarded for consortium activity with Case Western Reserve University in the amount of $182,710 ($114,194 direct costs + $68,516 facilities and administrative costs). Consortia are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH GPS is available at: http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15.1_general.htm.

Multi-PI
In keeping with NOT-OD-06-054 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-054.html), as this grant has multiple Principal Investigators (PIs), although the signatures of the PIs are not required on prior approval requests submitted to the agency, the awardee institution must secure and retain the signatures of all of the PIs within their own internal processes.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: Zephaun Harvey
Email: harveyz@mail.nih.gov **Phone**: 301 435-7859 **Fax**: 301-451-5434

Program Official: Joy Boyer
Email: boyerj@exchange.nih.gov **Phone**: 301-480-2247 **Fax**: 301-402-1950

SPREADSHEET SUMMARY
GRANT NUMBER: 1R01HG010168-01 REVISED

INSTITUTION: HASTINGS CENTER, INC.

Budget	Year 1	Year 2	Year 3
Salaries and Wages	$109,533	$117,789	$132,185
Fringe Benefits	$30,668	$32,980	$37,011
Personnel Costs (Subtotal)	$140,201	$150,769	$169,196
Consultant Services			$32,769
Travel	$2,942	$37,441	$17,529
Other	$1,000	$25,726	$27,491
Subawards/Consortium/Contractual Costs	$182,710	$180,046	$115,138
TOTAL FEDERAL DC	$326,853	$393,982	$362,123
TOTAL FEDERAL F&A	$105,884	$133,924	$154,613
TOTAL COST	$432,737	$527,906	$516,736

Facilities and Administrative Costs	Year 1	Year 2	Year 3
F&A Cost Rate 1	62.6%	62.6%	62.6%
F&A Cost Base 1	$169,143	$213,936	$246,985
F&A Costs 1	$105,884	$133,924	$154,613

PI: **Johnston, Josephine Marguerite**	Title: Actionable Ethics Oversight for Human-Animal Chimera Research	
Received: 10/03/2017	FOA: PA17-444	Council: 05/2018
Competition ID: FORMS-D	FOA Title: Ethical, Legal, and Social Implications (ELSI) of Genomics Research Project Grant Program (R01)	
1 R01 HG010168-01	Dual: HD	Accession Number: 4092479
IPF: 593801	Organization: HASTINGS CENTER, INC.	
Former Number:	Department:	
IRG/SRG: ZRG1 SEIR-B (80)	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 258,938 Year 2: 340,415 Year 3: 353,893	Animals: N Humans: Y Clinical Trial: N Current HS Code Evaluative Info HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Josephine Johnston	The Hastings Center	PD/PI
Insoo Hyun Ph.D	Case Western Reserve University	MPI
Patricia Marshall Ph.D	Case Western Reserve University	Co-Investigator
Karen Maschke Ph.D	The Hastings Center	MPI
Mildred Solomon	The Hastings Center	Co-Investigator
Carolyn Neuhaus Ph.D	The Hastings Center	Co-Investigator

Appendices

1249-AppendixA

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 | **Application Identifier**

c. Previous Grants.gov Tracking Number
GRANT12490190

5. APPLICANT INFORMATION

Organizational DUNS*: 0766726090000

Legal Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10524-4125

Person to be contacted on matters involving this application

Prefix: First Name*: Carol Middle Name: Last Name*: Wood-Nutter Suffix:
Position/Title: Director of Grants Management
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10524-4125
Phone Number*: 845-424-4040x259 Fax Number: 845-424-4545 Email: nutterc@thehastingscenter.org

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 13-2662222

7. TYPE OF APPLICANT* M: Nonprofit with 501C3 IRS Status (Other than 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*
Actionable Ethics Oversight for Human-Animal Chimera Research

12. PROPOSED PROJECT

Start Date* Ending Date*
07/01/2018 06/30/2021

13. CONGRESSIONAL DISTRICTS OF APPLICANT
NY019

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Josephine Middle Name: Marguerite Last Name*: Johnston Suffix:
Position/Title: Director of Research, Research Scholar
Organization Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10524-4125
Phone Number*: 845-424-4040x208 Fax Number: 845-424-4545 Email*: johnstonj@thehastingscenter.org

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$1,558,271.93
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$1,558,271.93
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*: Carol Middle Name: Last Name*: Wood-Nutter Suffix:
Position/Title*: Director of Grants Management
Organization Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 10524-4125
Phone Number*: 845-424-4040x259 Fax Number: 845-424-4545 Email*: nutterc@thehastingscenter.org

Signature of Authorized Representative*
Carol Wood-Nutter

Date Signed*
10/03/2017

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1235-CoverLetter.pdf

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:	The Hastings Center
Duns Number:	0766726090000
Street1*:	21 Malcolm Gordon Road
Street2:	
City*:	Garrison
County:	
State*:	NY: New York
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	10524-4125
Project/Performance Site Congressional District*:	NY-019

Project/Performance Site Location 1

❍ 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:	Case Western Reserve University
DUNS Number:	0777584070000
Street1*:	10900 Euclid Avenue
Street2:	
City*:	Cleveland
County:	
State*:	OH: Ohio
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	44106-4919
Project/Performance Site Congressional District*:	OH-011

Additional Location(s) File Name:

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

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

IRB Approval Date:

Human Subject Assurance Number 0001925

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*	1236-ProjectSummaryAbstract.pdf
8. Project Narrative*	1237-ProjectNarrative.pdf
9. Bibliography & References Cited	1238-BibliographyAndReferencesCited.pdf
10.Facilities & Other Resources	1239-FacilitiesAndOtherResources.pdf
11.Equipment	

PROJECT SUMMARY/ABSTRACT

Today, advances in human stem cell science and genetic engineering techniques are enabling researchers to more extensively and precisely insert human cells (and self-organizing mini-organ structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of vertebrate animals. These scientific advances are thrilling. Yet they also reveal conceptual, ethical, and procedural limitations in existing ethics guidance for human-animal chimera research. Two sets of influential guidelines for this research – one set from the National Academies of Sciences and the other from The International Society of Stem Cell Researchers – represent important landmarks in U.S. and international initiatives to offer oversight to the emerging science of human-animal chimera research. Our review of this guidance and preliminary exploration with major thought leaders, including many who have now agreed to serve on our proposed Working Group, make clear the need for two things: (1) conceptual clarity and normative analysis related to defining and measuring “humanization” and its significance to animal welfare, and (2) examination and improvement of the oversight system, including greater clarity about who should be responsible (and accountable) for certain aspects of the research and how best to integrate different sets of concerns into a streamlined, efficient review system. To enhance oversight and offer greater conceptual and operational clarity, the proposed project will carry out (1) review of relevant guidances and policies (2) conceptual and normative analyses of philosophical concerns, moral uncertainties, and value conflicts, and (3) empirical analyses of the views of scientists and members of stem cell and animal research oversight committees so that their lived experiences, goals and challenges will inform the actionable recommendations that will emerge from this research project. We will develop a set of educational materials that includes a casebook of challenging protocols with commentaries on how such protocols can be ideally managed and educational modules that help users unpack some of the complex normative issues. We will also develop a white paper that describes actionable recommendations for enhancing the integration of research institutions’ stem cell and animal research oversight committees (ESCROs & IACUCs). The educational materials we plan to develop will be designed to aid ESCRO committee and IACUC members in discharging their oversight responsibilities, and to help the public understand this kind of research, what it is, and what it is not.

PROJECT NARRATIVE

Advances in genome editing, embryology, and stem cell science are making it possible to imagine, and create, new kinds of human-animal chimeras that are both more biologically and more ethically complex than previously created chimeras. This project aims to develop clear, reasoned, and practical recommendations and educational materials to assist researchers, research institutions and their oversight bodies, funders and the public in identifying, understanding, and managing the ethical issues associated with human-animal chimera research.

FACILITIES AND OTHER RESOURCES

The Hastings Center

The Hastings Center is an independent, not-for-profit, nonpartisan bioethics research institute, committed to advancing scholarship in, and public understanding of, ethical issues raised by advances in health, health care, life sciences research, and the environment. The Hastings Center conducts research, organizes research meetings that are national and international in scope, and publishes articles and commentaries. We have a worldwide reputation for our independence and the ability to bring together people who hold divergent views to examine underlying values and principles in mutually respectful ways that lead to actionable policies. The Hastings Center is the home to two leading peer-reviewed journals, *Hastings Center Report* and *IRB: Ethics & Human Research*. Hastings has seven research scholars and an international network of more than 200 elected Fellows who are leading researchers in bioethics-related fields.

Facilities:

The Hastings Center is located in Garrison, NY, an hour north of New York City by car or commuter rail line. Hastings is easily accessible to major highways. The 17,000-square-foot facility, located on 54 acres, includes individual offices as well as meeting space. Support personnel are available to coordinate meeting logistics, etc. The facility meets ADA requirements.

All Hastings Center personnel and visitors have full time access to an on-site OCLC-member library with electronic databases and more than 9,000 volumes.

Information & Marketing Technology:

The Hastings Center has significant information and marketing technology capabilities that increase the impact of the work of our individuals and collaborative teams (internal and external). These capabilities allow Hastings to better promote its findings to, and communicate with, the bioethics field and general public.

Hastings has an office-wide, wireless, high-speed broadband network with a wide range of software and applications that allow onsite and mobile collaboration through e-mail, texting, phone-conferencing and videoconferencing.

Additionally, creative and communications staff all have state-of-the-art video, graphics, print, digital (website, e-mail) design and production tools, including Final Cut Pro Studio, Adobe Creative Suite and Constant Contact.

Hastings has two professional-grade video cameras and corresponding audio recording equipment and promotes video communications through its YouTube Channel and with it video distribution and broadcast partner Fora.tv. A 60-person capacity meeting room has multiple flat-screens for video conferencing and shared presentations.

Hastings relies on many analytic tools to track and improve information and marketing technology performance.

Tech support (for on-premise and remote users) performs system configuration, server administration, hardware/software purchasing, and general computer support. Hastings' core network and storage systems are located on site with multiple redundancies and secured access for business continuity. Hastings employs state-of-the-art virus and spam filtering, secure remote access, and internal control systems, including hard drive encryption when appropriate, to ensure our systems and networks are not compromised.

Case Western Reserve University

The School of Medicine (SOM) was organized in 1843 and has occupied its current site in University Circle on Cleveland's east side since 1924. The School was one of the first to employ full-time instructors in teaching and research and is one of only two schools mentioned in the Flexner Report as providing models for American medical education. The School is the leading medical research institution in Ohio with an annual research and training budget of more than $38 million from Federal agencies. The School is only one of 25 in the country with an NIH-funded Medical Scientist Training Program, which provides support to train physician-

scientists who earn both the Ph.D. and M.D. degrees. Nine hundred full-time faculty are currently divided among the 22 clinical and basic science departments; in addition; there are over 709 interdisciplinary centers and programs.

Case Western Reserve University School of Medicine

The School of Medicine was organized in 1843 and occupies its current site in University Circle on Cleveland's east side since 1924. The School was one of only two schools mentioned in the Flexner Report as providing models for American medical education. The School is the leading research institution in Ohio. It is now 9th in the nation in terms of NIH research grants, and recently ranked 13th in the nation in terms of grant amounts. Additionally, the School has an annual research training budget of over $38 million from federal agencies. Nine hundred full-time faculty are currently divided among the 22 clinical and basic science departments; in addition, there are over 709 interdisciplinary centers and programs.

The Department of Bioethics has provided advanced training in bioethics for students and professionals since 1995. The Department has over 7,000 square feel of office/library/conference room space. Offices are available for project staff, including temporary workspace for consultants and members of the research team from other locations to use when working on site. All CWRU faculty and staff have access to the latest software at no charge—e.g., Microsoft, Adobe Acrobat, etc. The faculty are nationally- and internationally-renowned, with backgrounds in medicine, nursing, philosophy, law, religious studies, anthropology, sociology and pubic health. The faculty have access to and utilize a variety of distance learning programs to assist in coordinating international intensive courses and collaborations with universities and professionals around the world.

Center for Genetic Research and Law (CGREAL): This project will be conducted within the context of the CWRU Center for Genetic Research and Law (CGREAL). CGREAL, an NIH National Human Genome Research Institute-funded Center of Excellence in Ethical, Legal and Social Implications of Genetics (ELSI) Research, is directed through a collaborative partnership between Case Western Reserve University (CWRU) and The Cleveland Clinic. Its mission is to conduct transdisciplinary studies of ethical and societal issues in human genetic research and introduce new genetic technologies into patient care and public health. This context augments the core resources available to our proposed project, and places it in a multi-disciplinary portfolio of ongoing research on related themes.

Libraries

The Kelvin Smith Library, a $27 million, 144,000 square foot building, houses most of the University Library's collections. This relatively new library allows users to integrate traditional resources and state-of-the-art technology into changing patterns of teaching, research, and learning. CWRUnet faceplate connections are available for nearly every seat in the library and are arranged in a flexible layout so that furniture arrangements can be adapted as usage patterns develop and change. Two multi-media rooms include scanners, sound, and video digitizer. There are a variety of seating types, from quiet individual study space to group meeting rooms, conference areas, and social gathering places. The use of compact shelving allows the library to keep much of the collection on-site, responding to users' requests for immediate access to print materials where feasible. The interface to the on-line catalog, databases, and other information resources is designed to be as self-explanatory as possible, allowing library staff to provide greater attention to in-depth work with faculty and students.

Cleveland Health Sciences Library. In addition to the Kelvin Smith Library, students and faculty have access to several other libraries that are located on campus: the *Cleveland Health Sciences Library,* which supports programs in bioethics, medicine, dentistry, nursing, and public health; the *School of Law Library*; the *Lillian and Milford Harris Library in the Mandel School of Applied Social Sciences*; the Kulas Music Library; and the Astronomy Library. Collections at the CWRU Libraries comprise more than 1.8 million volumes, nearly 14,000 serials and periodicals, and a wide range of electronic resources, including a CD-ROM reference database that is accessible through CWRUnet. CWRU is a member of the Association of Research Libraries and participates in various local and regional consortia. This includes OHIOLink, a state-funded network that links libraries at 18 Ohio institutions and offers access to research databases and other information resources.

The Health Sciences Libraries, which consist of the Health Center Library and the Allen Memorial Library, serve as the major libraries for holdings related to bioethics, medicine, nursing, dentistry, nutrition, biology, and public health. The Health Center Library houses 345,072 volumes, 2780 current periodicals, and audiovisual materials. The Allen Memorial Library is located one block away from the School of Medicine and the Center for Biomedical Ethics. The primary function of the Allen Library is to serve practicing physicians and hospitals in Northeast Ohio. It houses selected medical and scientific periodicals and texts.

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

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Josephine Middle Name Marguerite Last Name*: Johnston Suffix:

Position/Title*: Director of Research, Research Scholar
Organization Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10524-4125

Phone Number*: 845-424-4040x208 Fax Number: 845-424-4545

E-Mail*: johnstonj@thehastingscenter.org

Credential, e.g., agency login: eRA Commons User Name

Project Role*: PD/PI Other Project Role Category:

Degree Type: LLB Degree Year: 1996

Attach Biographical Sketch*: File Name: 1250-JohnstonBiosketch.pdf

Attach Current & Pending Support: File Name:

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: Insoo Middle Name Last Name*: Hyun Suffix: Ph.D

Position/Title*: Associate Professor
Organization Name*: Case Western Reserve University
Department:
Division:
Street1*: 10900 Euclid Avenue
Street2:
City*: Cleveland
County:
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 44106-4919

Phone Number*: 216-368-8658 Fax Number: 216-368-8713

E-Mail*: insoo.hyun@case.edu

Credential, e.g., agency login: eRA Commons User Name

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 1999

Attach Biographical Sketch*: File Name: 1251-HyunBiosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Patricia Middle Name Last Name*: Marshall Suffix: Ph.D

Position/Title*: Director, Center for Genetics Research Ethics
Organization Name*: Case Western Reserve University
Department: Department of Bioethics
Division:
Street1*: 10900 Euclid Avenue
Street2:
City*: Cleveland
County:
State*: OH: Ohio
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 44106-4919

Phone Number*: 216-368-2502 Fax Number:

E-Mail*: pam20@case.edu

Credential, e.g., agency login: eRA Commons User Name

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 1983

Attach Biographical Sketch*: File Name: 1252-MarshallBiosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Karen Middle Name Last Name*: Maschke Suffix: Ph.D

Position/Title*: Research Scholar
Organization Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10524-4125

Phone Number*: 845-424-4040x223 Fax Number: 845-424-4545

E-Mail*: maschkek@thehastingscenter.org

Credential, e.g., agency login: eRA Commons User Name

Project Role*: PD/PI Other Project Role Category:

Degree Type: PhD Degree Year: 1987

Attach Biographical Sketch*: File Name: 1253-MaschkeBiosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Carolyn Middle Name Last Name*: Neuhaus Suffix: Ph.D

Position/Title*: Research Scholar
Organization Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10524-4125

Phone Number*: 845-424-4040x255 Fax Number: 845-424-4545

E-Mail*: neuhausc@thehastingscenter.org

Credential, e.g., agency login: eRA Commons User Name

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2016

Attach Biographical Sketch*: File Name: 1254-NeuhausBiosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Mildred Middle Name Last Name*: Solomon Suffix:

Position/Title*: President
Organization Name*: The Hastings Center
Department:
Division:
Street1*: 21 Malcolm Gordon Road
Street2:
City*: Garrison
County:
State*: NY: New York
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 10524-4125

Phone Number*: 845-424-4040x201 Fax Number:

E-Mail*: solomonm@thehastingscenter.org

Credential, e.g., agency login: eRA Commons User Name

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: EdD Degree Year: 1991

Attach Biographical Sketch*: File Name: 1255-SolomonBiosketch.pdf

Attach Current & Pending Support: File Name:

BIOGRAPHICAL SKETCH

NAME Johnston, Josephine	POSITION TITLE Director of Research Research Scholar
eRA COMMONS USER NAME eRA Commons User Name	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Otago, Dunedin, New Zealand	B.A.	12/96	Theatre Studies
University of Otago, Dunedin, New Zealand	L.L.B. (Hons)	12/96	Law
High Court of New Zealand, Wellington, New Zealand	Barrister and Solicitor	09/97	Law (Admitted to the Bar)
University of Otago, Dunedin, New Zealand	Masters of Bioethics and Health Law	05/02	Bioethics, Health Law

A. Personal Statement

For over fifteen years, I have worked on ethical, legal, and policy issues in stem cell and genetics research and have participated in and cooperatively lead successful interdisciplinary ethics research projects on complex and controversial issues in science and medicine. A lawyer by training, I began researching ethical and policy issues in stem cell research in 2001, when I was asked by the New Zealand government to analyze laws and policies around the world affecting research with human stem cells. I subsequently completed a post-doctoral fellowship at Dalhousie University in Canada, which was co-funded by the Canadian Stem Cell Network, and have analyzed and conducted research related to stem cell science ever since. My most recent publications on stem cell research have been published in *Nature* and *Cell Stem Cell*, and reported on in the news media. In addition to my research expertise with these issues, I have over a decade of practical experience in the oversight of stem cell research, providing me with intimate knowledge of the real-world challenges posed by existing guidance in this area. Since 2006, I been a member of the Tri-Institutional Stem Cell Initiative ESCRO, which is one of the country's most active Embryonic Stem Cell Research Oversight Committees serving The Rockefeller University, Memorial Sloan Kettering, and Weil Cornell Medical College. In the course of this oversight work, I have carefully studied each version of the guidelines from the National Academy of Sciences' and ISSCR on, and have worked with my ESCRO to address, various aspects of stem cell research, including animal-human chimeras. I know first-hand how limited existing scholarship and guidance are in this area. Since joining the Hastings Center in 2003, I have developed the leadership and organizational skills to successfully lead multi-year, high-impact interdisciplinary research projects like the one proposed here. These projects have addressed a variety of issues in science and medicine, with an emphasis on new technologies and genetics. Currently, I am PI for an RO1 addressing ethical issues in next-generation prenatal testing, and Co-I for projects on the ethical, legal and social implications of psychiatric, neurologic and behavioral genetics research, gene editing, and the use of genome sequencing technology in newborns.

The following four publications highlight my experience and qualifications for this project.

1. Johnston, J. & Eliot, C., "Chimeras and 'Human Dignity'," *American Journal of Bioethics* 2003; 3(3):6a-8a.
2. Johnston, J., "U.S. Stem Cell Research Policy: An Introduction," In Atala, A., Lanza, R., Thompson, J.A., & Nerem, R.M. (ed.s), *Principles of Regenerative Medicine* (Burlington (MA): Elsevier, 2008) at pp. 1354-1365; republished in Atala, A., Lanza, L., Thompson, J.A. & Nerem, R.N. (ed.s), *Foundations of Regenerative Medicine* 2009, revised for 2nd edition 2011: 1131-1143, and with Zacharias, R.L. for 3rd edition (forthcoming 2017/18).
3. Wilkerson, A., Wongsatittham, K. & Johnston, J., "The NIH Stem Cell Registry: An Absence of Gamete Donor Consent," *Cell Stem Cell* 2013; 12(2):147-8.
4. Hyun, I., Wilkerson, A. & Johnston, J., "Revisit the 14-day Rule," *Nature* 2016; 533: 169-171.

B. Positions and Honors

Positions and Employment

1997-1999 Barrister and Solicitor, Chapman Tripp, Wellington, New Zealand.
1999 Lawyer, Clifford Chance, Frankfurt, Germany.
2001-2002 Research Assistant to Prof. Carl Elliot for NIH Grant "Ethnicity, Citizenship Family: Identity after the Human Genome Project," Center for Bioethics, University of Minnesota, Minneapolis.
2002-2003 Research Associate, Department of Bioethics, Dalhousie University, Halfax, Canada.
2003- Research Scholar (former title, Associate for Law and Bioethics), The Hastings Center, Garrison, New York.
2006-2012 Director of Research Operations, The Hastings Center.
2012-2014 Lecturer, Masters of Science in Bioethics Program, Columbia University, New York.
2012- Director of Research, The Hastings Center.

Other Experience and Professional Memberships

2006-2016 Member, Editorial Committee, *Hastings Center Report*.
2006- Member, Tri-Institutional Embryonic Stem Cell Research Oversight Committee, Weil Cornell Medical College, Memorial Sloan-Kettering Cancer Center, and The Rockefeller University.
2003- Member, American Society for Bioethics and Humanities.
2016 Reviewer, NIH Societal and Ethical Issues in Research study section

Honors

2011 Highly commended, British Medical Association Medical Book Awards for Murray, T.H. & Johnston, J. (ed.s), *Trust and Integrity in Biomedical Research: The Case of Financial Conflicts of Interest* (Baltimore (MD); Johns Hopkins University Press: 2010).
2014 Hope Award for Advocacy (awarded to The Hastings Center and The Yale School of Medicine for our project on multiple births and fertility treatment, Johnston J. (PI)), RESOLVE: The National Infertility Association.
2017 Honoree, Prestigious Speakers Series, Royal Society of New Zealand.

C. Contributions to Science

1. In a series of publications over the past fifteen years, I have assessed and analyzed various aspects of **stem cell research policy and practice**. This area of research, in particular when it involves human embryos or the cells derived from them, raises controversial and ethically complex questions for science policy and institutional research oversight. In these publications, my co-authors and I have identified strengths, inconsistencies, and gaps in laws and guidelines and assessed their real-world implications for stem cell science. In some cases, we have found that policies, such as those restricting embryonic stem cell research to embryos no longer needed for fertility treatment, are grounded in mistaken assumptions (in that case, that the majority of stored embryos were surplus to clinical need). In others, we identified previously overlooked inconsistencies between NIH and NAS guidelines on the issue of gamete donor consent, creating uncertainty around whether embryonic stem cell lines on the NIH registry could be used by investigators whose institutions have committed to following NAS guidelines. Most recently, we coordinated publication of our analysis of the intellectual and policy history of the fourteen day rule to coincide with publication of a groundbreaking scientific article in *Nature* reporting development of human embryos in vitro up to the fourteen day mark. My particular contribution to this work has generally been to identify the policy or oversight challenges, to place those challenges in a historical and regulatory context, to analyze legal and philosophical or conceptual questions, and to ensure that publications are written clearly for broad audiences. By closely following stem cell science and remaining directly involved in its oversight at an active institution, I have been able to identify and help address ethics and policy issues related to its development in timely and constructive ways. In additional to the four publications listed with my personal statement above, the following publications demonstrate my work in this area:
    a. Josephine Johnston, "New Rules for Embryo Research: The Assisted Human Reproduction Bill and CIHR's Stem Cell Research Guidelines," *Journal of Obstetrics and Gynaecology Canada* 2002; 24(9):722-6.
    b. Françoise Baylis, Brenda Beagan, Josephine Johnston, and Natalie Ram, "Cryopreserved Human Embryos in Canada and Their Availability for Research," *Journal of Obstetrics and Gynaecology Canada* 2003; 25(12):1026-31.

c. Josephine Johnston, “Stem Cell Protocols: The NAS Guidelines Are a Useful Start,” *Hastings Center Report* 2005; 35(5):16-17.
d. Josephine Johnston, “Paying Egg Donors: Exploring the Arguments,” *Hastings Center Report* 2006; 36(1):28-31.

2. In a large number of my publications, I have identified and analyzed **the implications of genetics research for individuals, families, and communities**. This investigation has been broad ranging and long running. I have considered the policy implications, implications for medical practice, and implications for how individuals and groups understand themselves and others (primarily via issues related to identity and responsibility). Many of these publications have resulted from large, multi-year interdisciplinary research projects like that proposed here. These publications therefore draw on the insights and research of a large variety of experts, and demonstrate my ability to synthesize research and develop well-reasoned, targeted recommendations and analysis. My role has been to frame the issues, draw together appropriate resources across disciplines, and to develop publications and deliver presentations that are accessible to broad audiences. The following publications demonstrate my work in this area:
   a. Johnston, J. & Elliott, C. (Guest Editors), “Special Issue: Identity and Genetic Ancestry Tracing,” *Developing World Bioethics* 2003; 3(2).
   b. Johnston, J. “Resisting a Genetic Identity: The Black Seminoles and Genetics Tests of Ancestry,” *Journal of Law, Medicine and Ethics* 2003; 31(2):262-71.
   c. Unpublished
   d. Unpublished

3. For more than a decade I have analyzed and developed responses to a series of issues posing **challenges to the trustworthy conduct of scientific research**. In this work, I have addressed the role of laws, regulations, policies, and practices in ensuring that science can progress with public support. Much of this work has been around the identification and management of financial conflicts of interest in science, but it has also extended to the conduct of ethically sensitive research such as research into the genetics of intelligence and to the impact of patenting and licensing practices on the progress of biomedical research and treatment. My role in this work has been to conduct legal analysis and to bridge that analysis with the practices and norms of scientific research. I have also taken the lead on identifying ethical values that can frame and guide policies and practices in this area. I have been responsible for producing publications and for giving presentations that are accessible and meaningful for broad audiences, including scientists, clinicians, policy makers, and the general public. The following publications demonstrate my work in this area:
   a. Murray, T.H. & Johnston, J. (ed.s), *Trust and Integrity in Biomedical Research: The Case of Financial Conflicts of Interest* (Baltimore (MD); Johns Hopkins University Press: 2010).
   b. Davis, M. & Johnston,J. “Understanding and Managing Conflict of Interest: A Comparative Analysis,” Appendix C in Lo, B. & Field, M. (ed.s) *Conflict of Interest in Medical Research, Education, and Practice* (Washington DC: National Academies Press, 2009) at pp C1-C43
   c. Johnston, J. & Wasunna, A. “Patents, Biomedical Research, and Treatments: Examining Concerns, Canvassing Solutions,” *Hastings Center Report* 2007; 37(1) (Special Report): S1-S36.
   d. Johnston, J., Banerjee, M.P. & Geller, G. “Trustworthy Research Institutions: The Challenging Case of Studying the Genetics of Intelligence,” *Hastings Center Report* 2015; 45(5): S59-S65.

4. I have a long-standing interest in and have conducted research to address, **the conduct of science and medicine in ethically controversial areas**, including psychiatry, neuroscience, embryo research, reproduction and fertility treatment. In this work, I have sought to identify the basis for controversy (although many people can identify controversial areas of medicine and science, they struggle to articulate the underlying reasons for or causes of that controversy), and to suggest ways of reframing the debate that better capture the basis of disagreement and, in many case, allow actors to find areas of agreement and compromise. I have often made the connection between debates, and between a debate and underlying social policy, law or social norms, thereby placing debates in a rick context and illuminating a variety of mechanisms to facilitate change. To understand these debates and to suggest constructive and inclusive ways to move them forward, I have analyzed public discourse, laws and regulations, social science research, and philosophical and legal analysis. I have also facilitated and analyzed expert workshops and

project meetings of the sort proposed here. The following publications demonstrate my work on these issues:

a. Parens, E. & Johnston, J. "Understanding the Agreements and Controversies surrounding Childhood Psychopharmacology," *Child and Adolescent Psychiatry and Mental Health* 2008; 2:5; www.capmh.com/content/2/1/5, reprinted in *Focus: The Journal of Lifelong Learning in Psychiatry* 2008; 6(3): 322-330. PMCID: PMC2275214
b. Parens, E., Johnston, J. & Carlson, G.A. "Pediatric Mental Health Care Dysfunction Disorder?" *NEJM* 2010; 362(20): 1853-1855.
c. Johnston, J., Gusmano, M.K. & Patrizio, P. "Preterm Births, Multiples, and Fertility Treatment," *Fertility and Sterility* 2014; 102(1): 36-40.
d. Johnston, J., Farrell, R.M. & Parens, E. "Supporting Women's Autonomy in Prenatal Testing," *NEJM* 2017; 377(6):505-7.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1 P50 HG007257-01 Appelbaum (PI) 04/01/2013-03/31/2018
Center for Research on the Ethical, Legal and Social Implications of Psychiatric, Neurologic and Behavioral (PNB) Genetics
This award supports a Center for Excellence in ELSI Research, focused on the ethical, legal and social implications of advances genetics related to psychiatric, neurological and behavioral genetics. The CEER is conducting research, provide training, and conduct translational activities.
Role: Co-I

1 U19 HD077627 01 Puck, Kwok, & Koenig (PIs) 09/05/2013-08/31/2018
Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening
The goal of this project is to consider whether sequencing newborn's genomes can provide useful medical information beyond that currently provided under existing newborn screening programs. The ELSI component includes work to: develop a participant protection framework for conducting whole genome/whole exome sequencing during the neonatal period; determine the views, perspectives, and value preferences of key stakeholders about the expansion of newborn screening to include whole genome sequencing; and development of policy recommendations regarding expanded newborn screening.
Pole: Co-I

1 R01 HG008805-01A1 Johnston (PI) 08/10/2015 – 05/31/2018
Goals and Practices for Next Generation Prenatal Testing (NGPT)
This project is undertaking normative research to identify the principles and values that should guide the use of NGPT; identify changes to policies and norms to support ethical use of NGPT; and create a research agenda for empirical and normative research aimed at improving policy and practice.
Role: PI

Gene Editing and Human Flourishing Solomon (PI) 11/01/2015-10/31/2018
Private Source
This project will clearly and accessibly articulate for a broad audience, including journalists, teachers and the general public, how and when gene-editing in humans could be used to deepen, but not to undermine, the flourishing of individuals, families and communities.
Role: Co-I

Completed Research Support

Fertility Treatment and Multiple Births: Ethical and Policy Issues on the Path to a Healthy Singleton
Private Source Johnston (PI) 10/31/2011-11/01/2012
The goals of this project was to identify and suggest ethically-sensitive ways to address policy and practice barriers to reducing the high rates of multiple birth following fertility treatment.
Role: PI

Interpreting Neuroimages: Interdisciplinary Engagement with the Complexities
Private Source Parens (PI) 01/01/2008-12/31/2009

The goals of this project were to understand and accessibly articulate what neuroimages can and cannot explain about human cognition and experience.
Role: Co-I

U13 MH78722 Parens (PI) 09/29/2006-09/30/2009
Pharmacological Treatment of Behavioral Disturbances in Children: Engaging the Controversies
The goals of this project were to identify and analysis the reasons for continuing controversy inside and outside psychiatry over the diagnosis and treatment of emotional and behavioral disturbances in children and, where possible, to recommend ways to move beyond those controversies to further science, treatment and social support for children and families.
Role: Co-I

OMB No. 0925-0001 and 0925-0002 (Rev. 11/16 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Insoo Hyun

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University	BA	1992	Philosophy
Stanford University	MA	1993	Philosophy
Brown University	PhD	1999	Philosophy

A. Personal Statement

The purpose of this proposed research is to develop guidelines for the ethical conduct of human-animal chimera research. As a philosophically-trained bioethicist with over a decade of international stem cell policy experience, I will be responsible for the administrative management of the project and overall coordination of research activities. My expertise is in research ethics and emerging biotechnologies. I am the past Chairperson of the Subcommittee on Human Biological Materials Procurement for the International Embryonic Stem Cell Guidelines Task Force, a multinational, multidisciplinary working group for the ISSCR (International Society for Stem Cell Research). In 2007 I served as Co-Chairperson of the ISSCR Task Force on International Guidelines for the Clinical Translation of Stem Cells. I am also the past Chairperson of the ISSCR's Ethics and Public Policy Committee. Most recently I served as a member of the ISSCR Working Group that revised the ISSCR guidelines for basic and translational stem cell research. I have served on national commissions for the Institute of Medicine and the National Academy of Sciences in Washington D.C. I am the author of over 50 scholarly articles and am a frequent contributor to *Science, Nature, Cell Stem Cell, The Hastings Center Report*, among many other journals. My book *Bioethics and the Future of Stem Cell Research* was published by Cambridge University Press in 2013.

B. Positions and Honors

Positions and Employment

1998-2003 Assistant Professor, Department of Philosophy, Western Michigan University, Kalamazoo, Michigan.
2003-2008 Assistant Professor, Department of Bioethics, Case Western Reserve University School of Medicine, Cleveland, Ohio.
2008-present Associate Professor, Department of Bioethics, Case Western Reserve University School of Medicine, Cleveland, Ohio.

Other Experience and Professional Memberships

2005-2010 Member, Institutional Animal Care and Use Committee (IACUC), Case School of Med.
2006-2007 Member, The International Society for Stem Cell Research (ISSCR), International Guidelines Task Force.
2006-2007 Chairperson, ISSCR International Guidelines Task Force Subcommittee on Human Biological Materials Procurement.

2006-2010	Chairperson, ISSCR Ethics and Public Policy Committee.
2007-2008	Co-Chairperson, ISSCR Clinical Translation Guidelines Task Force.
2010-present	Co-Director, Office of Bioethics, Cleveland Clinical Translational Science Collaborative
2010-present	Chairperson, CWRU Human Stem Cell Research Oversight (HSCRO) Committee
2014-2016	Member, ISSCR International Guidelines Revisions Task Force
2014-present	Member, University Hospitals IRB

Honors

2006	Wittke Undergraduate Teaching Award Finalist, Case Western Reserve University.
2007	Menzies Medal for Excellence in Science, Medicine, and the Law Melbourne, Australia, June 13, 2007

C. Contributions to Science

1. International Guidelines for the Conduct of Human Stem Cell Research

Over the past twelve years, I have been heavily involved in drafting and revising international stem cell research guidelines for the International Society for Stem Cell Research (ISSCR). I served as both Subcommittee Chairperson and Task Force Co-Chairperson for all three of these guidelines documents. As one of the chief bioethicists on each of these ISSCR guidelines efforts, I helped write the ethics portions of all these guidance documents, summaries of which were published in a number of high-impact journals.

Jonathan Kimmelman, Nissim Benvenisty, Timothy Caulfield, George Q. Daley, Helen E. Heslop, **Insoo Hyun**, et al., ISSCR Guidelines Update Task Force, *ISSCR Guidelines for Stem Cell Science and Clinical Translation*, May 12, 2016, http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2.

George Daley, **Insoo Hyun**, Jane F. Apperley, et al., "Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines," *Stem Cell Reports* 6, 2016: DOI: http://dx.doi.org/10.1016/j.stemcr.2016.05.001.

Jonathan Kimmelman, **Insoo Hyun**, Nissim Benvenisty, et al., "Global Standards for Stem-Cell Research," *Nature* 533, 2016: 311-313.

George Q. Daley, Lars Ahrlund-Richter, Jonathan Auerbach, Nissim Benvenisty, R. Alta Charo, Grace Chen, Hong-Kui Deng, Lawrence Goldstein, Kathy Hudson, **Insoo Hyun**, *et al.*, "The ISSCR Guidelines for Human Embryonic Stem Cell Research," *Science* 315, 2007: 603-604.

2. Chimera Research Ethics and Policy

As Chair of the ISSCR Ethics and Public Policy Committee, I led an effort to draft an advisory report on the conduct and review of stem cell-based chimera research – the very first report of this kind for the stem cell field. Since then, I have been asked by *Nature*, *PLoS Biology*, and *Development* to write commentaries addressing the ethics of stem cell chimera research.

Insoo Hyun, "Illusory Fears Must Not Stifle Chimaera Research," *Nature* 537, 2016: 281.

Insoo Hyun, "What's Wrong with Human/Nonhuman Chimera Research?" *PLoS Biology* 14, 2016: e1002535. doi:10.1371/journal.pbio.1002535.

Insoo Hyun, "From Naïve Pluripotency to Chimeras: A New Ethical Challenge?" *Development* 142, 2015: 6-8.

Insoo Hyun, *et al.*,"Ethical Standards for Human-to-Animal Chimera Experiments for Stem Cell Research," *Cell Stem Cell* 1, 2007: 159-163.

3. Human Embryo Research – Ethics and Policy

My bioethics work has also extended to high-impact publications dealing with the ethics of human embryo research. My first-authored article on the 14-Day Rule in *Nature* was named by that journal as one of their top 10 most influential commentaries of 2016.

Insoo Hyun, Amy Wilkerson, Josephine Johnston, "Revisit the 14-Day Rule," *Nature* 533, 2016: 169-171.

Insoo Hyun, "Regulate Embryos Made For Research," *Nature* 509, 2014: 27-28.

Insoo Hyun and Paul Tesar, "Cloning Advance Calls For Careful Regulation," *Nature* 478, 2011: 36-37.

Insoo Hyun, "Moving Human SCNT Research Forward Ethically," *Cell Stem Cell* 9, 2011: 295-297.

4. Human Biomaterials Procurement and Use for Research

My experience drafting guidelines for the procurement of human biomaterials for stem cell research has led to publications that address the ethics of research egg donation and somatic cell procurement in top journals.

Erica Haimes, Loane Skene, Angela J. Ballantyne, Timothy Caulfield, Lawrence Goldstein, **Insoo Hyun**, et al. "Position Statement on the Provision and Procurement of Human Eggs for Stem Cell Research," *Cell Stem Cell*12, 2013: 285-291.

Insoo Hyun, "Fair Payment or Undue Inducement?" *Nature* 442, 2006: 629-630.

Insoo Hyun, "Magic Eggs and the Frontier of Stem Cell Science," *Hastings Center Report* 36, no. 2, 2006:16-19.

5. Stem Cell Tourism and Medical Innovation

Besides chimera research, one of the most controversial areas in stem cell research concerns the use of stem cells in patients outside a clinical trials context. My work in this area was heavily influenced by my experiences as Co-Chairperson of the ISSCR Task Force that wrote the first stem cell guidelines for translational research.

Megan Munsie and **Insoo Hyun**, "A Question of Ethics: Selling Autologous Stem Cell Therapies Flaunts Professional Standards," *Stem Cell Research*, 2014: DOI: 10.1016/j.scr.2014.04.014.

Insoo Hyun, "Therapeutic Hope, Spiritual Distress, and the Problem of Stem Cell Tourism," *Cell Stem Cell*12, 2013: 505-507.

Insoo Hyun, "Allowing Room for Innovative Stem Cell-Based Therapies Outside Clinical Trials: Ethical and Practical Challenges," *Journal of Law, Medicine, and Ethics* 38, no. 2, 2010: 277-285.

Olle Lindvall and **Insoo Hyun**, "Medical Innovation Versus Stem Cell Tourism,"*Science* 324, 2009: 1664-1665.

6. The Ethics of iPS Cell Research

I was the first bioethicist to write about the ethics of induced pluripotent stem (iPS) cell research, beginning with a 2007 ethics publication co-authored with the founder of iPS cell technology, Shinya Yamanaka.

Insoo Hyun, "The Bioethics of iPS Cell-Based Drug Discovery," *Clinical Pharmacology and Therapeutics* 38, no.5, 2011: 646-647.

Insoo Hyun, Wenlin Li, Sheng Ding, "Scientific and Ethical Reasons Why iPS Cell Research Must Proceed with Human Embryonic Stem Cell Research," *Stanford Journal of Law, Science & Policy* November 2010.

Timothy Caulfield, Christopher Scott, **Insoo Hyun**, *et al.*, "Stem Cell Research Policy and iPS Cells," *Nature Methods* 7, 2010: 28-33.

Insoo Hyun, Konrad Hochedlinger, Rudolf Jaenisch, Shinya Yamanaka, "New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells," *Cell Stem Cell* 1, 2007: 367-368.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/52007706/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Marshall, Patricia

eRA COMMONS USER NAME (agency login): eRA Commons User Name

POSITION TITLE: Professor of Bioethics, School of Medicine, Case Western Reserve University

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Kentucky, Lexington, KY	BA	1974	Behavioral Science, Anthropology
University of Kentucky, Lexington, KY	MA	1977	Anthropology
University of Kentucky, Lexington, KY	PhD	1983	Anthropology

A. PERSONAL STATEMENT

My training is in medical anthropology and I have worked in the field of bioethics for nearly thirty years. I am Professor of Bioethics and Anthropology and Director of the Center for Genetic Research Ethics and Law (CGREAL) in the Department of Bioethics at the School of Medicine, Case Western Reserve University. My research and scholarly publications have focused on national and international research ethics, informed consent, and cultural diversity and bioethics practices. In recent years my work has focused on ethical and social issues associated with genetics and genomics. **My role as Co-Investigator on the proposed study, "Actionable Ethics Oversight for Human-Animal Chimera Research," builds on my work in the area of research ethics and oversight and my empirical expertise in the design and implementation of quantitative and qualitative research.** From 1998 to 2000, I was a consultant to the President's National Bioethics Advisory Commission (NBAC) on its initiative to examine ethical issues in US publicly- and privately-funded international health research. In 1999, I was a consultant on the revision of the CIOMS/WHO (Council of International Organizations of Medical Sciences/World Health Organization) international ethics guidelines for research, addressing cross-cultural challenges in the informed consent process in international settings. In 2001, I was appointed to the National Academy of Sciences Study Panel on IRBs, Surveys and Social Science Research. I served on SACHRP (Secretary's Advisory Committee for Human Research Protections, Office of Human Research Protection (OHRP), Dept. Health and Human Services from 2007 to 2011. I am currently a member of the H3Africa Ethics and Regulatory Working Group (Human Heredity and Health in Africa), and I am a founding member of *ELSI 2.0 International Collaboratory for Genomics and Society.* Selected publications are included below in the section on Contribution to Science.

B. POSITIONS AND HONORS

Positions

1984-87	Research Associate, Erikson Institute/Advanced Study of Child Development, Chicago, IL.
1987	Clinical Assistant Professor, Department of Pediatrics, Pritzker School of Medicine, University of Chicago, Chicago, IL
1987-93	Assistant Director/Assistant Professor, Medical Humanities Program, Department of Medicine, Loyola University of Chicago, Stritch School of Medicine, Maywood, IL
1994-99	Associate Director/Associate Professor, Medical Humanities Program, Department of Medicine, Loyola University of Chicago, Stritch School of Medicine, Maywood, IL
2000-06	Associate Professor, Department of Bioethics, School of Medicine, Case Western Reserve University, Cleveland, OH
2006-	Professor, Department of Bioethics, and Department of Anthropology, Case Western Reserve University, Cleveland, OH
2010-	Director, Center for Genetics Research Ethics and Law, Department of Bioethics, Case Western Reserve University

Selected Professional Activities

1993-96	Member, Executive Board, Society for Medical Anthropology
1997-99	Member, Executive Board, American Society for Bioethics and Humanities
1999-01	Member, Advisory Board, Fogarty International Center, National Institutes of Health
2001-02	Member, Study Panel, National Academy of Sciences, National Research Council; IRBs, Surveys and Social Science Research, 2001-2002. (Panel on IRBs, Survey, and Social Science Research, Citro-C, Ilgen D, Marrett C, Eds. *Protecting Participants and Facilitating Social and Behavioral Sciences Research.* Washington, DC: National Academies Press 2003)
2003-05	Member, Council on Accreditation, Association for the Accreditation of Human Research Protection Programs, Inc (AAHRPP)
2004-	2004-Member, International Advisory Board, West African Bioethics Training Program, University Hospital, University of Ibadan, Oyo State, Nigeria
2007-11	Member, Secretaries Advisory Committee Human Research Protection (SACHRP), Office of Human Research Protection (OHRP), Dept. Health and Human Services
2012-	Steering Committee, ELSI 2.0 Collaboratory for Genomics and Society
2012-	Member, H3Africa Ethics and Regulatory Issues Working Group

Honors

1991-94	Kellogg National Fellowship Program, Group 12. Three year creative leadership award
2005	Mather Prize for Women's Scholarship, School of Medicine, Case Western Reserve University

C. Contribution to Science

In this section, I have focused my attention on contributions reflecting my scholarly work and research on ethical and social issues associated with genetic and genomics in the following areas: a) policy; b) informed consent practices; c) health disparities and genetic/genomic research; d) patient perceptions of bioengineered probiotics and clinical metagenomics; and e) attitudes of IRB members towards review of genetic research. Publications from my participation on the HapMap Project, an international consortium to develop a haplotype map for the human genome, are available on request. I was a Co-Investigator with Dr. Charles Rotimi's (PI) team for the African sites of the HapMap Project; I assisted with the design and implementation of community engagement strategies for the Yoruba site in Ibadan, Nigeria, and two sites in Kenya.

1. Selected publications listed below illustrate my contributions to the development of initiatives to promote research on genomics and society, the translational potential of research on ethical and social issues of genomics for policy development, and policy related issues associated with genetic/genomics research in African settings.

    a. Kaye J, Meslin E, Knoppers B, Juengst E, Deschênes M, Cambon-Thomsen, Chalmers D, De Vries J, Edwards K, Hoppe N, Kent A, Adebamowo, Marshall P, Kato K. ELSI 2.0: A New International Collaboratory for Genomics and Society Research, *Science* 2012.
    b. Burke W, Appelbaum P, Dame L, Marshall P, Press N, Pyeritz R, Sharp R, Juengst E. *Genet Med*. 2015 The translational potential of research on the ethical, legal, and social implications of genomics. Jan;17(1):12-20. doi: 10.1038/gim.2014.74. Epub 2014 Jun 19. Review. PMC4272334
    c. H3Africa Consortium, Rotimi C, Abayomi A, Abimiku et al (with P Marshall). Research capacity. Enabling the genomic revolution in Africa. *Science*. 2014 Jun 20;344(6190):1346-8. doi: 10.1126/science.1251546. PMC4138491
    d. de Vries J, Abayomi A, Brandful J, Littler K, Madden E, Marshall P, Ouwe Missi Oukem-Boyer O, Seeley J.A perpetual source of DNA or something really different: ethical issues in the creation of cell lines for African genomics research. *BMC Med Ethics*. 2014 Aug 7;15:60. doi: 10.1186/1472-6939-15-60 PMC4134117

2. Informed consent generally, and consent to biomedical research specifically, has been an important focus of my work for many years. In addition to addressing broad concerns associated with the process of informed consent in clinical and research settings, I have conducted research on knowledge, attitudes and practices associated with consent to genetic research. For example, my research experience includes

being the PI of a four-year continuation NIH-funded R01 grant (completed 2009) to conduct a multi-site international randomized trial of an educational videotape to improve informed consent in genetic epidemiological research in urban and rural Nigeria, Washington, DC, and Cleveland, Ohio. *Selected articles on informed consent are listed below:*

a. Marshall P, Adebamowo C, Adeyemo A, et al. Voluntary participation and informed consent to international genetic research. *Am J Public Health* 2006; 96(11)1989-95. PMC1751828
b. Rotimi C, Marshall P. (2010) Tailoring Informed Consent in Genomic Research. *Genome Medicine* 2010; 2(3):20. PMC2873798
c. Marshall PA, Adebamowo CA, Adeyemo AA, Ogundiran TO, Strenski T, Zhou J, Rotimi CN. Voluntary participation and comprehension of informed consent in a genetic epidemiological study of breast cancer in Nigeria. *BMC Med Ethics*. 2014 May 13;15:38. doi: 10.1186/1472-6939-15-38. PMC4032563
d. Munung NS, Campbell MM, Littler K, Marshall P, Masiye F, Oukem-Boyer OO, Seeley J, Stein DJ, Tindana P, de Vries J, for H3Africa Consortium. Obtaining informed consent for genomics research in Africa: Analysis of H3Africa consent documents. *J Medical Ethics*. 2016 Feb;42(2):132-7. doi: 10.1136/medethics-2015-102796. Epub 2015 Dec 7. PMID: 26644426

3. Genetic/genomic research and health disparities has been a topic of interest to me for many years. My recent investigations have included an NIH-funded ARRA (PI: Marshall) community-based study to explore genetic research and health inequalities with low-income, ethnically-diverse individuals residing in Cleveland (including African Americans), and an NIH-funded study to examine the influence of trust on attitudes toward cancer genomics research. *Selected articles on this topic are listed below:*

a. Sankar P, Cho MK, Condit CM, Hunt LM, Keonig B, Marshall P, Lee SS, Spicer P. Genetic Research and Health Disparities. *Journal American Medical Association* 2004; 291(24):2985-2989. PMC2271142
b. Goldenberg AJ, Harmann CD, Morello L, Brooke S, Solon-Zimmerman K, Marshall PA. Gene-environment interactions and health inequalities: views of underserved communities. *J Community Genet*. 2013 Oct; 4(4):425-34. PMC3773320
c. Goldenberg A, Marshall P, Sharp R. Next-generation disadvantages: identifying potential barriers to integrating genomics into underserved medical settings. *Personalized Medicine* 2013; 10(7)1-3.
d. Hartmann CD, Marshall PA, Goldenberg A. Is There a Space for Place in Family History Assessment? Underserved Community Views on the Impact of Neighborhood Factors on Health and Prevention. J *Primary Prevention*. 2015 Apr;36(2):119-30. PMID: 25663552.

4. I was a Co-Investigator on Dr. Richard Sharp's (PI) NIH funded study to examine patient perceptions of bioengineered probiotics and clinical metagenomics. In this project, I assisted with analysis of qualitative data from focus groups. *Selected articles listed below:*

a. Harrison KL, Geller G, Marshall P, Tilburt J, Mercer M, Brinich MA, Highland J, Farrell RM, Sharp RR. Ethical Discourse about the Modification of Food for Therapeutic Purposes: How Patients with Gastrointestinal Diseases View the Good, the Bad, and the Healthy. *AJOB Prim Res*. 2012 Jul 1;3(3):12-20. Epub 2012 Jun 19. PMC3389757
b. Mercer MB, Brinich MA, Geller G, Harrison K, Highland J, James K, Marshall P, McCormick JB, Tilburt J, Achkar JP, Farrell RM, Sharp RR. How patients view probiotics: Findings from a multicenter study of patients with irritable bowel disease and irritable bowel syndrome. *Journal of Clinical Gastroenterology*. 2012; 46(2):138-144. PMC3202682
c. Harrison KL, Farrell RM, Brinich MA, Highland J, Mercer MB, James K, McCormick JB, Tilburt J, Geller G, Marshall P, Sharp RR. "Someone should oversee it": Patient perspectives on the ethical issues arising with the regulation of probiotics. *Health Expectations* 2015 Apr;18(2):250-61. PMC4022694

5. Reflecting my long standing interest in IRB practices and genetic/genomic research, I worked with a collaborative team from the NIH funded centers of excellence for ethical, social, and legal issues in genetic

and genomic research at Case Western Reserve University and the University of Washington on a study of attitudes of IRB members towards genetic research review. *Selected articles are listed below:*

a. Lemke AA, Smith ME, Wolf WA, Trinidad SB; GRRIP Consortium (with P Marshall). Broad data sharing in genetic research: views of institutional review board professionals. *IRB.* 2011; 33(3):1-5. PMC3394177
b. Edwards KL, Lemke AA, Trinidad SB, Lewis SM, Starks H, Snapinn KW, Griffin MQ, Wiesner GL, Burke W; GRRIP Consortium (with P Marshall). Genetics researchers' and IRB professionals' attitudes toward genetic research review: a comparative analysis. *Genet Med*. 2012; 14(2):236-42. PMC3448270
c. Dressler LG, Smolek S, Ponsaran R, Markey JM, Starks H, Gerson N, Lewis S, Press N, Juengst E, Wiesner GL; GRRIP Consortium(with P Marshall). IRB perspectives on the return of individual results from genomic research. *Genet Med.* 2012; 14(2):215-22. PMC3493147

Additional publications relevant to the topics above and publications reflecting my scholarly work on the cultural foundations of bioethics, my earlier research on organ donation and transplantation in India, and my work with a national team of investigators on an epidemiological and ethnographic study of factors associated with injection drug use are available on request.

D. Research Support

Active:

Co-Investigator:
1 U01 HG008226-01 12/01/14-11/30/17
NIH, National Human Genome Research Institute
PI: Jantina deVries (Cape Town, South Africa)
Title: Stigma in African genomics research on Schizophrenia and Rheumatic Heart Disease
Specific Aims: To conduct focus groups and individual interviews with patients diagnosed with schizophrenia and rheumatic heart disease to explore issues associated with stigma and genomic research.

Private Source 9/1/2012-8/31/2017
PI: Amoah, Albert (Accra, Ghana)
Co-Investigators: Multinational consortium, with *Collaborator,* P Marshall.
Title: Research partnership to assess the burden and aetiology of non-communicable diseases (NCDs) in sub-Saharan Africa (SSA)
Specific Aims**:** To develop a sustainable partnership that will facilitate large-scale, multi-center genetic and genomic research to assess the burden and etiology of diabetes across sub-Saharan Africa (SSA).

Completed:

Principal Investigator
P50-HG-003390-06 8/5/10-7/31/16 (no cost extension) EFFORT
NIH, National Human Genome Research Institute
PI: Patricia A. Marshall, Ph.D., Department of Bioethics, CWRU.
Center for Genetic Research Ethics and Law
Specific Aims: To coordinate and support interdisciplinary research projects examining the ethical and legal issues arising in six kinds of human genetic research: genetic family studies, community-based genetic epidemiology, human genetic variation research, genome-wide scanning research, commercially-based research and research aimed at genetic enhancements. My responsibilities include participation in overall Center activities and directing the project on community engagement in international genetics research.

1RC1HG005789-01 9/25/2009-8/31/2012 EFFORT
NIH, National Human Genome Research Institute
PI: Patricia A. Marshall, PhD

Community Voices on Health Disparities and Translational Genomics Research
Specific Aims: The goals of this study are to examine beliefs and experiences that influence understanding of genomic research and its application to health disparities among underserved and minority populations in Cleveland, Ohio, to identify barriers to genomics research relevant to health disparities.

2R01HG002207-08A1 9/27/2010-8/31/2012
EFFORT
NIH, National Human Genome Research Institute
PI: Patricia Marshall, PhD;
ELSI Issues: Colon Cancer and Cancer Genomics Research
Specific Aims: To describe the effect of being a colon cancer patient, compared to being a patient without a cancer history, on attitudes toward cancer genomics research and willingness to participate in genomics research.

Co-Investigator:

1R01 CA122217-01A1 9/4/07-7/31/12
EFFORT
NIH/National Cancer Institute
PI: Eric Kodish, M.D.
Informed Consent in Pediatric Phase I Cancer Trials
Institution: Cleveland Clinic Lerner College of Medicine-CWRU
The primary goal of this research project is to understand communication, comprehension, and decision-making in Phase I childhood cancer trials.

OVERLAP:
None

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Karen Joann Maschke

eRA COMMONS USER NAME (credential, e.g., agency login) eRA Commons User Name

POSITION TITLE: Research Scholar

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Georgia State University	B.S.	06/1977	Urban Politics
Georgia State University	M.S.	12/1981	Political Science
Johns Hopkins University	Ph.D.	12/1987	Political Science
Case Western Reserve University	M.A.	06/1999	Bioethics

A. Personal Statement

As a researcher with training in political science, legal studies, and bioethics, I focus on policy and ethical issues related to the introduction, use, regulation, and oversight of new biomedical technologies. My work has contributed to institutional and national policy and practice regarding the ethical conduct and oversight of research with human subjects (including genetics/genomic research). I use a variety of social science methods including case studies, legal and policy analysis, and qualitative/quantitative studies. I have extensive experience as a member of collaborative teams engaged in research, writing, developing and holding professional/lay educational sessions and discussion groups, and developing policy and practice recommendations for various stakeholder groups (IRBs; leaders in research, legal affairs, data management, and privacy protections at medical research institutions).

For the proposed research project, “Actionable Ethics Oversight for Human-Animal Chimera Research,” I will build on my work in the areas of institutional and national policy and practice regarding oversight of biomedical research. From 2011-2016, I was a co-Investigator on the NHGRI/ELSI project, “Advancing Collaborative Genetic Research,” an empirical project that examined how institutional officials and genetics researchers interpreted and applied federal regulations and guidance for human subjects research and its oversight. The project also examined written IRB policies to determine whether and how those policies interpreted and operationalized federal regulations and guidance regarding privacy and confidentiality of genetic research data, consent for genetic research, and identifiable and de-identifiable biospecimens and associated data. I also bring to the proposed project my experience as the bioethics member of the NIH Chimpanzee Research Use Panel (2014-2015). I reviewed protocols for NIH-funded research with chimpanzees to determine if they were consistent with the Institute of Medicine’s principles and criteria for biomedical and behavioral research with chimpanzees.

From 2012-2014, I was an ethics consultant to the bioethics program at the Mayo Clinic to help support the bioethics activities of the Mayo Clinic Biobank. In my role as the co-chair of the biobank’s community advisory board (CAB) I helped develop lay-friendly educational materials for CAB members and biobank participants, gave presentations at CAB meetings, and conducted a focus group session with CAB members.

B. Positions and Honors

Positions and Employment

1985–1989	Assistant Professor of Political Science, Oakland University
1989–1996	Assistant Professor of Political Science, University of Georgia
1999–2000	Clinical Bioethics Fellow, Department of Bioethics, Cleveland Clinic
2003	Adjunct Faculty, Department of Political Science, Georgia Highlands Colledge
2003-	Editor, *IRB: Ethics & Human Research*, The Hastings Center
2003-	Research Scholar, The Hastings Center
2009-	Reseach Affiliate, Yale Interdisciplinary Center for Bioethics

Other Experience and Professional Memberships

2016	NIH Grant Review Panel: Precision Medicine Initiative® Cohort Program Biobank (U24)
2014-2015	NIH Chimpanzee Research Use Panel: Bioethics Member
2013	NHGRI Grant Review Panel: Chair. Human Heredity and Health in Africa (H3Africa): Ethical, Legal, and Societal Issues (ELSI) Research Program (U01)
2013	NIH Grant Review Panel: Reviewer. Genomic Sequencing and Newborn Screening Disorders (U19)
2011	NIH Grant Review Panel: Reviewer. The Electronic Medical Records and Genomics (eMERGE) Network, Phase II – Pediatric Study Investigators
2011	NHGRI Grant Review Panel: Reviewer. Development of a Preliminary Evidence Base to Inform Decision-making about Returning Research Results to Participants in Genomic Studies
2010	NHGRI Project, Participant. December 2010-May 2011. Managing Incidental Findings & Research Results in Genomic Biobanks & Archives: NHGRI #2-R01-HG003178, PI: Susan Wolf
2010	Member of grant review panel for proposals submitted to the Congressionally Directed Medical Research Programs (CDMRP) Review Committee for the Fiscal Year 2010 Prostate Cancer Research Program (Impact Award)
2009-2010	Co-Chair, Ethics Subgroup. Cancer Human Biobank (caHUB), Office of Biorepositories and Biospecimen Research, National Cancer Institute
2009	Member of grant review panel for proposals submitted to the Congressionally Directed Medical Research Programs (CDMRP) for the Behavioral and Psychological Health and Operational Health and Performance Program
2009	Member of grant review panel for proposals submitted to the Congressionally Directed Medical Research Programs (CDMRP) for the Fiscal Year 2009 Prostate Cancer Research Program
2008	Member of grant review panel for proposals submitted to the Congressionally Directed Medical Research Programs (CDMRP) for the Fiscal Year 2008 Breast Cancer Research Program

Honors

1980-1983	Fellowship, Political Science Department PhD program. Johns Hopkins University
1988	Summer Fellowship. National Endowment for the Humanities
2000	The Bernard A. Loeschen Pastoral Care Award, for excellence as a teacher, advocate, and ethics consultant. The Cleveland Clinic

C. Contribution to Science

The findings of the ELSI-funded project, “Advancing Collaborative Genetic Research,” identified the lived experience and concerns of researchers and IRB administrators and members regarding ethical challenges related to research with human biospecimens and associated data. I also wrote about ethical and policy challenges regarding proposed and actual governance and oversight approaches for national and institutional biobanks.

a. **Maschke Karen J**. Governance Issues for Biobanks and Biospecimen Research. In: *Specimen Science: Ethics and Policy Implications.* Suzanne M. Rivera, Barbara E. Bierer, and I. Glenn Cohen, eds. Cambridge: MIT Press, forthcoming October, 2017.

b. Rivera SR, Goldenberg A, Rosenthal B, Aungst H, **Maschke KJ**, Rothwell E, Anderson RA, Botkin J, Joffe S. Investigator experiences and attitudes about research with biospecimens. *Journal of Empirical Research on Human Research Ethics* 2015;10(5):449-456. PMCID: PMC4646730

c. Goldenberg AJ, **Maschke KJ**, Joffe S, Botkin JR, Rothwell E, Murray TH, Anderson R, Deming N, Rosenthal BF, Rivera SM. IRB practices and policies regarding the secondary research use of biospecimens. *BMC Medical Ethics* 2015 May 8;16:32. doi: 10.1186/s12910-015-0020-1. PMCID: PMC4426182

d. Rothwell E, **Maschke KJ**, Botkin JR, Goldenberg A, Murray TH, Rivera SM. Biobanking research and human subjects protections: Perspectives of IRB leaders. *IRB: Ethics & Human Research* 2015;37(2):8-13.

As a bioethics consultant to the Mayo Clinic Biobank, I worked with research teams that examined biobank participants' concerns about genomic research data in the medical record, the use of genomic data for personalized medicine, and a biobank's contribution and role in fostering personalized medicine.

a. Kimball BC, Nowakowski KE, **Maschke KJ**, McCormick J. Genomic data in the electronic medical record: Perspectives from a biobank community advisory board. *Journal of Empirical Research on Human Research Ethics* 2014;9(5:16-24.
b. Bielinski SJ, Olson JE, Pathak J, Weinshilboum RM, Wang L, Lyke KJ, Ryu E, Targonski PV, Van Norstrand MD, Hathcock MA, Takahashi PY, McCormick JB, Johnson KJ, **Maschke KJ**, Rohrer Vitek CR, Ellingson MS, Wieben ED, Farrugia G, Morrisette JA, Kruckeberg KJ, Bruflat JK, Peterson LM, Blommel J H, Skierka JM, Ferber MJ, Black JL, Baudhuin LM, Klee EW, Ross JL, Veldhuizen TL, Schultz CG, Caraballo PJ, Freimuth RR, Chute CG, Kullo IJ. Preemptive genotyping for personalized medicine: Design of the right drug, right dose, right time, using genomic data to individualize treatment protocol. *Mayo Clinic Proceedings* 2014;89(1):25-33. PMCID: PMC3932754
c. Olson JE, Ryu E, Johnson KJ, Koenig BA, **Maschke KJ**, Morrisette JA, Liebow M, Takahashi PY, Fredericksen ZS, Sharma RG, Anderson KS, Hathcock MA, Carnahan JA, Pathak J, Lindor NM, Beebe TJ, Thibodeau SN, Cerhan JR. The Mayo Clinic Biobank: A building block for individualized medicine. *Mayo Clinic Proceedings* 2013;88(9):952-962. PMCID: PMC4258707

I was also a participant of a recommendations work group for an ELSI-funded project that developed consensus recommendations for how researchers, biobanks, and research institutions should address a range of ethical challenges related to incidental findings and research results in genomics research.

a. Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, Cho MK, Christman MF, Green RC, Hall R, Illes J, Keane M, Knoppers BM, Koenig BA, Kohane IS, Leroy B, **Maschke KJ,** McGeveran W, Ossorio P, Parker LS, Petersen GM, Richardson HS, Scott JA, Terry SF, Wilfond BS, Wolf WA. Managing incidental findings and research results in genomic research involving biobanks and archived data**.** *Genetics in Medicine* 2012;14(4):361-384. PMCID: PMC3597341

D. Research Support

Ongoing Research Support

Completed Research Support

National Science Foundation, Award No. 1353433 Kaebnick (PI) 07/01/14-06/30/17
Values in Impact Assessment
Role: Co-Investigator

This project examines the values embedded in the formal mechanisms, such as risk assessment and cost benefit analysis, that could be used to assess the impact of emerging technologies, with synthetic biology as a case study. The project aims to refine the understanding of these mechanisms, facilitate their thoughtful use in policy-making, deepen the social debate about synthetic biology, and advance the debate about the values that ought to guide impact assessment for emerging technologies generally. The project sets out three applications of synthetic biology, develops impact assessments for them, and convenes a panel of experts who, collectively, have expertise in synthetic biology, governance of technologies, and the theory and use of impact assessments.

Private Source

Private Source 09/1/15-08/31/16
Consultant and member of the BIG ethics committee. Assisted Le Bonheur's BIG initiative to identify and address the ethical, legal, and policy challenges regarding the development of consent policies and procedures, the return of research results, and community engagement.

NIH/NHGRI, R01 HG005691 Rivera (formerly Cuttler) (PI) 05/26/11-02/28/16
Advancing Collaborative Genetic Research
Role: Co-Investigator
This project examined the human subject protection policies of academic health centers in the NIH's Clinical and Translational Science Awards (CTSA) program that collect, store, use, and share biospecimens and associated data (i.e., biobanking). Variation in policies on core issues such as informed consent to obtain and share biospecimens and/or data can impede or prevent collaborative research. Following an analysis of the range and variation of policies and practices among CTSA institutions for human subject protection in biobanking and the ethical and regulatory issues that frame policies on informed consent and sharing biospecimens/datasets across institutions, the project will develop a set of policy recommendations.

Private Source

Role: Bioethics Consultant; Member, Biospecimen Trust Oversight Group; Member, Private Source Access Committee Member; Co-chair, Community Advisory Board. 2012 - 2014
Provided ongoing ethics consultation on issues related to consent for biobanking research and the return of genomic research results. Collaborator on an empirical study that examined the hopes, concerns, and expectations of Private Source participants who enrolled in a pharmacogenomics study that involves inserting some of participants' genomic research information into their electronic medical record.

National Cancer Institute Biomedical Informatics Grid (caBIG), Data Sharing and Intellectual Capital Workspace
Role: Bioethics Consultant 2007 - 2011
Served as a Subject Matter Expert on the areas of consent, privacy/confidentiality, ethics review, and regulatory frameworks regarding collection, storage and use of human biospecimens and sharing of research data.

NHGRI, R01 HG002579 Murray (PI) 01/01/04-06/30/05
Ethical Decision-making for Newborn Genetic Screening
Role: Project Member
This project focused on the impact of changes in new screening technologies on newborn screening, an on-going public health program that tests virtually all newborns for genetic disorders. The long-term objective was to provide guidance to the professionals, policymakers, and members of the public who must make decisions about newborn screening in this new technological environment.

NIH/NHGRI R25 HG002503 Rothstein (PI) 05/03/02-04/30/05
Education in Genetics Ethics (EDGE)
Role: Faculty Collaborator
The Institute for Bioethics, Health Policy, and Law at the University of Louisville, and collaborators from The Hastings Center, Stanford University Center for Biomedical Ethics, and Michigan State University, developed, and offered a training program in research ethics and human genetics called EDGE, or Education in Genetics Ethics.

OMB No. 0925-0001 and 0925-0002 (Rev. 11/16 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Carolyn P. Neuhaus

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: Research Scholar

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Georgetown University	BA	05/2009	Philosophy
The Graduate Center, CUNY	MA	02/2014	Philosophy
The Graduate Center, CUNY	PhD	06/2016	Philosophy
NYU School of Medicine	Postdoctoral	06/2017	Medical Ethics

A. Personal Statement

I have the expertise, training, and motivation necessary to successfully carry out the proposed research project. I am a young philosopher whose research has focused primarily on genetically modifying non-human organisms for a variety of public health purposes, including genetically modifying laboratory animals to create model organisms, releasing genetically modified insects into the wild to prevent insect-borne diseases, and creating chimeras as part of research to advance xenotransplantation.

Relevant publications include:

1. Neuhaus C.P. (2017). Ethical Issues when modelling brain disorders in non-human primates. *Journal of Medical Ethics* [Epub ahead of print].
2. Neuhaus C.P. & Caplan A.L. (2017). Genome Editing – Bioethics Shows the Way. *PLoS Biology* 15(3):e2001934. PMCID: PMC5354253.
3. Caplan A.L., Parent B., Shen M., & Plunkett [Neuhaus], C. (2015). No Time to Wait – The Ethical Challenges of CRISPR. *EMBO Reports* 16(11): 1421-1426. PMCID: PMC5354253.

I will bring to the proposed project an understanding of the philosophical literature on animals' moral status and use in biomedical research as well as a deep commitment to translating philosophical literature on these topics into clear, actionable recommendations for the oversight of animal research and guidelines for oversight committee members. I was a member of NYU School of Medicine's Institutional Animal Care and Use Committee (IACUC) from July 2016-June 2017, and bring first-hand experience reviewing protocols, as well as in-depth knowledge of IACUC regulations and practice.

This project matches how I envision the role of bioethics in pursuit of responsible science. As I wrote in a recent co-authored commentary: "Bioethics pushes scientists to acknowledge that they operate not within a vacuum but within a society in which diverse perspectives and values must be engaged. Bioethicists give voice to those divergent perspectives and provide a framework to facilitate informed and inclusive discussions that spur progress, rather than stall it" (Neuhaus CP, Caplan AL (2017) Genome Editing: Bioethics Shows the Way. PLoS Biol 15(3): e2001934). Chimera research is stalled in some arenas. The proposed project will look for avenues for the science to continue in an ethically responsible and accountable manner, and to provide

oversight committee members with enough guidance to apply the recommendations consistently. This project fits with my overall approach to bioethics, and how I envision bioethicists' role in promoting responsible science more generally.

Prior to June 2016, I published under the name Carolyn Plunkett.

B. Positions and Honors

Positions and Employment

2011-2014	Graduate Teaching Fellow, City College of New York
2014-2015	Writing Across the Curriculum Fellow, City College of New York
2014-2016	Research Associate, Division of Medical Ethics, NYU School of Medicine
2015- 2017	Co-Director, High School Bioethics Program, NYU School of Medicine
2016-	Adjunct Professor, Einstein-Cardozo Bioethics Education Program, Einstein School of Medicine
2017-	Research Scholar, The Hastings Center

Fellowships

2010-2015	Enhanced Chancellor's Fellowship, The Graduate Center, City University of New York
2013-2017	Ethics Fellowship, The Bioethics Program, Icahn School of Medicine at Mount Sinai
2015-2016	Dissertation Year Fellowship, The Graduate Center, CUNY
2016-2017	Rudin Postdoctoral Fellowship, Division of Medical Ethics, NYU School of Medicine

Other Experiences and Professional Memberships

2010-	Member, New York Society for Women in Philosophy
2013-	Member, American Philosophical Association
2013-	Member, International Neuroethics Society
2013-	Member, American Society for Bioethics & Humanities
2016-	Member, Public Responsibility in Medicine & Research (PRIM&R)
2016-2017	Member, Institutional Animal Care & Use Committee, NYU School of Medicine
2016-2017	Community Member, Ethics Review Committee, Visiting Nurse Services of New York
2016-	Member, Emerging Professionals Working Group, PRIM&R
2017-	Member, Editorial Committee, *Hastings Center Report*

C. Contributions to Science

1. Ethical Analysis of Genetically Modifying Laboratory Animals

My postdoctoral research focused on various issues surrounding genetically modifying non-human organisms for a variety of public health purposes, including as part of biomedical research. Drawing on philosophical frameworks spelling out the necessary conditions of animal research, I have argued that genetically modifying laboratory animals, including non-human primates, can be justified when there is an expectation of producing knowledge that advances important human interests, when that knowledge could not be gained through other means, and when the research does not unjustifiably impede animal welfare. Recent advances in genome editing bring routine editing of larger animals, such as pigs or sheep or dogs, well within reach, but scientists should not use these tools just because they can. Furthermore, public input is needed to determine what forms of knowledge advance human interests, that is, what we ought to learn and ought to know. This is a central pillar of ethical animal use.

a. Neuhaus C.P. (2017). Ethical Issues when modelling brain disorders in non-human primates. *Journal of Medical Ethics* [Epub ahead of print].

b. Neuhaus C.P. & Caplan A.L. (2017). Genome Editing – Bioethics Shows the Way. *PLoS Biology* 15(3):e2001934. PMCID: PMC5354253.
c. Neuhaus C.P. (2016). Get the Public Involved in Chimera Research at NIH. *Bioethics.net*, published online 15 Aug.
d. Caplan A.L., Parent B., Shen M., & Plunkett [Neuhaus], C. (2015). No Time to Wait – The Ethical Challenges of CRISPR. *EMBO Reports* 16(11): 1421-1426. PMCID: PMC5354253.

2. Ethical Analysis of Issues Surrounding the Release of Genetically Modified Insects

My postdoctoral research focused on various issues surrounding genetically modifying non-human organisms for a variety of public health purposes, including genetically modifying moths to prevent blights to plants and genetically modifying mosquitoes to prevent malaria, dengue fever and other mosquito-borne illnesses, including through the use of gene drives. Following on increasing calls for public engagement ahead of releasing genetically modified (GM) insects, my research critiques current public engagement mechanisms and defends the philosophical framework for redesigning public engagement strategies ahead of GM insect releases. I defend the notion of "community authorization" to field trials of GM insects and animals and make practical suggestions about how to educate people about genetic technologies and incorporate them into the research design and oversight process.

a. Unpublished

b. Neuhaus, C.P. & Caplan A.L. (2017) Ethical lessons from a tale of two genetically modified insects. *Nature Biotechnology* 35(8):713-716.
c. Neuhaus C.P. & Caplan A.L. (2017). Genome Editing – Bioethics Shows the Way. *PLoS Biology* 15(3):e2001934. PMCID: PMC5354253.
d. Caplan A.L., Parent B., Shen M., & Plunkett [Neuhaus], C. (2015). No Time to Wait – The Ethical Challenges of CRISPR. *EMBO Reports* 16(11): 1421-1426. PMCID: PMC5354253.

3. Ethical Analysis of Animal Use in Biomedical Research

Following on an interest in genetically modifying animals for a variety of purposes, I have recently been grappling head on with the justification for the use of animals in biomedical research and structural obstacles to meeting the conditions of ethically justified research. Papers in progress critique the condition of ethically justified research that requires research involving animals to produce net benefits to humans. For epistemic, practical, and ethical reasons, I propose rearticulating the expectation of net benefit as the expectation of knowledge production, which requires both that the research tests a hypothesis that, whether proved or disproved, advances an important human interest, and that the research can and will be performed to the highest standards of research integrity.

a. Unpublished

b.

c. Neuhaus, C.P. (2017). Reflections on Voracious Science, Vulnerable Animals. *Ampersand: The PRIM&R Blog*, published online 18 Jul.

4. Ethical Analysis of Various Issues in Clinical Trial Design

I have explored various ethical issues that come in the context of designing a clinical trial and choosing a study population. Work on designing a clinical trial in the context of Ebola calls for flexibility in research methodology tailored to what is feasible and acceptable to the study population. Work on clinical trial design for CRISPR-mediated gene therapies calls for careful attention to the study population enrolled and, again for flexibility in trial design owing to a lack of clinical equipoise in many cases. And finally, work on research on anorexia nervosa calls for enrolling teenagers in ongoing research, on the grounds that the benefits of research ought to extend to teenagers, who make up the majority of persons with anorexia nervosa. Categorically excluding

teenagers from research on the disease further disenfranchises the population from the benefits of research. In my writing and presentations on research ethics, I always draw attention to the ethical trade-offs required when balancing respect for persons who take part in research and the ethical requirement that research produce generalizable knowledge.

a. Neuhaus C.P. (2016). Teens and Research: Should adolescents be enrolled in trials of deep brain stimulation for anorexia nervosa? *Cambridge Quarterly of Healthcare Ethics* 25(4): 659-673.
b. Caplan A.L., Parent B., Shen M., & Plunkett [Neuhaus], C. (2015). No Time to Wait – The Ethical Challenges of CRISPR. *EMBO Reports* 16(11): 1421-1426. PMCID: PMC5354253.
c. Caplan A.L., Plunkett [Neuhaus], C., & Levin B. (2015). The Perfect Must Not Overwhelm the Good: Response to Open Peer Commentaries on "Selecting the Right Tool for the Job". *American Journal of Bioethics* 15(4): W8-W10.
d. Caplan A.L., Plunkett [Neuhaus], C., & Levin B. (2015). Selecting the Right Tool for the Job. *American Journal of Bioethics* 15(4): 4-10.

5. Ethical Analysis of the Use of Deep Brain Stimulation in Research and Clinical Practice

Deep brain stimulation challenges our understanding of the self and the role of the emotions in producing the self. My work on deep brain stimulation has explored philosophical questions surrounding the nature of the self, and the relationship between the self and the brain.

a. Neuhaus C.P. (2016). Teens and Research: Should adolescents be enrolled in trials of deep brain stimulation for anorexia nervosa? *Cambridge Quarterly of Healthcare Ethics* 25(4): 659-673.
b. Plunkett [Neuhaus], C. (2015). Widening the use of deep brain stimulation: Ethical considerations in research on DBS to treat anorexia nervosa. *The Neuroethics Blog*, published online 24 Nov.
c. Plunkett [Neuhaus], C. 2013. Can unwilling addicts provide informed consent to ongoing deep brain stimulation of reward centers? *American Journal of Bioethics – Neuroscience* 4(2): 52-4.

D. Additional Information: Research Support and/or Scholastic Performance

OMB No. 0925-0001 and 0925-0002 (Rev. 11/16 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Mildred Z. Solomon

eRA COMMONS USER NAME (credential, e.g., agency login): eRA Commons User Name

POSITION TITLE: President, The Hastings Center and Professor (part-time), Harvard Medical School

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Smith College, Northampton, MA	B.A.	1971	English Literature
University of Newcastle-upon-Tyne, UK	Dipl. Ed.	1976	Drama-in-Education
Harvard University, Cambridge, MA	EdD	1991	Human Development, Adult Learning & Educational Research Methods

A. Personal Statement

I am a social science researcher who studies ethical issues in medicine and health care, focusing on areas where there is moral uncertainty, political controversy and ambiguous evidence. Using both quantitative and qualitative methods, my research has contributed to education, policy, and practice on a national and international scale in adult and pediatric end-of-life care, organ donation, pain management, sexually transmitted disease prevention, protection of human research participants, and promotion of evidence-based health care.

I have had a lifelong commitment to ensuring that research informs practice and policy. Thus, in addition to carrying out research studies, I have gone on to build lasting organizations and international initiatives, that have sustained themselves well beyond the initial grant period. For example, early in my career, I studied how various stakeholders (physicians, nurses, lawyers and bioethicists) viewed end-of-life decisions about the use of life support. Our group's findings revealed major concerns of conscience and disconnections across groups. As a result, we were able to develop a professional education program that reflected the views of these stakeholders; it has been used across more than 200 U.S. hospitals by 40,000 clinicians and translated into German for use in Germany and Switzerland. Similarly, I studied and then developed *PainLink*, a professional education intervention to enhance pain management, used in 50 hospitals. Most recently, I worked with leaders in academia and industry to create more transparent and effective global standards for the responsible conduct and ethical oversight of clinical trials in the developing world. Based on our group's preliminary research, I then organized more than 10 work groups that outlined new standards and developed content for training principal investigators, researchers and community advisory boards. We then created the Multiregional Clinical Trials project, which is now a university-industry partnership based at Brigham and Women's Hospital and Harvard Medical School, with hundreds of researchers in communities worldwide, working to improve human subjects protection.

In 2010, I was recruited by the Association of American Medical Colleges to help build the capacity of academic medical centers in implementation science and comparative effectiveness research. Basic bench research has high prestige in these institutions, while more applied science that could speed the uptake of evidence-based medicine is neglected. I began by undertaking a qualitative research study of 75 leaders of academic medical centers to learn their views about incentives and barriers. Based on

those findings, the AAMC enabled me to establish a program called Research on Care Community (ROCC). Today there are well over 200 systems participating in this network, which shares best practices and policies for adopting evidence-based medical practices, particularly through implementation science and comparative effectiveness research.

I have been directly involved in national and international policy making in a number of ways. I sat on the U.S. Secretary of Health and Human Services' Federal Advisory Committee on Organ Transplantation. I was also a member of a National Research Council, National Academies of Science committee, charged with enhancing biosecurity and safety in chemical labs in developing countries. Currently, I sit on the Global Health Advisory Council of the Open Society Foundations, where I advise on grantmaking priorities and global health policy. I recently consulted to the Aspen Institute's Health Strategies Group, which is a bipartisan effort (co-chaired by former Secretaries Kathleen Sibelius and Tommy Thompson) to address seemingly intractable health policy problems. And I am now in the middle of a two-year term as a member of the Global Futures Council on Technology, Values and Policy of the World Economic Forum.

I am the president of The Hastings Center, I am also a professor (part-time) and founding core faculty at the Center for Bioethics at Harvard Medical School, where I direct a fellowship program in bioethics for Harvard teaching hospitals. I have directly mentored 165 fellows over the 15 years that I have directed this program.

At The Hastings Center, in addition to my leadership of the organization, I have continued my own scholarship. I am a co-investigator on a current RO1 funded by the National Human Genome Research Institute on policies and practices for next generation prenatal testing. The findings from this project, expected in early 2018, will situate our team at Hastings for the next step: namely, building a lasting institutional structure, much like a federal advisory committee. Our goal is to fill an important governance gap in how best to use the next generation of noninvasive prenatal tests, which have the power to transform what is known about fetal health and how pregnancy will be experienced by millions of prospective parents.

I am also very engaged in the study of other emerging biomedical technologies, including genome modification in humans and in non-human animals and plants. I look forward to the opportunity to use my leadership skills and past experience building successful team initiatives,accessible, meaningful policy and educational resources for scientists, clinicians, and the public on a wide variety of 21st century challenges related to breathtaking advances in science

B. Positions and Honors

Employment

1987-1996	Senior Scientist, EDC. Conceptualization, fiscal and admin mgmt of numerous research and curriculum development projects. Oversaw budgets exceeding $11 million
1997-2010	Director, EDC's Center for Applied Ethics and Professional Practice
2002-2010	Vice President, Education Development Center, $120 million nonprofit R & D organization
2010-5/2012	Senior Director for Implementation Science, Association of American Medical Colleges
2002-Present	Professor of Anaesthesia & Medical Ethics (part-time) & Director HMS Fellowship in Bioethics, Harvard Medical School, Boston, MA
2004-2012	Director of Clinical Research, Division of Medical Ethics, Harvard Medical School
6/2012 –Present	President, The Hastings Center, Garrison, NY

Other Experience and Professional Memberships (Selected)

1993-present	Member 7 Hastings Center Task Forces: e.g. "Clinical Care and the Law," "Cultural Diversity End of Life Care," "Choices in Health Care Decisionmaking," "End-of-Life Care Guidelines 2"
1996-1999	Co-chair, RWJ Fdn, Last Acts Providers' Task Force on End-of-Life Institutional Change
1999-2000	Consultant, Institute of Medicine Committee on Non-Heart beating Organ Donation
2001-2002	Consultant, Institute of Medicine Committee on Pediatric Palliative Care
2004-Present	Member, U.S. Secretary of HHS' Advisory Committee on Organ Transplantation

2008 Consultant, Open Society Foundations' Law and Health Initiative on Human Rights in the Health Care Systems of Eastern Europe
2008 Consultant, National Academies of Sciences, National Research Council, Committee on Safety and Biosecurity in Life Science Laboratories
2008 Adviser, U.S. Holocaust Memorial Museum. On development of professional education programs for government leaders, the military and police on human rights and civil liberties.
2008 Consultant, *The National Research Council of the National Academies of Science to the* Committee, "Dual Use Research in the Life Sciences."
2008 Consultant, *Open Society Foundations, Human Rights and Patient Care Task Force*. Promoting human rights and patient-centeredness within health care systems of Eastern Europe and southern and eastern Africa.
2008 Member, National Academies of Science, National Research Council, Committee on Safety and Biosecurity in Chemical Laboratories in Developing Countries
2015 - 2016 Member, Global Health Advisory Committee, Open Society Foundations
Adviser to Aspen Institute, Aspen Health Strategies Group

Honors

1986 Silver Award, Houston International Film Festival, for human sexuality films
1995 Assoc of Academic Health Centers for Outstanding Contribution to Public Health & Med Ed
1997 Anne Frank Named Lectureship, University of Basel Bioethics Center, Basel Switzerland
2008 Elected Fellow of The Hastings Center
2016 World Economic Forum, Member, Global Futures Council on Technology, Values and Policy

C. Contributions to Science

My first empirical ethics study (a national survey, clinician interviews and focus groups) revealed barriers to achieving the idealized model of decision making near the end of life, espoused in national ethical and legal recommendations. Our findings brought physicians' views to the attention of bioethicists and bioethicists' views to the attention of physicians and resulted in a widely used professional education program. See, for example:

- **Solomon, MZ**, O'Donnell, L, Jennings B et al., Decisions near the end of life: Health care professionals' views on the use of life-sustaining medical treatments. *American Journal of Public Health* 1993 Jan; 83(1): 1 – 23
- **Solomon MZ**. How physicians talk about futility: Making words mean too many things. *Law, Medicine and Health Care* 1993; 21(2): 231 – 237.

I have continued to write on end-of-life policy over the course of my career. Recent examples include:

- Blinderman CD, Krakauer EL and **Solomon MZ**. Time to revise the approach to determining cardiopulmonary resuscitation status. *JAMA* 2012 March; 37(9): 917-918
- **Solomon MZ**. Modern dying: From securing rights to meeting needs. *Annals of NY Academy of Sciences*. November 2014; 1330(1): 105-110.
- **Solomon, MZ.** On patient wellbeing and physician authority. *Hastings Center Report* 47, no.1 (2017):26 – 27.

With AHRQ funding, I studied cancer pain, which provided insights into the paradox of why patients who report high levels of pain also report high levels of patient satisfaction. See for example:

- Dawson R, Spross JA, Jablonski ES, Hoyer DR, Sellers DE, and **Solomon MZ**. Probing the paradox of patient satisfaction with inadequate pain management. Journal of Pain and Symptom Management 2002; 23(3): 211 – 20.
- Dawson R, Sellers DE, Spross JA, Jablonksi ES, Hoyer DR and **Solomon MZ**. Do patients' beliefs act as barriers to effective pain management behaviors and outcomes in cancer patients with cancer-related or non-cancer pain? *Oncology Nursing Forum*, 2005; Mar 5; 32(2):363 – 74.

For over a decade, I served as principal investigator of a project devoted to understanding and improving pediatric palliative care. We published extensively, including for example:

- **Solomon MZ**, Sellers DE, Heller KS, Dokken D., Levetown M, Rushton C, Truog RD and Fleischman AR. New and lingering controversies in pediatric end-of-life care. *Pediatrics* 2005; 116: 872-883.
- Meyer EC, Sellers DE, Browning DM, McGuffie K, **Solomon MZ**, and Truog RD. Difficult conversations: Improving communication skills and relational abilities in health care. *Pediatric Critical Care Medicine* 2009; 10(3): 352 - 9.
- **Solomon MZ,** Browning D, Dokken D, Merriman M and Rushton C. Learning that Leads to Action: Impact and Characteristics of a Professional Education Approach to Improve the Care of Critically Ill Children and Their Families. *Archives of Pediatric and Adolescent Medicine* 2010 April; 164(4): 315 – 22.

I have also written on the importance of implementation science and comparative effectiveness research, on the challenges to providing ethical oversight for these kinds of studies, and the unsettled nature of evidence. For example:

- **Solomon MZ**. The ethical urgency of advancing implementation science. *American J of Bioethics* 2010 Aug; 10(8): 31 – 2.
- Bonham AC and **Solomon MZ**. Moving comparative effectiveness research into practice: Implementation science and the role of academic medicine. *Health Affairs* 2010 Oct; 29(1):1901 – 1905.
- Fleischman AR and **Solomon MZ**. Comparative effectiveness research: Ethical and regulatory guidance. *JAMA Pediatrics* 2014; 168(12): 1089-1090.
- **Solomon MZ**, Gusmano MK and Maschke K. The Ethical Imperative and Moral Challenges of Engaging Patients and the Public with Evidence. *Health Affairs* 2016; *35*(4): 583-589.

D. Additional Information: Research Support

I have been the PI on 17 grants and a co-investigator on 7. Examples include:

NIH-NCRR-funded Infrastructure Grant for Harvard Clinical and Translational Science Center
(Grant# UL1RR025758 (Nadler, principal investigator) 2008 – 2013
This CTSA grant supported CATALYST, the Harvard-wide CTSC which promotes clinical and translational research from bench to bedside to community. I sat on the ethics subgroup of CATALYST. Responsible for developing scholarly work and education related to the ethics of human research participation in translational research.
Role: Co-Investigator
National Institute of Child Health and Human Development. (Grant#1 R01 HD050463-02)
Promoting Self-Management: Cystic Fibrosis as a Model Case 2007-2010
Role: Co-Investigator
National Institute of Nursing Research (Grant #1 R01 NR00928-03)
Toward Optimal End-of-Life Care in the PICU 2005-8/2009
This project examined the quality of end-of-life care and the quality of dying and death in the pediatric intensive care setting through interviews with clinicians and bereaved parents and chart audits in 7 children's hospitals.
Role: Co-Investigator
National Heart Lung and Blood Institute (Grant # 1 R01 HL072938-05)
Quality of Life in Advanced CF in a Transplantation Era 2003-2009
This longitudinal study followed the first generation of patients with cystic fibrosis to survive into adulthood. Goal was to discover needs and experiences of patients families and caregivers to improve quality of life.
Role: Co-Investigator
Office of Science Education and the Clinical Bioethics Center
at the National Institutes of Health. 2006-8/2009
Developed and fieldtested a bioethics curriculum supplement on ethical issues in the life sciences, which the NIH has disseminated to 12,000 high school biology classrooms across the nation.

Role: Principal Investigator/Project Director

eRA Commons User Name

eRA Commons User Name

1999-7/2008

This project encouraged a family-centered approach to the care of children living with life-threatening conditions. Needs assessment included a survey of nearly 2000 clinicians in 7 children's hospitals, interviews with parents and clinicians, and an expert advisory group which identified quality domains for improving care. Findings informed development of a 6-module curriculum with 30 hours of instructional materials and six award-winning videos;1000 clinicians trained.

Role: Principal Investigator

National Cancer Institute (GRANT R01 CA089521) 2002-2007

Factors Influencing the Use of Cancer Genetics by Physicians

This study identified primary care physician (PCP) needs for education in cancer genetics. Included: 1) In-depth interviews to document PCP understanding of cancer genetics opportunities they saw for enhancing cancer family history-taking; 2) a survey of PCPs in three types of practice settings to provide a generalizable assessment of their cancer genetics knowledge.

Role: Co-Investigator

Health Resources and Service Administration (GRANT 1 H39 OT 00016-01) 2000-2002

Increasing Organ Donation by Enhancing End-of-Life Care

Evaluation of a multi-faceted intervention that created a clinical pathway to ensure “timely referral” of patients with severe neurological injury, and activated a Family Support Team. Referral of medically suitable potential donors increased from 81% to 99% at pilot (N=3) versus 87% to 94% at comparison hospitals (N=17). Consent rates stayed stable.

Role: Principal Investigator

Agency for Healthcare Research and Quality/National Cancer Institute (GRANT RO1 HS08691)

Cancer Pain Relief in a Managed Care Setting 1996-2002

This group-randomized trial evaluated a dissemination strategy to reduce pain among cancer patients. Intervention encouraged adoption of routine procedures for pain screening and assessment and 2) provided education to improve opioid knowledge and prescribing confidence. Evaluation data included 1733 interviews with 791 patients, clinician surveys, and prescription records. Treatment clinic clinicians prescribed more opioids than those in control clinics and demonstrated increased knowledge and opioid prescribing self-efficacy, but patients in the treatment clinics did not report better pain outcomes. Results suggested that institutional mandates rather than voluntary adoption of new procedures may be required.

Role: Principal Investigator

National Human Genome Research Institute (NHGRI) at NIH (GRANT 1R01-HG008805) 2015-2018

Goals and Practices for Next Generation Prenatal Testing.

Approximately 4 million women give birth in the US each year. A new generation of prenatal genetic tests is revolutionizing the amount of information available about fetal health. These tests, including new noninvasive tests available for use early in pregnancy, are becoming an ever more routine part of prenatal care, yet there is virtually little to no guidance about which tests should be performed and whether or how information should be shared with prospective parents. This project has convened an interdisciplinary group of experts and stakeholders, including – for example - patient advocates, bioethicists, clinicians, historians of medicine, practice leaders from the National Institute for Child Health and Development (NICHD), the American College of Obstetrics and Gynecology, the Association for Reproductive Medicine and The Genetic Alliance. The project is producing analysis and recommendations regarding what values and principles should guide decisions about what should be tested for and how such testing should be offered, integrated into clinical care, and supported by public policy.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0766726090000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The Hastings Center

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Josephine	Marguerite	Johnston		PD/PI	Institutional Base Salary	EFFORT			43,586.55	12,204.23	55,790.78
2 .		Karen		Maschke	PhD	PD/PI					30,869.24	8,643.39	39,512.63
3 .		Carolyn		Neuhaus	PhD	Co-Investigator					20,447.95	5,725.43	26,173.38
4 .		Mildred		Solomon	PhD	Co-Investigator					3,740.00	1,047.20	4,787.20

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **126,263.99**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical	EFFORT					
1	Research Assistant				10,888.97	3,048.91	13,937.88
1	**Total Number Other Personnel**					**Total Other Personnel**	**13,937.88**
						Total Salary, Wages and Fringe Benefits (A+B)	**140,201.87**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0766726090000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: The Hastings Center

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	3,542.25
2. Foreign Travel Costs	
Total Travel Cost	**3,542.25**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0766726090000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: The Hastings Center

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	182,710.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Journal articles	1,000.00
Total Other Direct Costs	**183,710.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**327,454.12**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	62.60	169,744.10	106,259.80
		Total Indirect Costs	**106,259.80**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Regina DiGennaro, 212-264-2069

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**433,713.92**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-BudgetJustification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0766726090000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The Hastings Center

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Josephine	Marguerite	Johnston		PD/PI	Institutional Base Salary	EFFORT			44,458.28	12,448.32	56,906.60
2 .		Karen		Maschke	PhD	Pd/PI					31,486.62	8,816.25	40,302.87
3 .		Carolyn		Neuhaus	PhD	Co-Investigator					20,856.90	5,839.93	26,696.83
4 .		Mildred		Solomon	PhD	Co-Investigator					9,350.00	2,618.00	11,968.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **135,874.30**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical	EFFORT					
1	Research Assistant				11,106.75	3,109.89	14,216.64
1	Administrative Assistant				2,646.33	740.97	3,387.30
2	**Total Number Other Personnel**					**Total Other Personnel**	**17,603.94**
						Total Salary, Wages and Fringe Benefits (A+B)	**153,478.24**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0766726090000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: The Hastings Center

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	42,641.20
2. Foreign Travel Costs	
Total Travel Cost	**42,641.20**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0766726090000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: The Hastings Center

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	184,420.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Journal articles	1,000.00
9 . Honoraria	21,000.00
10 . Meeting Expense	6,966.00
Total Other Direct Costs	**213,386.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**409,505.44**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	62.60	225,085.44	140,903.48
		Total Indirect Costs	**140,903.48**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**550,408.92**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-BudgetJustification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0766726090000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: The Hastings Center

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Josephine	Marguerite	Johnston		PD/PI	Institutional Base Salary	EFFORT			45,347.44	12,697.28	58,044.72
2 .		Karen		Maschke	PhD	Co-PD/PI					32,116.36	8,992.58	41,108.94
3 .		Carolyn		Neuhaus	PhD	Co-Investigator					21,274.04	5,956.73	27,230.77
4 .		Mildred		Solomon	PhD	Co-Investigator					18,700.00	5,236.00	23,936.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **150,320.43**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	EFFORT			11,328.88	3,172.09	14,500.97
1	Administrative Assistant				2,699.25	755.79	3,455.04
1	Director of Communications				4,320.72	1,209.80	5,530.52
1	Director, Editorial Dept				4,756.17	1,331.73	6,087.90
1	Managing Editor				2,694.93	754.58	3,449.51
1	Art Director				2,274.11	636.75	2,910.86
6	**Total Number Other Personnel**					**Total Other Personnel**	**35,934.80**

Total Salary, Wages and Fringe Benefits (A+B) **186,255.23**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0766726090000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: The Hastings Center

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	21,321.60
2. Foreign Travel Costs	
Total Travel Cost	**21,321.60**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0766726090000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: The Hastings Center

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	35,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	128,853.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Journal articles & production, printing, art licenses	6,800.00
9 . Honoraria	21,000.00
10 . Meeting Expense	3,483.00
Total Other Direct Costs	**195,136.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**402,712.83**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	62.60	273,859.83	171,436.26
		Total Indirect Costs	**171,436.26**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**574,149.09**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-BudgetJustification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12490267
Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

BUDGET JUSTIFICATION

Personnel

The following table summarizes the percentage of time dedicated to this project by staff members at The Hastings Center across the three years:

Name	**Year 1**	**Year 2**	**Year 3**
Karen Maschke, PhD	EFFORT	EFFORT	EFFORT
Josephine Johnston			
Carolyn Neuhaus, PhD			
Mildred Solomon, EdD			
Elizabeth Dietz			
Vicki Peyton			
Susan Gilbert			
Gregory Kaebnick, PhD			
Laura Haupt			
Nora Porter			

Josephine Johnston, JD, MBHL, Principal Investigator. Ms. Johnston will share overall project responsibility with PIs Maschke and Hyun. She will co-lead (with Maschke and Hyun) the activities for the Policy Review, Conceptual Analysis, and Synthesis components of the project. She will work jointly with Maschke and Hyun to: (1) develop agendas and background materials for PI conference calls and in-person meetings and for WG conference calls and in-person WG meetings, (2) identify the specific facts, questions, issues, or arguments for WG members to address in their presentations, (3) facilitate and lead sessions at WG meetings, (4) oversee the fiscal and administrative management of the project, (5) supervise the work of the RAs, (6) develop any required progress reports, (7) develop and deliver professional presentations about the project's findings, and (8) develop and write manuscripts for publication. Ms. Johnston will work with PIs Maschke and Hyun and the Co-Investigators to develop the projects' recommendations. Ms. Johnston will lead the WG review of the project's recommendations and will work with PIs Maschke and Hyun and Co-Investigator Solomon to develop the project's educational materials, including a Protocol Casebook. Ms. Johnston is designated as the overall project contact person.

Karen Maschke, PhD, Principal Investigator. Dr. Maschke will share overall project responsibility with PIs Johnston and Hyun. She will co-lead (with Johnston and Hyun) the activities for the Policy Review, Conceptual Analysis, and Synthesis components of the project. She will work jointly with Johnston and Hyun to: (1) develop agendas and background materials for PI conference calls and in-person meetings, and for WG conference calls and in-person WG meetings, (2) identify the specific facts, questions, issues, or arguments for WG members to address in their presentations, (3) facilitate and lead sessions at WG meetings, (4) oversee the fiscal and administrative management of the project, (5) supervise the work of the RAs, (6) develop any required progress reports, (7) develop and deliver professional presentations about the project's findings, and (8) develop and write manuscripts for publication. Dr. Maschke will work with PIs Johnston and Hyun and the Co-Investigators to develop the projects' recommendations and will work with PIs Johnston and Hyun and Co-Investigator Solomon to develop the project's educational materials, including a Protocol Casebook. She will lead the Research Team's development of a Special Report of the *Hastings Center Report*.

Carolyn Neuhaus, PhD, Co-Investigator. Dr. Neuhaus will share in the intellectual and administrative work for the Policy Review, Empirical Investigation, and Synthesis components of the project, including co-leading the Conceptual Analysis activities. She will assist the PIs in (1) developing agendas and background materials for WG conference calls and in-person WG meetings, (2) identifying the specific facts, questions, issues, or arguments for WG members to address in their presentations, (3) facilitating and leading sessions at WG meetings, (4) developing the projects' recommendations, and (5) and developing other work products, including professional presentations about the project's findings, and manuscripts for publication.

Mildred Solomon, EdD. Dr. Solomon will share in the intellectual work for the Policy Review, Empirical Investigation, and Synthesis components of the project and in developing the projects' recommendations and

other work products, including manuscripts for publication. She will lead the development of the project's educational materials, aimed at scientists, members of ESCRO committees and IACUCs, and trainees.

Elizabeth Dietz, Research Assistant. The Research Assistant will work under the supervision of Ms. Johnston and Dr. Maschke throughout the project. The primary responsibility for the Research Assistant will be to support the research team by assisting with research and development of agendas and background materials for PI conference calls and in-person meetings, and for WG conference calls and in-person WG meetings, (2) taking notes at all conference calls and in-person meetings and from the notes developing for the PIs summaries and action items from those meetings, (3) assisting the PIs in obtaining and reviewing relevant ESCRO committee and IACUC policies for human-animal chimera research, and (4) providing on-going research assistance for the literature review and analysis throughout the 3-year project.

Vicki Peyton, Administrative Assistant. Ms. Peyton will work under the supervision of Ms. Johnston and Dr. Maschke in years two and three of the project. She will be responsible for all logistical planning for the Work Group meetings, including coordinating travel for all Work Group members, managing all meeting space logistics, coordinating all the meals, and compiling and distributing all background readings. Ms. Peyton will process and manage payment of all honoraria and all travel reimbursements.

Susan Gilbert, Director of Communications. In year three, Ms. Gilbert will develop a series of press releases about the project findings, which will be sent to our database of more than 4,000 health and health policy journalists (newspapers, magazines, TV, radio, and leading online publications), as well as relevant professional organizations. She will also manage other communications activities such as disseminating information about the project and its findings in one or more issues of the weekly *Hastings Center News* and through Hastings' Twitter and Facebook social media platforms.

Gregory E. Kaebnick, PhD, Director, Editorial Department. Gregory E. Kaebnick is editor of the *Hastings Center Report* as well as a scholar at The Hastings Center. He is the editor of *The Ideal of Nature: Debates about Biotechnology and the Environment* (John Hopkins, 2011), and a co-editor of *Synthetic Biology and Morality: Artificial Life and the Bounds of Nature* (MIT Press, 2013). During year 3 of the project, Dr. Kaebnick will coordinate the editorial and production activities related to publication of the *Hastings Center Report* supplement.

Laura Haupt, Managing Editor. Laura Haupt is the managing editor of the *Hastings Center Report*. As such, she coordinates peer review, serves as liaison with authors during the production process, and copyedits and proofreads all material appearing in the *Hastings Center Report*, including supplements. During year 3 of the project, Ms. Haupt will serve in this capacity for publication of the supplement.

Nora Porter, Art Director. Nora Porter's role in the publication of the special supplement is to design and lay out the publication, select and acquire any artwork or illustrations for the piece, and oversee the printing of the publication. Her work will take place in year 3 of the project. Ms. Porter is the Hastings Center's Art Director. She is responsible for design and production of all printed matter at the Hastings Center, including the Center's journals, the *Hastings Center Report* and *IRB: Ethics & Human Research*.

COLA
2% year-over-year cost of living increase is built into the salaries. We understand that this may not be approved.

Fringe
The Hastings Center's fringe rate of 28% applies to all staff and covers all employee benefits, including payroll taxes, health insurance, worker's compensation, unemployment insurance, and pension contributions.

Travel Costs
Estimated travel budgeted for year one:

Travel is budgeted for 3 staff members to attend a team meeting in Cleveland, OH	
Airfare/Train -	3 staff x $500 = $1,500
Ground transportation	3 staff x $400 = $1,200 to/from the Garrison to airport
Lodging	3 staff x 1 night @ $160 = $480
Per diem Meals	3 staff x 1 day of meals @ $69 per day = $207
Per diem Meals	3 staff x 1 travel day of meals @ $51.75 per day = $155.25

Meeting Expense
There will be two workgroup meetings in year two and one workgroup meeting in year three to take place in Garrison, NY. The following table estimates the cost of each meeting:

Airfare	13 participants x $500 = $6,500
Mileage	8 participants will travel by car. Total of 2360 miles x $.535 per mile = $1,262.60
Ground transportation	13 participants x $400 to/from the airport to Garrison = $5,200
Ground transportation	21 participants x $120 for 3 trips to/from hotel to Hastings Center = $2,520
Lodging	21 participants x $139 x 2 nights = $5,838

In addition, the following expenses will be incurred for each of the three meetings. There will be 21 invited participants, 4 Hastings Center staff, and 2 Case Western staff.

Breakfast	27 participants x $12 x 2 days = $648
Breaks	27 participants x $5 x 3 = $405
Lunch	27 participants x $15 x 2 nights = $810
Dinner	27 participants x $60 x 1 day = $1,620

Other Expenses
20 journal articles will be purchased for $50 per article for a total of $1,000 each year.

In year three, the following costs will be incurred in the production of The Hastings Center Report Special Supplement. Production, printing and distribution are estimated at $5,000. Art licenses will be purchased at a cost of $300. A fee of $500 will be incurred for 500 additional hard copies of the report.

Consultant Costs
The project will complete a set of educational materials to assist members of ESCRO committees and IACUCs in interpreting key concepts and guidelines, and equip them for protocol reviews. Versions of these materials will also be developed for scientists and for the general public. One of the educational products we are envisioning would be a casebook of protocols, representing a range of the kinds of chimeric research likely to come to ESCRO committees and IACUCs with commentary on the key issues they raise and how to approach review of them. Other products will include descriptions of the recommendations with annotated reasons behind them. Mildred Solomon, who holds a doctorate in education and was a curriculum developer for many years, has a track record of developing a wide variety of educational materials on numerous ethics topics. She will conceptualize the overall approach and oversee the writing of these materials. We have budgeted $30,000 for a consultant to work with her drafting the material. We have a pool of such consultants we can draw upon, with whom both Hastings and Dr. Solomon have worked on numerous educational programs. The graphic design funds of $5,000 are essential for design and visual appeal of the materials.

Honoraria
In year two, 21 workgroup members will receive $500 to attend each of the workgroup meetings for a total of $21,000. In year three, 21 workgroup members will receive $1,000 to prepare and attend the third workgroup meeting and to participate in final recommendations development by one or more conference calls after the third workgroup meeting for a total of $21,000.

Subcontractor Costs
Case Western University
The Hastings Center will contract with Case Western University for the following personnel in addition to other direct costs included in Case Western's budget justification.

Insoo Hyun, PhD (Co-PD/PI, EFFORT of effort and salary support requested for three years). Dr. Hyun is Associate Professor of Bioethics at Case Western Reserve University School of Medicine. Dr. Hyun will be responsible for administrative management of the project and overall coordination of research activities. He will conduct in-depth reviews of institutional policies for chimera research across each of the institutions involved in the study, obtain informed consent, and help conduct 60 qualitative interviews. He will also help draft recommendations for the chimera research guidebook.

Patricia Marshall, Ph.D. (Co-Investigator, EFFORT of effort and salary support requested for three years). Dr. Marshall is Professor of Bioethics and Director of the Center for Genetic Research Ethics and Law at Case Western Reserve University. Dr. Marshall will assist Dr. Hyun in the in-depth review of institutional policies for chimera research, help design the interview instrument, and help interpret the qualitative data.

TBA (Research Assistant, 6 calendar months' of effort and salary support requested for Years 1 and 2). This position will be responsible for scheduling interviews, conducting the interviews, helping to develop codebooks, coding the data, and assisting with basic data analysis. He/she will also be responsible for data entry and management.

Indirects
Indirects are included at 62.6%. Our current indirect cost rate negotiated with the U.S. Department of Health and Human Services (DHHS) dated September 27, 2016 includes total direct costs excluding capital expenditures, and that portion of each subaward in excess of $25,000.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		412,458.72
Section B, Other Personnel		67,476.62
Total Number Other Personnel	9	
Total Salary, Wages and Fringe Benefits (A+B)		479,935.34
Section C, Equipment		
Section D, Travel		67,505.05
1. Domestic	67,505.05	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		592,232.00
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services	35,000.00	
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	495,983.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	8,800.00	
9. Other 2	42,000.00	
10. Other 3	10,449.00	
Section G, Direct Costs (A thru F)		1,139,672.39
Section H, Indirect Costs		418,599.54
Section I, Total Direct and Indirect Costs (G + H)		1,558,271.93
Section J, Fee		

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0777584070000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Case Western Reserve University

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Insoo		Hyun	PhD	PD/PI	Institutional Base Salary	EFFORT			33,660.00	10,266.00	43,926.00
2 .		Patricia		Marshall	PhD	Co-Investigato					20,541.00	6,265.00	26,806.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **70,732.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	6.00			22,500.00	6,863.00	29,363.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**29,363.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**100,095.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0777584070000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: Case Western Reserve University

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,151.00
2. Foreign Travel Costs	
Total Travel Cost	**5,151.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		3,600.00
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**3,600.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12490267
Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0777584070000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: Case Western Reserve University

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	2,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Transcription	3,348.00
Total Other Direct Costs	**5,348.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**114,194.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	60.00	114,194.00	68,516.00
		Total Indirect Costs	**68,516.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, Uyen Tran, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**182,710.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1240-BudgetJustificationCaseWestern.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12490267
Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0777584070000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Case Western Reserve University

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Insoo		Hyun	PhD	PD/PI	Institutional Base Salary	EFFORT			34,333.00	10,643.00	44,976.00
2 .		Patricia		Marshall	PhD	Co-Investigator					20,952.00	6,495.00	27,447.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **72,423.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Assistant	6.00			22,950.00	7,115.00	30,065.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**30,065.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**102,488.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0777584070000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: Case Western Reserve University

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	7,448.00
2. Foreign Travel Costs	
Total Travel Cost	**7,448.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		2,400.00
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**2,400.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12490267
Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0777584070000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: Case Western Reserve University

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period:** 2

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	510.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Transcription	2,304.00
Total Other Direct Costs	**2,814.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**115,150.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	60.00	115,150.00	69,090.00
		Total Indirect Costs	**69,090.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Uyen Tran, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**184,240.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1240-BudgetJustificationCaseWestern.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0777584070000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: Case Western Reserve University

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Insoo		Hyun	PhD	PD/PI	Institutional Base Salary	EFFORT			35,020.00	11,031.00	46,051.00
2 .		Patricia		Marshall	PhD	Co-Investigato					21,371.00	6,732.00	28,103.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **74,154.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Total Number Other Personnel					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**74,154.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0777584070000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: Case Western Reserve University

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,359.00
2. Foreign Travel Costs	
Total Travel Cost	**5,359.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12490267
Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0777584070000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: Case Western Reserve University

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	520.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**520.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**80,033.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	61.00	80,033.00	48,820.00
		Total Indirect Costs	**48,820.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS, Uyen Tran, (214) 767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**128,853.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1240-BudgetJustificationCaseWestern.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Budget Justification

Personnel:
Insoo Hyun, Ph.D. (PI, EFFORT of effort and salary support requested for three years). Dr. Hyun is Associate Professor of Bioethics at Case Western Reserve University School of Medicine. Hyun will share overall project responsibility with PIs Johnston and Maschke. He will co-lead (with Johnston and Maschke) the activities for the Policy Review, Conceptual Analysis, and Synthesis components of the project. He will work jointly with Johnston and Maschke to: (1) develop agendas and background materials for PI conference calls and in-person meetings and for WG conference calls and in-person WG meetings, (2) identify the specific facts, questions, issues, or arguments for WG members to address in their presentations, (3) facilitate and lead sessions at WG meetings, (4) oversee the fiscal and administrative management of the Case subcontract, (5) develop any required progress reports, (6) develop and deliver professional presentations about the project's findings, and (7) develop and write manuscripts for publication. Hyun will work with PIs Johnston and Maschke and the Co-Investigators to develop the projects' recommendations and will work with PIs Johnston and Maschke and Co-Investigator Solomon to develop the project's educational materials, including a Protocol Casebook. He will oversee and assist with the subcontract work of the Empirical Component of the project.

Patricia Marshall, Ph.D. (Co-Investigator, EFFORT of effort and salary support requested for three years). Dr. Marshall is Professor of Bioethics and Director of the Center for Genetic Research Ethics and Law at Case Western Reserve University. Marshall will lead the Empirical Component of the project to develop the research protocol and interview guide, and will pilot the interview guide. She will conduct the expert interviews and lead the coding and analysis of the interview data. Marshall will have responsibility for managing submission of the research protocol to Case Western's IRB. She will present the findings of the interviews in a presentation at one of the WG meetings and participate in drafting manuscripts about the empirical component of the project.

TBA (Research Assistant, 12 calendar months' of effort and salary support requested for Years 1 and 2). This position will be responsible for assisting with the literature review and assisting in conducting the qualitative interviews and analysis. He/she will also be responsible for data entry and management.

The fringe benefits rate is 30.5% in Year 1, 31% in Year 2, and 31.5% in Year 3. Salaries are increased by 2% per year, though we understand this may not be approved.

Travel:
Funds are requested for one trip to The Hastings Center for a project meeting in Year 1. Costs for airfare, hotel, ground transport, meals, and parking are $2,151 for Drs. Hyun and Marshall. Two trips to The Hastings Center in Year 2 are budgeted at $4,388. One trip to The Hastings Center in Year 3 is budgeted at $2,238. Funds are also requested for Drs. Hyun and Marshall to attend one national meeting per year to present study findings ($3,00 in Year 1, and increased by 2% per year in succeeding years. Total travel budget is $$5,151 in Year 1, $7,448 in Year 2, and $5,359 in Year 3.

Supplies:
$500 is requested in Year 1 for consumable research supplies; this amount is increased by 2% per year. The supply budget will also cover copying and printing costs. $1,500 is requested in Year 1 to purchase a laptop computer for the Research Assistant. Total supply budget is $2,000 in Year 1, $510 in Year 2, and $520 in Year 3.

Other Expenses:
Sixty interviews will be conducted in Years 1 and 2 (36 in Year 1 and 24 in Year 2). Participants will be given $50 gift cards ($1,800 in Year 1; $1,200 in Year 2). Each one-hour interview requires 3 hours of transcription. Transcription costs for 36 interviews in Year 1 total $3,348 (36 interviews x 3

hours x $31/hour). Transcription costs for 24 interviews in Year 2 total $2,304 (24 interviews x 3 hours x $32/hour).

Indirect Costs:
Indirect costs are calculated at 60% of direct costs in Years 1 and 2. In Year 3, the indirect cost rate increases to 61%.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		217,309.00
Section B, Other Personnel		59,428.00
Total Number Other Personnel	2	
Total Salary, Wages and Fringe Benefits (A+B)		276,737.00
Section C, Equipment		
Section D, Travel		17,958.00
1. Domestic	17,958.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		6,000.00
1. Tuition/Fees/Health Insurance		
2. Stipends	6,000.00	
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		8,682.00
1. Materials and Supplies	3,030.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	5,652.00	
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		309,377.00
Section H, Indirect Costs		186,426.00
Section I, Total Direct and Indirect Costs (G + H)		495,803.00
Section J, Fee		

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Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Category	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	258,938	340,415	353,893	0	0	**953,246**

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 10/31/2018

1. Human Subjects Section

Clinical Trial? ○ Yes ● No

*Agency-Defined Phase III Clinical Trial? ○ Yes ○ No

2. 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 proved scientific justification

3. *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)

Funding Opportunity Number: PA-17-444 . Received Date: 2017-10-03T12:38:19.000-04:00

PHS 398 Cover Page Supplement

4. 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, please 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):

5. Inventions and Patents Section (RENEWAL)

*Inventions and Patents: ○ Yes ○ No

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

*Previously Reported: ○ Yes ○ No

6. 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:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Introduction	
1. Introduction to Application (Resubmission and Revision)	
Research Plan Section	
2. Specific Aims	1241-SpecificAims.pdf
3. Research Strategy*	1242-ResearchStrategy.pdf
4. Progress Report Publication List	
Human Subjects Section	
5. Protection of Human Subjects	1243-ProtectionOfHumanSubjects.pdf
6. Data Safety Monitoring Plan	
7. Inclusion of Women and Minorities	1244-InclusionOfWomenAndMinorities.pdf
8. Inclusion of Children	1245-InclusionOfChildren.pdf
Other Research Plan Section	
9. Vertebrate Animals	
10. Select Agent Research	
11. Multiple PD/PI Leadership Plan	1246-MultiPILeadershipPlan.pdf
12. Consortium/Contractual Arrangements	1247-ConsortiumContractualArrangement.pdf
13. Letters of Support	1248-LettersOfSupport.pdf
14. Resource Sharing Plan(s)	
15. Authentication of Key Biological and/or Chemical Resources	
Appendix	
16. Appendix	1249-AppendixA.pdf

SPECIFIC AIMS

Today, rapid advances in human stem cell science and new gene editing techniques are enabling researchers to more extensively and precisely insert human cells (and self-organizing structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of vertebrate animals. These scientific advances are very exciting. Yet they also are revealing conceptual and ethical limitations in existing ethics guidance for human-animal chimera research and a lack of knowledge about how best to oversee this research.

For example, national and international guidelines suggest that high levels of human cells in brains of the non-human animals might be ethically problematic. Yet an explicit goal of some new gene editing and stem cell research is to create animal-human chimeras with previously unattainable levels of human cells in the animal's central nervous system. This suggests that the concept of "humanization" may no longer be an appropriate construct, or that it would be more useful, if better defined. Further, existing practice has been to manage concerns about humanizing germ cells by keeping human-animal chimeras in sex segregated cages, but studies of the intergenerational effects of gene editing will likely require breeding of animals into whose germline human genes have been introduced. A lack of clarity about what humanization means, how to measure or detect it, and when it is and is not ethically problematic, creates uncertainty for researchers and oversight challenges for institutions and funders, all of which risks undermining the progress of trustworthy science.

This project is based on two premises: that existing guidance regarding the ethics of animal-human chimera research is not sufficiently conceptually clear or operationalizable, and that optimal ways of organizing the oversight of human-animal chimera research are not yet known. A preliminary analysis, which the proposed investigator team has undertaken in preparing this application, reveals a lack of conceptual clarity and an absence of clear rules or decision-points to guide research and oversight. In exploring these issues with thought leaders in U.S. research institutions active in stem cell and gene editing research, we have also found that institutions have adopted a variety of approaches to the oversight of human-animal chimera research, although the exact scope of those approaches, and the benefits and challenges of different approaches, are not yet known.

In response to these knowledge gaps, this project aims to develop clear, reasoned, and practical recommendations and educational materials to assist researchers, research institutions and their oversight bodies, funders and the public in identifying, understanding, and managing the ethical issues associated with human-animal chimera research.

Aim 1. Identify and critically analyze unresolved conceptual and ethical questions relevant to human-animal chimera research.

We will analyze guidelines, recommendations, laws, regulations, funder requirements and the academic literature to discern concepts and ethical issues relevant to oversight of human-animal chimera research. Working with scientists engaged in this kind of research and with members of the relevant oversight bodies (i.e., ESCRO committees and IACUCs), we will then undertake an interdisciplinary analysis aimed at resolving inconsistencies and uncertainties including, where necessary, developing new concepts and frameworks.

Aim 2. Identify the strengths and challenges of existing oversight approaches to research involving human-animal chimeras.

Little is currently known about how research institutions oversee this research. We will use mixed methods, including interviews with scientists doing this kind of research and members of relevant oversight committees to better understand the strengths and challenges of current oversight approaches.

Aim 3. Develop actionable recommendations and educational materials for enhancing oversight of human-animal chimera research. Drawing on the findings of Aims 1 and 2, and the deliberations of an interdisciplinary Work Group, we will craft actionable recommendations and educational resources for oversight of this rapidly changing area of research.

RESEARCH STRATEGY

A. SIGNIFICANCE

Research involving the insertion of human cells into non-human animals (hereinafter animals) has been underway for decades, but the science is rapidly evolving. Today, advances in human stem cell science and genetic engineering techniques are enabling researchers to more extensively and precisely insert human cells (and self-organizing mini-organ structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of vertebrate animals.[1] These scientific advances are thrilling. Yet they also reveal conceptual, ethical, and procedural limitations in existing ethics guidance for human-animal chimera research.

The proposed project presents an interdisciplinary, evidence-based approach for learning about, and enhancing, ethical oversight of this important field of research. We will build actionable recommendations and educational materials, by researching the insights and experiences of scientists, who are themselves doing this kind of work, and members of oversight bodies that have faced the challenges of having to make decisions about the advance of such work. Our proposed investigation grows out of preliminary analyses we have already undertaken, which suggest that scientists and members of oversight bodies such as Embryonic Stem Cell Research Oversight (ESCRO) committees and Institutional Animal Care and Use Committees (IACUCs), are themselves calling for greater conceptual clarity and more streamlined and understandable oversight procedures. Their letters of support (in Letters of Support) document and reveal their calls for improvement.

To offer greater conceptual and operational clarity, The Hastings Center will carry out normative analyses using its well-honed and internationally regarded Work Group (WG) approach to the analysis of foundational philosophical concerns, moral uncertainties, and value conflicts, and integrate empirical research, which will be carried out by our partner, Case Western Reserve University. Informed by both nuanced conceptual analyses and the empirical findings from a set of interviews with key leaders, the project will result in guidance to investigators, research institutions, oversight bodies (i.e., ESCRO committees and IACUCs), funders, and ultimately the public. Final project deliverables will also offer greater conceptual clarity as well as standardization and efficiency to the oversight process, enabling the trustworthy advance of this kind of science. In the remainder of this section, we lay out the rationale for undertaking this project.

A. 1. Promising Science: New Biologically and Ethically Complex Chimeras

Scientists create human-animal chimeras to answer a wide range of important questions.[2] Advances in genome editing, embryology, and stem cell science are making it possible to imagine, and create, new kinds of chimeric organisms that are both more biologically and more ethically complex than previously created. They are biologically complex in combining methods from gene editing, stem cell science, and embryology. In just the last year, a laboratory published findings based on mice with human glial progenitor cells using human induced pluripotent stem cells (hiPSCs) derived from patients with childhood-onset schizophrenia.[3] Scientists might also derive brain tissue from human stem cells, creating an in vitro “organoid,”[4] and transplant the organoid into the brain of a non-human primate that’s been genetically modified to exhibit symptoms of schizophrenia.

Evidence that xenotransplantation of solid organs might one day be possible comes from a report this summer that a laboratory created human-pig chimeric embryos by inserting human stem cells into the pig blastocyst, and allowed them to develop for 28 days.[5] A proof of concept rat-mouse chimera study[6] suggests that scientists might use genome editing tools to insert human stem cells into a non-human embryo with an “organ niche” created through genome editing, in order to learn about the early development of organ systems, or so that the animal develops human organs or tissues in the desired location (e.g., a human liver, heart, or brain).[7] These new kinds of chimeras are ethically complex insofar as all three branches of science – gene editing, stem cells, and embryology - touch on questions related to human and animal nature, human dignity, animal welfare, and species boundaries. All three have also, historically, been the target of the public’s criticism and attention by some members of Congress.[8] The combination of these methods in the creation of chimeras challenge ethical constructs as well as oversight paradigms, and demand thoughtful, intentional analysis so the science can progress responsibly.

Interest in creating these new forms of chimeras is motivated by its expected benefits: (1) more accurate models of human disease owing to exact tissue matches between the model organism and humans; (2) a

reliable and inexpensive source of human eggs, sperms, and embryos for research; (3) and a reliable source of tissues and/or organs suitable for transplantation into humans, an enormous need in the United States. Already, we have evidence from preliminary explorations we have undertaken that both scientists themselves and those charged with oversight, such as the members of ESCRO committees, feel the need for greater guidance as they wade into more biologically and ethically complex territory.

A.2. Why This Project *Now*?

Given the NIH's current funding moratorium on certain kinds of chimera research, it might seem counterintuitive to propose our study. However, this may be the best time to do so. With the speed of innovation going on in genome editing, stem cell science and embryology, leaders at the NIH and other scientists may soon wish to lift the moratorium. Analyses and tools of the kind we are proposing will be highly facilitative.

Second, the funding moratorium is only a partial ban of certain kinds of chimera research. At present, no federal funds from the NIH can be used for research that involves inserting human stem cells into early-stage animal embryos, including embryos of non-human primates, and for research creating animals with human sperm and human eggs.[9] However, the NIH is funding some types of human-animal chimera research.[10] And, states and private donors have funded research that the NIH will not fund.[11]

We aim to do the intellectual work now that is necessary for building public trust in this research in the future. Indeed, we have seen a similar trajectory in the area of human genome editing: scientists themselves called for a moratorium on the use of CRISPR Cas9 in humans, windows opened for normative analysis and public discussion, and some forms of the research were then permitted to go forward.[12]

Getting ahead of the curve on human-animal chimera research is particularly important, because it raises major concerns among laypersons. When the NIH asked for public comment on its draft policy for chimera research in August 2016, it received twenty thousand responses, with the vast majority highly negative.[13] The project's educational materials will be designed both to aid ESCRO committee and IACUC members in the discharge of their oversight responsibilities, but these materials will also include content to help the public understand this kind of research, what it is, and what it is not.

A.3. Current Guidelines and Oversight Only Go So Far

There are two sets of influential guidelines for human-animal chimera research and its oversight. One set is from the National Academies of Science (NAS), the *Guidelines for Human Embryonic Stem Cell Research*, released in 2005 and updated in 2010,[14] and the other from The International Society of Stem Cell Researchers (ISSCR), the *Guidelines for Stem Cell Research and Clinical Translation,* originally released in 2006 and updated in 2016.[15] ISSCR's guidelines are accompanied by an Advisory Report that provides further guidance to ESCRO committee members.[16] Both represent important landmarks in U.S. and international initiatives. However, as important as these guidances are, they remain vague and hard to operationalize. It is significant that several contributors to the 2016 update of the ISSCR guidelines have themselves noted limitations of the guidelines and see them still as works-in-progress.[17] As just one example, the ISSCR guidelines say that human-animal chimera research triggers special review by an ESCRO committee, "when the degree of functional integration is considerable enough to raise concerns that the nature of the animal host may be substantially altered."[18] However, neither the guidelines nor the Advisory Report meant to clarify them specify what would count as "altering the nature" of an animal host.

During Summer 2017, Hastings Center scholars held in-depth phone calls (and in one case, email exchange) with thought leaders in the ESCRO community, which included 7 of the individuals proposed as WG members in this application, as well as 3 people with in-depth knowledge of the IACUC world. Each of these individuals, have served, or are serving on, ESCRO committees that regularly review research involving chimeras. In addition, PIs Hyun and Johnston serve on ESCRO committees, and PI Hyun, Co-I Neuhaus, and 4 members of our proposed WG have served on IACUCs.

Everyone with whom we spoke agreed that lack of conceptual clarity in the NAS and ISSCR guidances is causing confusion, struggle, and frustration among ESCRO committee members. One informant acknowledged struggling with philosophical issues, asking, "What is the concern? Creating something more

human than we want it to be? If consciousness is our concern, how can we identify it in an animal if we don't know what it is in humans?" Another informant asks, "How human is too human—is it self-awareness? Is humanized the right word?"

Additionally, they expressed concern about the pace of chimera research and their institutions' ability to keep up. One said that researchers at her university were actively engaged in autism research that would create chimeras with significant contribution of human cells to the animals' brains and central nervous system. She anticipates this will challenge both ESCRO committees and IACUCs. Another WG member sees the entire chimera research enterprise as "important but at risk."

Finally, our preliminary investigation showed that review of chimera research is siloed. ESCRO committees are responsible for assessing issues related to "humanization" of the research animal. But IACUCs are responsible for assessing how chimerism affects animal welfare. These concerns are not unrelated, but committee members do not talk to each other or compare notes. ESCRO committee members noted that they were often reviewing a protocol that had already been approved by an IACUC, so they assume that "welfare issues" have been properly assessed, but never feel sure. They often have questions about the welfare implications, but lack the expertise or institutional support to find them out, as such matters, officially, are not their purview.

Our review of existing guidances and our preliminary exploration with major thought leaders, including many who have now agreed to serve on our proposed WG, make clear the need for two things: (1) conceptual clarity and normative analysis related to defining and measuring "humanization" and its significance to animal welfare, and (2) examination and improvement of the oversight system, including greater clarity about who should be responsible (and accountable), and how best to integrate different sets of concerns into a streamlined, efficient review system. We say a bit more below about each of these two issues, and then in Section C. Approach, we discuss the mixed methods we will use to address them.

A.4. The Need for Greater Conceptual Clarity and Normative Analysis

Published analyses of the NAS and ISSCR guidelines, as well as the experiences of ESCRO committee members, point to a need for greater conceptual clarity. So far, we have detected three areas that require further conceptual and/or normative analysis. Conceptual analysis refers to clarifying the meaning of words, such as "humanization," that appear in guidances but are difficult to interpret and operationalize. Normative analysis guides actions by asking what we ought to do in a particular situation.

Humanization. Both the NAS and ISSCR guidelines for chimera research state that "humanization" of the chimera is a chief moral concern, and that chimeras likely to involve functional integration of human cells into the central nervous system or brain are especially worrisome because they may result in the animal attaining human like cognition, awareness, or sensation. To begin with, there are important questions about whether "humanization" is the appropriate ethical construct with which to analyze moral status. If humanization turns out to be a useful construct, there would remain ambiguity both about *why* it is useful and *how* to apply it to protocols in question, as we've heard repeatedly in our conversations from WG members.

The "why" question asks about the relationship between capacities, moral status, and determining what we owe to certain creatures. Philosophers have long debated these issues. It brings up questions such as: What is the relevance of human-like cognition or awareness or sentience to moral status? What are our responsibilities to self-aware creatures?[19] The goal of our study is not to resolve these enduring, nearly irresolvable foundational questions. Rather, we have a more practical goal. We seek to clarify concepts to understand what is motivating so-called humanization concerns and to find a reasonable path forward that most people can accept and operationalize.

Crucially, whatever one's answer to the *why* question of what types of capacities would indicate humanization, serious questions remain about *how* to determine that a chimeric organism has the attribute in question, whether that is human-like cognition, awareness, or some other mental attribute. Measurement is a problem because the ISSCR guidelines call for establishing baseline animal data for chimeric organisms and then close follow up. But several ESCRO members with whom we spoke said, it is "difficult to communicate to the researchers what exactly should be considered humanization." Another went on to say she struggles because "we just don't know how to measure or assess humanization."

Animal Welfare and Well-Being. Whether or not an animal is "humanized" there remain serious welfare concerns surrounding the creation and use of chimeras.[20] Even if introducing human progenitor cells into the mouse brain does not create "human" cognition, it may nonetheless heighten a mouse's awareness of its surroundings or otherwise change its species-typical behavior.[21]

As Dr. Insoo Hyun, one of our proposed PIs, has written, "…people tend to assume the presence of human cells in an animal's brain might enhance it above its typical species functioning. Yet this seems to be an extreme form of anthropocentric arrogance…The much more likely outcome of neurological chimerism is not moral humanization of the animal in this sense but rather an increased chance of animal suffering and acute biological dysfunction and disequilibrium, if our experience with transgenic animals can be a guide."[22]

The ISSCR recommends that research involving novel kinds of chimeras be reviewed much like research involving novel transgenic organisms, according to a "watch and wait" approach which will closely watch chimeras to observe baseline behavior and any deviances from the species' norm. Still that assumes clear guidance for inferring from animals' behavior changes in their sense of awareness and/or increased suffering, which assumes conceptual clarity about what scientists would look for, and why. Our WG brings together philosophers with expertise in animal cognition, animal studies scholars, and IACUC members and chairs to contribute to actionable guidelines for chimera welfare considerations.

Justification of Animal Use. If an animal has the potential to demonstrate humanized cognition, awareness, or other mental attributes, the ISSCR Advisory Report says, it would take "an extraordinary degree of justification" to approve the protocol."[23] But what would constitute an extraordinary degree of justification? To be useful, guidelines need either to define thresholds or be modified. Otherwise, they cannot be operationalized and can confuse and potentially obfuscate. The proposed project will articulate what proposed uses of chimeras with heightened cognition, awareness, or mental attributes would meet "an extraordinary degree of justification."

A.5 The Need for Examination of Optimal Oversight Approaches

Our preliminary analysis suggests that the oversight system is fragmented with great uncertainty about where the authority for oversight rests. As already noted, two different institution-based committees have authority: ESCRO committees and IACUCs. We note 3 areas that merit review.

IACUC Capacity to Review Chimera Research. The NAS and the ISSCR guidances that pertain to chimera research task ESCRO committees with considering concerns about the "humanization" of chimeras when assessing research protocols and leave it to IACUC's to consider animal welfare. However, the U.S. Public Health Service Policy on the Humane Care and Use of Laboratory Animals and its guidelines set forth in the *Guide for the Care and Use of Laboratory Animals* (*The Guide*),[24] lays out specific guidelines for humane animal care and use, but makes no mention of chimera research. IACUC members are not educated about welfare or other issues specific to chimeric organisms. As one member of our WG, an IACUC chair, points out in his letter of support, "While national and international guidelines exist for Embryonic Stem Cell Research Oversight (ESCRO) committee members specifically about reviewing chimera protocols, there is no analog in the IACUC world."

Interaction between IACUCs and ESCRO Committees. The guidelines provide no specific guidance about whether and how an institution's ESCRO committee and IACUC should interact in overseeing chimera research. A common insight of several people we talked to in preparing this proposal was uncertainty about whether ESCRO committees and IACUCs are properly engaged in overseeing human-animal chimera research, what oversight challenges they face, or whether the current siloed approach is optimal. We can easily imagine conflict between committees in their analysis of whether a particular experiment is justified. There are also likely areas that fail to receive attention by either body.

Best Practices. Our prospective WG members indicated that different ESCRO committees approach chimera research differently. One person noted that it would be laudable to take stock of and "workshop" different oversight approaches to get a better sense about the strengths and weaknesses of current and alternative approaches. We will do just that at WG Meeting #2, inviting participants to give presentations on their respective approaches to different kinds of protocols.

A.6 Significant Project Accomplishments: New Knowledge and Practical Deliverables
The primary reason the proposed study is highly significant is that it represents an essential step toward advancing chimera research in a trustworthy way. To do so, we will develop both scholarly analysis, yielding new knowledge about the concepts and norms that should guide this research and crucial insights about how best to optimize oversight of this kind of research.

In addition, the investigator team is committed to developing practical deliverables to help ESCRO committees and IACUC members, scientists, funders, policy makers, and the public. As we discuss later in the Approach Section C., these deliverables will include: scholarly analyses in the form of a *Hastings Center Report* special supplement that will immediately place the WG's analyses into the published literature via an open access route, other peer-reviewed publications to be placed in other major academic journals, such as *Cell Stem Cell* or *Science*, op-eds, blogposts and other writing for lay audiences to assist the public in understanding the importance of this research; and a wide range of educational materials, including a Protocol Casebook, for oversight committee members, which will be disseminated through many channels, identified in Section C. 5.

B. Innovation
The proposed study is innovative and novel in several ways. First, through the 60 interviews we plan to undertake, we will seek the views of scientists and of members of ESCRO committees and IACUCs themselves, so that their lived experiences, goals and challenges will inform the normative analyses and actionable recommendations that will emerge from our study. To our knowledge, in-depth key stakeholders' views on this topic have not yet been studied in any systematic way.

Second, the project is innovative in bringing together a range of diverse thought leaders – scientists that create chimeras, animal studies scholars, scientists, and research oversight experts - for a sustained series of in depth face-to-face WG meetings. The Hastings Center has a worldwide reputation for knowing how to purposefully bring together people with diverse views and interdisciplinary backgrounds to deliberate respectfully and productively, yielding world class scholarship that also offers practical guidance. Our method is not new, as it is time-tested and one for which we are well known, but it ***is*** innovative – in that there are few other institutions that routinely apply our approach, and none that have done so with regard to human-animal chimera research.

Finally, another innovative feature of the project is development of a set of educational materials aimed at scientists, ESCRO committees and IACUC members and the public. Hastings Center president, Mildred Solomon, a world leader in bioethics teaching and curriculum development, will oversee this part of the project. The 2009-2017 Presidential Commission for Bioethics developed user guides, teacher tools, and primers to accompany all of their normative reports. The proposed project follows the Commission's innovative lead.

C. APPROACH
C. 1 Overview of Approach
Figure 1 presents the study's three aims. To achieve these aims, we will deploy a mixed methods approach, including policy review, empirical investigation, and conceptual analysis. Knowledge from all methods will be synthesized through WG deliberation and analysis by the Research Team (lead investigators and co-investigators).

Figure 1: Specific Aims

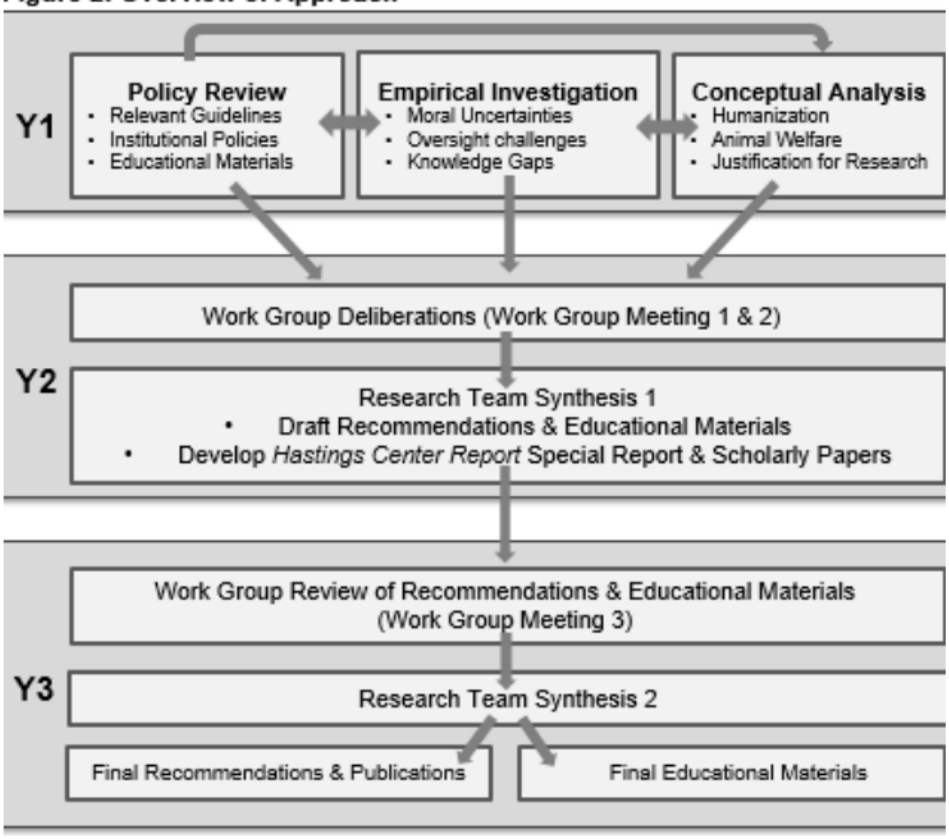
Aim 1. Identify and critically analyze unresolved conceptual and ethical questions relevant to human-animal chimera research.

Aim 2. Identify the strengths and challenges of existing oversight approaches to research involving human-animal chimeras.

Aim 3. Develop actionable recommendations and educational materials for enhancing oversight of human-animal chimera research.

All three methods – policy review, empirical investigation, and conceptual analysis – will provide data relevant to all three aims. For example, the questionnaire will include questions relevant to all three aims, probing for concepts and unsettled normative questions about which informants would like greater clarity (Aim 1), asking how they organize oversight at their institutions and how it might be improved (Aim 2), and eliciting best practices to inform actionable policy recommendations (Aim 3). Figure Two provides more detail on the steps we will take in each year of the study.

Figure 2: Overview of Approach



C. 2 Purpose and Methods for Each Type of Investigation

Policy Review

Purpose. To identify inconsistencies, misunderstandings, and uncertainties regarding human-animal chimera research as they arise in relevant laws and institutional policies. This review will elucidate which concepts and normative questions require further clarification and provide the foundation for (a) the Working Group's background readings, agendas, and meeting discussions, (b) the qualitative interviews, and (c) the project's recommendations and other products.

Method. In addition to comprehensively analyzing of the NAS and ISSCR guidelines, the Research Ream will review the relevant written policies and guidelines of the ESCRO committees and IACUCs in the interview sample, with the thought that some institutional committees may have created their own method or policy for chimera research oversight. To obtain existing documents, the Research Team will examine the publicly available websites of the ESCRO committees and IACUCs to determine if relevant policies and guidelines have been posted on those sites. If no relevant documents are publicly available, or if the committees do not have a publicly accessible website, the team will contact a relevant administrator at the institution to determine if they can obtain any of the committees' relevant policies.

Empirical Investigation

Purpose. The interviews are meant to ensure that the study's conceptual analyses and ultimate policy recommendations will be highly informed, empirically, about the beliefs, views, hopes and challenges that scientists doing chimera research and members of oversight bodies experience, including their perceptions regarding institutional best practices for oversight.

Method. We will conduct a total of 60 in-depth interviews with scientists (n = 30) engaged in human-animal chimera research, members of ESCRO committees (n = 15) that receive a high volume of chimera research protocols for review, and IACUC members (n = 15) with chimera research portfolios.

Interview Sample. The starting sample from which to recruit interviewees will be research institutions at ten sites in three states: California (Salk Institute for Biological Studies, Stanford University, UC Davis, UC San Diego, UC San Francisco); Massachusetts (Harvard University, MIT); and New York (Memorial Sloan-Kettering Cancer Center, Rockefeller University, Weill Medical College of Cornell University). These states and research sites were chosen because they are home to stem cell research laboratories very active in the human-animal chimera research field, and each of the states supports chimera research through multiple funding sources, including dedicated state and private funds. This makes it very likely that such research will continue to be funded in these states during the duration of our proposed study, regardless of whether federal funding restrictions are in place for some types of human-animal chimera research.

Recruitment Strategy. Initial contact with the 15 chairs of ESCRO committees and the 15 IACUC chairs will be made via USPS Priority Mail, followed within one week by email or telephone contact, with two

additional email or telephone calls to confirm, answer questions, and schedule interviews with those who consent. The invitation letter will describe the purpose of the project, the project investigators, and the members of the WG. If an invited individual suggests a designee, we will request contact information and approach the designee in a similar manner. If an ESCRO committee/IACUC chair declines to participate and does not suggest a designee to interview, we will use a random selection process to select a medical college from the AAMC membership list, identify the relevant committee chair at that site, and use the recruitment process described above. If necessary, we will repeat the random selection process to reach the enrollment goal of 15 ESCRO committee and 15 IACUC chairs (or their designees).

We will use snowball sampling[25] to recruit the scientists. We will begin by asking the ESCRO and IACUC committee chairs for the names of 2 investigators at their institution (N=20). We will use the initial recruitment and random selection processes described above to invite investigators to participate in an interview. We will ask the investigators who agree to be interviewed for the names of other researchers at their institution or at other institutions, with the goal of obtaining enough names to conduct 10 additional interviews. If we have difficulty obtaining a total of 30 investigator interviewees, we will use the snowball sampling approach by contacting members of our WG and other informants we know at research institutions and professional organizations to obtain names of investigators conducting chimera research. We also anticipate that the policy review will identify particularly engaged scientists whom we will approach.

Co-Investigator Marshall, one of the nation's most accomplished medical anthropologists, will conduct the telephone interviews, which will last 45-60 minutes and be audio-taped (or recorded via written notes if permission is not granted). Participants who complete the interviews will receive a $100 gift certificate.

Interview Guide. Figure 3 below summarizes the domains we intend to explore through the interviews. A draft questionnaire appears in Appendix A with sample domains and questions. We intend to review the questionnaire in light of findings that will emerge from the policy review. Dr. Marshall will then pilot test the guide at Case Western Reserve University, where she and one of our PIs (Hyun) are located. It will be piloted with 2 scientists involved in stem cell research and 2 members of the Human Stem Cell Research Oversight Committee.

Figure 3. Semi-structured Interview Topics

Ethical and Conceptual Challenges • Humanization • Animal welfare • Animal justification
Oversight Approaches • Scope of ESCRO and IACUC authority • Strengths and challenges of existing approaches • Need for better integration?
Recommendations & Educational Materials • Clarification of key concepts and ethics recommendations • Suggestions for enhanced oversight approaches • Need for practical tools and educational resources?

Data analysis. Audiotapes of the interviews will be transcribed with no identifying names; transcriptions will be imported into a separate NVivo file. With assistance from a trained research assistant, Dr. Marshall will use standard coding procedures to develop a coding scheme, a codebook, and ways to resolve coding discrepancies.[26] In addition to basic descriptive analysis of the emerging themes, reports about the interview findings will include representative quotes from respondents about their perspectives, concerns, and experiences regarding the ethical, conceptual and policy challenges raised by human-animal chimera research and its oversight. We will provide access to the interview guide, code book, and redacted interview transcripts to other researchers on request.

Work Group Deliberations

Purpose. The goal of the interdisciplinary WG is to undertake analysis of conceptual and normative problems requiring clarification, deliberation, compromise, and where possible consensus. Each WG session will have a different focus, building on from the discussions and findings presented at earlier meetings.
We are proposing three WG meetings, each with its own distinct goal:

Work Group Meeting #1. Will identify and critically analyze unresolved conceptual and ethical questions relevant to human-animal chimera research. The policy review will be complete and will help to identify the key areas to be discussed.

Work Group Meeting #2. Will examine existing oversight approaches and the help, or challenges, current approaches pose to scientists and oversight bodies. Interview results will be presented.

Work Group Meeting #3. Will respond to a draft version of the recommendations the Research Team will have circulated in advance. This meeting will also include review of preliminary versions of the *Hastings Center Report* special report and the key educational materials being developed.

Work Group Composition. We have created a diverse and expert 19-member WG, with the knowledge needed to address our Specific Aims and the ability to influence policy and practice. The WG includes scientists doing various kinds research with human stem cells, including human-animal chimera research, members of ESCRO committees and IACUCs, experts in animal behavior and cognition and animal care and welfare, philosophers, bioethicists, lawyers, a political scientist, and an anthropologist. (Detailed list at C.7)

Letters of Support from these individuals are included. As their letters show, our WG members are leaders in research and policy. They endorse the need for this project and welcome the opportunity to share their research and perspectives to help create actionable ethics oversight for chimera research.
Benefits of Work Group Methodology. Three facts demonstrate the value of WG meetings. They are interdisciplinary, multi-perspectival, and entail face-to-face interaction over time[27]—all features that make WGs well-suited for analyzing complex ethical issues and producing useful recommendations. Studies of interdisciplinary research support their efficacy[28] and intellectual power.[29] In addition, the NIH Roadmap[30] and leaders in ELSI research have emphasized the value of interdisciplinary research.[31] The meetings' in-person nature is supported by studies showing that the success of collaborative research depends on regular face-to-face meetings[32] in settings that foster respect.[33]

Hastings Center researchers have been convening this kind of interdisciplinary, interactive WG meeting for over 4 decades. We have significant experience identifying the necessary expertise, crafting agendas, working with presenters to hone their subtopics, facilitating the meeting itself, and analyzing the results. In managing discussion and debate, Hastings facilitators manage meeting discussion to ensure that all attendees are treated equally and can share their work and views, thereby fostering an atmosphere of respect for divergent and diverse perspectives.

Meetings such as this are off the record (i.e., attendees' remarks are never quoted without subsequent permission), which helps attendees explore controversial ideas and arguments and be frank about their doubts and the limits of their positions. Our meeting attendees often remark that by interacting with an interdisciplinary group of this kind, in the facilitated manner that Hastings has developed, they are forced to take a fresh look at their research and to consider new perspectives.

Function of WG Meetings. WGs help the Research Team answer the study's Specific Aims. Through presentations and discussion, WG members provide the information and concepts (the "raw data", if you like) that the project needs to undertake conceptual and normative analysis (Aim 1); examine oversight approaches (Aim 2), and develop actionable ethics recommendations tailored to key stakeholders (Aim 3).

Because the information and concepts that WG members bring to the project are offered to the whole group, data is not only collected from them, it is also interpreted and analyzed by them during the extensive group discussion periods that follow each meeting presentation.

Structure of WG Meetings. The WG will convene in-person for three 1½ day meetings; WG members will be seated around a large conference table (if one or two WG members cannot attend a meeting in person, we can bring them in with our video-conferencing system). The agenda for each meeting will be drafted several months in advance by the Research Team. Each WG member will make one 20-30 minute-long presentation at a WG meeting. Presentations will be tailored to specific elements of the project's aims and the PIs will work closely with each presenter to identify the specific facts, questions, issues, or arguments to be addressed in his or her presentation. Following each presentation, the WG will engage in 40 – 60 minutes of whole group discussion and debate of the issues and their significance for the project's overall policy, conceptual, and empirical analysis.

Meeting Summaries. The in-person meetings will be recorded and detailed notes of presentations and discussion will be created by the project's Research Assistant. The detailed notes will be systematically

analyzed by the Research Team (with help from the Research Assistant) after each meeting. These summaries will identify new facts, recurrent and new themes, recurrent and new arguments, suggested practices and policies, and areas of disagreement and contention. A summary of each meeting will be circulated to all meeting attendees, who will be invited to suggest edits to the summary.

C. 3 Research Team Synthesis & Iterative Development of Recommendations & Educational Materials
The lead investigators and co-investigators set the agenda and determine the presentations and readings before each WG meeting and the summaries after each meeting. Between meetings, and after the third and final WG meeting, the Research Team will undertake synthesis of information and ideas from across all sources. After WG review of early draft recommendations and educational materials, we will finalize all deliverables. Selected members of the WG will be invited to co-author many of the deliverables, especially essays planned for the edited volume that will be turned into a special report of *The Hastings Center Report.*

The Research Team will compare the results of their policy review and conceptual and normative analysis with their analysis of the notes from WG meetings. After the second WG meeting the Research Team will undertake an iterative process to develop draft recommendations. Before the third and final WG meeting, we will send the draft recommendations to the full WG. At WG Meeting #3, the WG members will pilot test the draft recommendations by using sample protocols that pertain to ESCRO committee and IACUC protocol review. The recommendations will be assessed on several criteria, including clarity and actionability. After further discussion and refinement of the recommendations at WG Meeting #3 and further synthesis within the Research Team, the Research Team will circulate via email the final recommendations to WG members.

The goal will be to obtain consensus on the final recommendations from the WG. Consensus is defined as all members of the Research Team and the WG finding the final recommendations acceptable, i.e., that they lend support to the recommendations, even if less than wholeheartedly.[34] We are aware of the twin risks that can plague efforts to offer answers to ethically charged questions and to develop policy-relevant ethics recommendations. If we aspire to articulate highly specific recommendations on this genuinely controversial area, and if we have created a truly diverse WG, there may be no consensus. If, on the other hand, we do achieve consensus, there is the risk that our recommendations will be at a level of generality that verges on the banal. We recognize these risks and will discuss them with the WG, emphasizing the urgent need for recommendations that are specific and actionable. Where we cannot achieve consensus, we will make clear the specific options that different WG members believe should be on the table, in each case saying why these options were supported by some and not others, so that readers can thoroughly assess the various options. Members of the Research Team and/or of the WG who cannot reach this level of consensus agreement will have the opportunity to register their concerns about the final recommendations in a commentary in the project's Special Report to the *Hastings Center Report* that will be published at the end of the 3-year project. The recommendations will be presented in an Executive Summary, with analysis of the recommendations appearing as the lead article in the *Hastings Center Report* special report (see below). A short summary will also be published in a prominent science journal. Section C. 4 lists all deliverables.

C. 4 Deliverables
At this stage, we anticipate at least the 6 products listed below:

1. *Hastings Center Report* Special Report, the *Hastings Center Report (HCR)* is a prominent peer-reviewed journal with readers in medicine, basic and applied science, social science, and the humanities. The Research Team will develop a Special Report of *HCR* describing the purpose and aims of the 3-year project, its empirical and conceptual findings, and its recommendations for chimera research and oversight. Various WG members will be invited to write about an issue in their area of expertise and comment on the recommendations and key conceptual issues that emerged through the deliberations. The *HCR* is distributed to a global audience by John T. Wiley & Sons. All *HCR* Special Reports are available **open-access** by special contract between The Hastings Center and Wiley & Sons.

2. **Executive Summary of Recommendations**

3. Review of Recommendations in Prominent Science Journal

4. Two to Three Additional Scholarly Publications, presenting findings from policy review, empirical investigation, and conceptual analysis in discipline-specific journals.

5. Conference Presentations, such as the American Academy for the Advancement of Science (AAAS) annual meeting, PRIM&R's annual IACUC conference, and the annual conference of the ISSCR.

6. Educational Materials, **including a Protocol Casebook**, for ESCRO committees, IACUCs, scientists, and trainees that clarify ethical, conceptual and policy issues raised by human-animal chimera research and that contain the project's practicable recommendations for research oversight. Some of the materials will also be suitable for a general public interested in this research, and contribute to enhancing the public's understanding of this research by providing clear definitions and the rationale for chimera creation, as well as the moral uncertainties that surround them.

C. 5 Dissemination

The Hastings Center will vigorously disseminate the project's publications, taking advantage of its extensive network, which includes a database of 5,000 journalists with whom we are in frequent contact, a social media platform, including Twitter and Facebook, that routinely reaches thousands of scientists, leaders in science policy, health policymakers, bioethics scholars, and the general public. In addition, Hastings publishes a weekly *Hastings News* that goes directly into 20,000 emails; recipients include many leaders in science policy, scholars, journalists, and engaged members of the public. *Bioethics Forum*, the blog of the *HCR* is another vehicle that Hastings can make available to ensure widespread discussion of the findings and to alert potential audiences of the availability of the educational materials we will produce. And we have begun a podcast series, called *Hastings Conversations*, in which Mildred Solomon interviews scholars and authors of our reports, which creates a lasting archive. Finally, our Communications Department will develop a press release, reaching more than 20,000 viewers, to bring attention to the publication of the special report and other publications that will emerge from this project.

Several people on the WG are members of ISSCR and have served on ISSCR committees They will assist with dissemination of the educational materials to the ISSCR membership.

In addition, we have secured the active involvement of Public Responsibility in Medicine and Research (PRIM&R) to ensure that our findings, scholarly publications and educational materials will reach IACUC members. PRIM&R is a national leader in developing and conducting educational and professional development programs for IACUC members and educators. The Executive Director of PRIM&R (Dr. Elisa Hurley) is on our WG and has made an in-principle commitment to co-developing educational materials tailored to PRIM&R's membership as well as the general public, and widely disseminating them (see Letters of Support). This will include disseminating the Protocol Casebook to IACUC Directors, who are responsible for organizing training for IACUC members and chairs, as well as scientists and trainees at their institutions. This is our target audience. In addition, Dr. Hurley will contribute to the development of discussion guides regarding the conceptual, ethical, and policy challenges of human-animal chimera research and its oversight to include in PRIM&R's on-line Knowledge Center, a robust repository for education and practice change directed to members of institutional review boards that oversee human subjects research and IACUCs. Additional opportunities include a webinar and/or pre-conference workshop at the organization's annual meeting.

The Hastings Center will also host educational materials on its website. All educational materials created will be publicly available.

C. 6 Research Team & Management Plan

Principal Investigator, Josephine Johnston, LLB, MBHL: Hastings Center Director of Research and Research Scholar. Will share overall project responsibility with PIs Maschke and Hyun. Will co-lead (with Maschke and Hyun) the activities for the Policy Review, Conceptual Analysis, and Synthesis components and will lead the WG review of recommendations. Johnston has developed and led projects of this kind for over a decade and has been a member of the ESCRO committee of the Tri-Institutional Stem Cell Initiative (Rockefeller University, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine) since 2006.
Principal Investigator, Karen Maschke, PhD: Hastings Center Research Scholar and editor of Hastings' *IRB: Ethics & Human Research*. Will share overall project responsibility with PIs Johnston and Hyun. Will co-lead (with Johnston and Hyun) the activities for the Policy Review, Empirical Investigation, and Synthesis components and the WG deliberations, and will lead the Research Team's development of a Special Report of the *HCR*. Maschke has been a member of projects of this kind for over a decade, including NIH-funded

projects that investigated institutional and national oversight policies and practices for addressing ethical and conceptual challenges of human subjects research.

Principal Investigator Insoo Hyun, PhD: Associate Professor, Department of Bioethics at Case Western Reserve University and Director of the CWRU Stem Cell Ethics Center. Will share overall project responsibility with PIs Johnston and Maschke. Will co-lead (with Johnston and Maschke) the activities for the Policy Review, Empirical Investigation, Conceptual Analysis, and Synthesis components. Hyun has served in several leadership positions on ISSCR task forces and working groups and was a primary author of the ISSCR's original and updated guidelines for stem cell and chimera research.

Co-Investigator, Carolyn Neuhaus, PhD: Hastings Center Research Scholar. Will share in the intellectual and administrative work for the Policy Review, Empirical Investigation, and Synthesis components, including co-leading the Conceptual Analysis activities. Neuhaus has worked on issues related to genetically modifying laboratory animals to create model organisms, and creating chimeras as part of research to advance xenotransplantation. She has expertise in the philosophical literature on chimeras, animal use, and genome editing of non-human animals and served on NYU School of Medicine's IACUC from 2016-2017.

Co-Investigator Patricia Marshall, PhD: Professor of Bioethics and Anthropology and Director of the Center for Genetic Research Ethics and Law (CGREAL) in the Department of Bioethics at CWRU. An internationally renowned medical anthropologist, Marshall has conducted qualitative research for over 30 years and has published widely on the ethical, social, and oversight issues of genetic research. Marshall will lead the development and piloting of the interview guide, conduct the interviews, carry out the qualitative analysis, and present a summary report of the findings to the WG.

Co-Investigator Mildred Solomon, EdD. President of The Hastings Center. Solomon is an international expert in the relationship between normative and empirical ethics[35] and in bioethics teaching and curriculum development.[36] She has been the principal investigator on many federally- and foundation-funded research studies that have a "shape" similar to the one being proposed here: beginning with empirical and normative research, which then leads to recommendations and educational materials. She has developed policy recommendations and educational materials, based on both empirical and normative studies, in areas ranging from pediatric and adult end-of-life care to organ donation policies and practices, pain management, STD prevention, the ethical oversight of comparative effectiveness research, and the promotion of learning health systems.[37] Dr. Solomon also helped to found the Multiregional Clinical Research Trials (MRCT) initiative, now based at Harvard Medical School, which has developed best practices, new policies and educational materials on research ethics for thousands of biomedical researchers working across the globe.[38]

C. 7 Working Group

Juan Carlos Izpisua Belmonte, PhD: Professor and Roger Guillemin Chair at the Gene Expression Laboratory at the Salk Institute for Biological Studies. His team discovered a new type of stem cell that allowed them to develop the first reliable method for integrating human stem cells into an animal embryo.

Kara Manning Drolet, PhD: Director of Oregon Health and Science University's Research Integrity Office, where she manages the OHSU's oversight of gene editing research, embryonic stem cell research, and human-animal chimera research.

Lawrence Goldstein, PhD: Director of the Sanford Consortium for Regenerative Medicine at UCSD and Distinguished Professor of Cellular & Molecular Biology and Neurosciences. His lab uses hIPSCderived neurons, astrocytes and microglia to study the molecular basis for Alzheimer's disease and other neurodegenerative diseases.

Hank Greely, JD: Director of Stanford's Center for Law and the Biosciences, it's Program in Neuroscience and Society, and chair of California's Human Stem Cell Research Advisory Committee. He has published extensively about ethical and policy issues in human-animal chimera research.

Lorraine R. Hill, DVV: Deputy Department Chair, Department of Veterinary Medicine and Surgery, Univ. of Texas MD Anderson Cancer Center and a member of AAALAC's International Council on Accreditation. This non-profit organization promotes the humane treatment of animals in science through voluntary accreditation and assessment programs provided to institutions conducting animal research.

Elisa Hurley, PhD: Executive Director of PRIM&R. She has served as a nonaffiliated member of an IACUC and is the PI of PRIM&R's three-year NSF-funded project, "IACUC Institute: Improving Oversight of Animal Care and Use Programs Through Active Learning."

Robert Kesterson, PhD: Professor of Genetics, Univ. of Alabama at Birmingham, Director of the Transgenic & Genetically Engineered Models facility, member of the Institutional Biosafety Committee, and Chair of the

IACUC. His laboratory uses genetically modified animal models to study numerous physiological and behavioral processes.

Jonathan Kimmelman, PhD: Associate Professor in the Biomedical Ethics Unit/Social Studies of Medicine, McGill Univ. He is past chair of the ISSCR's ethics committee and a former member of the Stem Cell Oversight Committee of the Canadian Institutes of Health Research.

Nancy M.P. King, JD: Professor in the Department of Social Sciences & Health Policy at Wake Forest Univ. School of Medicine, with cross-appointments in the Institute for Regenerative Medicine and the Translational Science Institute. Former member of the NIH's Recombinant DNA Advisory Committee, with expertise on issues related to the development, oversight, and use of experimental technologies.

Geoff Lomax, Dr. PH: Senior Officer to the Standards Working Group at the California Institute for Regenerative Medicine, where he manages the development and evaluation of oversight regulations for all CIRM-funded research, including chimera studies. He was an external reviewer of the NAS's 2010 report on embryonic stem cell research.

Melissa Lopes, JD: Senior Research Compliance Officer, Office of the Vice Provost for Research, Harvard Univ. Directs the operations of the ESCRO committee and was co-chair to the Interstate Alliance on Stem Cell Research and a member of the UMASS Stem Cell Advisory Committee.

Pearl O'Rourke, MD: Director of Human Research Affairs, Partners HealthCare, and Associate Professor of Pediatrics, Harvard Medical School. She is a former member of an ESCRO committee, and as Deputy Director of the NIH's Office of Science Policy, worked on issues related to the derivation of and research with embryonic stem cells.

Steven Peckman: Associate Director for Administration & Planning, UCLA Broad Stem Cell Research Center where is he involved with the creation of oversight mechanisms for human-animal chimera research. He has published on ethical and oversight issues related to research with human pluripotent stem cells.

Monika Piotrowska, PhD: Assistant Professor in the Department of Philosophy at the Univ. of Albany, SUNY. Her research is in the philosophy of biology and bioethics. She has written about biological similarity in the context human-nonhuman chimeras.

Jeff Sebo, PhD: Clinical Assistant Professor of Environmental Studies and Director of the Animal Studies M.A. Program at NYU. He is on the board of several non-profit organizations whose missions include promoting respect and compassion for all animals and serving as a bridge between the academic field of animal studies and organizations concerned with animal protection.

Chris Stodgell, PhD: Chair of the Univ. Committee on Animal Resources (UCAR) at the Univ. of Rochester Medical Center. He has investigated how early embryonic exposures known to cause autism affects developmental gene expression in rodent models and has conducted studies with rats specifically bred to develop type-II diabetes.

Rob Streiffer, PhD: Associate Professor, Bioethics and Philosophy, Department of Medical History & Bioethics, School of Medicine and Public Health, Univ. of Wisconsin. His research encompasses bioethics (both medical and agricultural), ethical theory, and political philosophy, with a focus on ethical and policy issues arising from modern biotechnology.

Lorenz Studer, MD, PhD: Founder and Director of the Center for Stem Cell Biology at Memorial-Sloan Kettering Cancer Center. In 2015, Studer was named a recipient of the MacArthur Fellowship (also known as the "Genius Grant") for his innovative work on stem cell and Parkinson's disease research.

Amy Wilkerson: Associate VP for Research Support at The Rockefeller Univ, where she is involved in the oversight of Rockefeller's human pluripotent stem cell research through the Tri-Institutional Stem Cell Initiative (Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine).

Figure 4. Timeline	**Year 1**				**Year 2**				**Year 3**			
	1	2	3	4	1	2	3	4	1	2	3	4
Policy Review	■	■										
Empirical Investigation	■	■	■	■	■	■						
Conceptual Analysis & Literature Review	■	■	■	■	■	■	■	■	■	■		
Working Group Meetings					■		■		■			
Draft recommendations					■	■	■	■				
Finalize recommendations									■	■		
HCR Special Report: commission essays, edit, publish							■	■	■	■	■	■
Create & Disseminate Education Materials & Protocol Book							■	■	■	■	■	■
Conference presentations: apply, plan, present							■	■	■	■	■	■
Science Journal article: draft and submit									■	■	■	

PROTECTION OF HUMAN SUBJECTS

The activities in the proposed project are minimal risk interventions (interviews with professionals).

1. Risks to the participants.

1.A. Human participants' involvement and characteristics.

The human subjects participating in the interviews will be ages 18 and older, with the expected age range 30 and older. Pregnant women will not be excluded from participating because the interviews are minimal risk interventions. Most of the participants will have advanced degrees. They will have a range of professional backgrounds and expertise, e.g., stem cell science/research, animal research, medicine, and oversight of scientific research. They will also come from a variety of age ranges, race/ethnicities, institution types, and geographic locations.

We will interview chairs of 15 ESCRO committees, the chairs of 15 IACUCs, and 30 investigators who conduct chimera research, for a total of 60 interviews. The starting sample from which to recruit interviewees will be research institutions at ten sites in three states: California (Salk Institute for Biological Studies, Stanford University, UC Davis, UC San Diego, UC San Francisco); Massachusetts (Harvard University, MIT); and New York (Memorial Sloan-Kettering Cancer Center, Rockefeller University, Weill Medical College of Cornell University).

1.B. Sources of materials.

The materials will consist of interview recordings and transcripts. The interviews will be audio-recorded with explicit permission from the participants; if permission is not granted we will record responses in written notes. Participants will be identified by code numbers only in the database and in transcripts. Confidentiality procedures are described below in "Protection against Risk."

1.C. Potential Risks.

This is a minimal risk study. Loss of confidentiality is the primary risk. This project poses unique challenges to protection of confidentiality because participants' identities may be difficult to disguise due to their unique positions. Unless explicitly permitted to do so by participants, we will not identify participants in reporting the interview data or their institution. We will use generic position titles/roles whenever possible (e.g., stem cell scientists; chair of an ESCRO committee; chair of an IACUC)

2. Adequacy of Protection against Risks.

2.A. Recruitment & informed consent.

<u>Interviews</u>

After finalizing the interview instrument, initial contact with the 10 chairs of ESCRO committees and the 10 IACUC chairs will be made via USPS Priority Mail, followed within one week by email or telephone contact, with two additional email or telephone calls to confirm, answer questions, and schedule interviews with those who consent. The invitation letter will describe the purpose of the project, the project investigators, and the members of the Work Group. If an invited individual suggests a designee, we will request contact information and approach the designee in a similar manner. If an ESCRO committee/IACUC chair declines to participate and does not suggest a designee to interview, we will use a random selection process to select a medical college from the AAMC membership list, identify the relevant committee chair at that site, and use the recruitment process described above. If necessary, we will repeat the random selection process to reach the enrollment goal of 15 ESCRO and 15 IACUC chairs (or their designees).

Using snowball sampling to identify investigators to recruit for interviews, we will ask the ESCRO committee and IACUC chairs for the names of 2 investigators at their institution (N=20). We will use the initial recruitment and random selection processes described above to invite investigators to participate in an interview. We will ask the investigators who agree to be interviewed for the names of researchers at their or other institutions, with the goal of obtaining enough names to conduct 10 additional interviews. If we have difficulty obtaining a total of 30 investigator interviewees, we will use the snowball sampling approach by contacting members of our Working Group and other informants we know at research institutions and professional organizations to obtain names of investigators conducting human-animal chimera research.

2.B. Protection against risk.

The interviews in this study pose unique challenges to protecting the privacy of the informants, as their identities may be difficult to disguise due to their unique positions. This issue will be highlighted in the recruitment letter and before beginning the interview. We will also inform individuals that redacted transcripts may be made available to researchers and journal editors who request them. Interview data will be kept in locked file cabinets and/or on a secure server at Case Western and accessible only to the study team. We will tag all responses with an identifying number or pseudonym. The code key will be stored electronically on the secured server at Case Western and available only to the PIs. Audio files will be deleted from the portable digital recorders after transcription. During transcription, Dr. Marshall will proofread and de-identify as much as possible the transcripts to remove any embedded identifiers; any names will be replaced with either code numbers or pseudonyms as appropriate.

Excerpts from the interviews may be published but participants' privacy will be maintained in all published and written data resulting from the study. Quotations will be attributed by profession, not name, for example, "an executive at a biotechnology company stated x, y, z" or "as a senior staff member at a patient advocacy organization noted, a, b, c." If, based on a participant's unique position, it is impossible to obscure identity in a publication, we will ask explicit permission for use of the data.

3. Potential benefits

There are no potential benefits to individuals who participate in the interviews.

4. Importance of the knowledge to be gained.

Research involving the insertion of human cells into non-human animals (hereinafter animals) has been underway for decades, but the science is rapidly evolving and its ethical oversight has not kept up. Today, advances in human stem cell science and genetic engineering techniques are enabling researchers to more extensively and precisely insert human cells (and self-organizing mini-organ structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of vertebrate animals. These scientific advances are thrilling. Yet they also reveal conceptual, ethical, and procedural limitations in existing ethics guidance for what we call in this proposal "human-animal chimera research. The proposed project is highly significant, because it presents a thoughtful, evidence-informed way, that will be built in part on the insights and experiences of scientists who are themselves doing this kind of work and on oversight bodies that have faced the challenges of having to make decisions about the advance of such work. Our proposed investigation grows out of preliminary analyses we have already undertaken, which suggest that scientists and members of oversight bodies such as Embryonic Stem Cell Research Oversight (ESCRO) committees and Institutional Animal Care and Use committees (IACUCs), are themselves calling for greater conceptual clarity and more streamlined and understandable oversight procedures. Informed by both nuanced conceptual analyses and the empirical findings from a set of interviews with key leaders, the project will result in guidance to investigators, research institutions, oversight bodies (i.e., ESCRO committees and IACUCs), funders, and ultimately the public.

INCLUSION OF WOMEN AND MINORITIES

1. Targeted/Planned Distribution of Subjects

Please see the “Targeted/Planned Enrollment Table” for the anticipated sex, racial, and ethnic distributions.

2. Subject Selection Criteria and Rationale for Selection of Sex and Racial/Ethnic Group Members

We will not exclude individuals from participating based on sex or identification with a particular racial or ethnic group. We have no specific plans to over-enroll representatives from particular groups, as we do not anticipate significant differences in our results based on these categories.

3. Rationale for Exclusion of any Sex or Racial/Ethnic Group

We will not exclude individuals on the basis of sex, race, or ethnicity. Pregnant women will not be excluded. Because we are interviewing elite leaders from selected organizations, some populations may not be represented.

4. Proposed Outreach Programs for Recruiting Sex and Racial/Ethnic Group Members

We are not proposing any special outreach to racial or ethnic group members or women.

PHS Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

OMB Number:0925-0001 and 0925-0002
Expiration Date: 10/31/2018

***Study Title:** Actionable Ethics Oversight for Human-Animal Chimera Research

***Delayed Onset Study?** ❑ Yes ☑ No

If study is not delayed onset, the following selections are required:

Enrollment Type ☑ Planned ❑ Cumulative (Actual)

Using an Existing Dataset or Resource ❑ Yes ☑ No

Enrollment Location ☑ Domestic ❑ Foreign

Clinical Trial ❑ Yes ☑ No

NIH-Defined Phase III Clinical Trial ❑ Yes ☑ No

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					0
Asian	0	10		0	0					10
Native Hawaiian or Other Pacific Islander	1	2		0	0					3
Black or African American	0	2		0	0					2
White	15	30		0	0					45
More than One Race	0	0		0	0					0
Unknown or Not Reported										
Total	16	44		0	0					60

Report 1 of 1

Funding Opportunity Number: PA-17-444. Received Date: 2017-10-03T12:38:19.000-04:00

INCLUSION OF CHILDREN

We will not include children in this study. The study assessing professionals' views about issues related to evidence-based medicine. Thus, interviewing children is outside the aims of our proposal.

MULTIPLE PI LEADERSHIP PLAN

Rationale

The multiple PI approach for this research project maximizes a multidisciplinary team approach to undertake (1) normative analysis of foundational philosophical concerns, moral uncertainties, and value conflicts raised by human-animal-chimera research and its oversight, (2) empirical research with scientists and leaders of institutional oversight committees, and (3) develop guidance for investigators, research institutions, ESCRO committees and IACUCs, funders, and ultimately the public. The integrated approaches of this project require specific and complementary expertise to achieve the project's aims: moral philosophy and stem cell science (Hyun); stem cell research oversight (Hyun and Johnston); national and institutional policies and practices for oversight of science and technology (Maschke).

Governance and Organizational Structure

PIs Johnston and Maschke at The Hastings Center and PI Hyun at Case Western Reserve University will share overall responsibility of the project and each will oversee specific project activities. If a need arises to make changes to the overall aims of the project or to the distribution of funds, the PIs will decide jointly on how to proceed. Johnston, Maschke, and Hyun will collaborate to oversee and develop NIH progress reports. Johnston will be the contact PI and have responsibility for submitting progress reports and for any communication with program officers or other relevant officials at the NIH. Publication authorship will be based on relative contributions to the manuscripts submitted for publication.

Communication Plan

The PIs will communicate by regular email and monthly teleconference to discuss, design and implement the research project. They will communicate more frequently if necessary to address project developments that might affect funding distributions or necessitate changes to the project's activities and timeline. The PIs will meet in person for one PI meeting at Case Western Reserve University, for one PI meeting at The Hastings Center, and during the three Working Group meetings held at The Hastings Center.

Roles and Responsibilities

The PIs will work collaboratively in (1) developing materials for and holding conference calls with the other investigators, researcher assistants, and member of the project's Working Group, (2) developing agendas for the Working Group meetings, and (3) drafting and finalizing the project's recommendations. They will work collaboratively to oversee the tasks to achieve the project's aims. For Aim 1, Hyun and Johnston will lead the research activities and Working Group meetings that focus on the conceptual clarity and normative analysis related to defining and measuring "humanization" and its significance to animal welfare. For Aim 2, Maschke and Hyun will oversee the empirical research activities and lead the research activities and Working Group meetings that focus on identifying the strengths and challenges of existing oversight approaches to research involving human-animal chimeras. For Aim 3, Maschke, Johnston, and Hyun will lead the research activities and Working Group meetings that focus on synthesizing the findings of Aims 1 and 2 and that involve drafting and finalizing the project's recommendations and educational materials.

Conflict Resolution

Procedures for conflict resolution will adhere to Hastings Center and Case Western policies with the option to involve institutional senior leadership as well as NHGRI program officers if disputes cannot be resolved.

Change in PI Availability

A new PI (or PIs) will join the project to assume any duties that one (or more) of the current PIs for this project is unable to carry out.

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STATEMENT OF INTENT TO ESTABLISH A CONSORTIUM AGREEMENT

Date: September 19, 2017

FOA: PA-17-444

Application Title: Actionable Ethics Oversight for Human-Animal Chimera Research

Proposed Project Period: July 1, 2018 – June 30, 2021

The appropriate programmatic and administrative personnel of each institution involved in this grant application will establish written inter-institutional agreements that will ensure compliance with all pertinent Federal regulations and policies in accordance with the "NIH Grants Policy Statement," PHS 398 "Application for Public Health Service Grant," and the NIH "Guidelines for Establishing and Operating Consortium Grants."

NIH-Specific Requirements Promoting Objectivity in Research Applicable to Subrecipients (42 CFR Part 50 Subpart F):

> 42 CFR Part 50. 604 requires that institutions conducting PHS-funded research "*Maintain an up-to-date, written, enforced policy on financial conflicts of interest.*" Further, "*If the Institution carries out the PHS-funded research through a subrecipient (e.g., subcontractors or consortium members), the Institution (awardee Institution) must take reasonable steps to ensure that any subrecipient Investigator complies with this subpart by incorporating as part of a written agreement with the subrecipient terms that establish whether the financial conflicts of interest policy of the awardee Institution or that of the subrecipient will apply to the subrecipient's Investigators.*"

Subrecipient designates herein that it applies its own financial conflicts of interest policy; therefore, by execution of this Intent to Establish a Consortium Agreement, it certifies that its policy complies with 42 CFR Part 50.

CASE WESTERN RESERVE UNIVERSITY
(Subrecipient)

Principal Investigator
Inaoo Hyun
Date: September 19, 2017

Official Authorized to sign for Institution
Dawn Richards

The Hastings Center

Principal Investigator
Josephine Johnston, LLB, MBHL
Date: October 3, 2017

Official Authorized to sign for Institution
Cathy Meisterich, CFO/COO, The Hastings Center
Date: October 3, 2017

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Juan Carlos Izpisua Belmonte
Roger Guillemin Chair
Professor
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September 25, 2017

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Cleveland, OH 44106

Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research. " I understand that as a Working Group member, I will be asked to present my research involving human-non-human animal chimeras at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am currently Professor and Robert Guillemin Chair of the Gene Expression Laboratory at the Salk Institute for Biological Sciences. My colleagues and I study how genes and molecules orchestrate the development of an embryo. The questions addressed by the laboratory include: How does one cell give rise to millions of cells, and how do they come to be organized into complete structures such as limbs, a heart or brain? How stem cells differentiate and give rise to over 200 cell types that constitute the human body? How certain animals are able to regenerate their tissues and organs, i.e., what are the genetic pathways responsible for epimorphic regeneration, a complex biological process by which animals can regenerate tissues and even entire organs throughout their lifetime after injury or amputation?

We use a variety of methods to answer these – and other questions – including in vivo modeling, in silico modeling approaches, and ex vivo studies. Some of our recent findings highlighted the promise of chimeric organisms for science and medicine. Creating human-non-human chimeras will help researchers study evolution and disease, test therapeutic drugs, and possibly grow transplantable organs.

I am well aware this human-non-human chimera research raises some alarm bells. I have contributed to discussions at the National Institutes of Health, International Society for Stem Cell Research and other institutions on this topic. But I am also keenly aware that work on chimeras is right now at the basic

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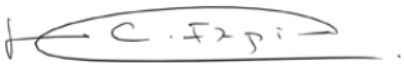
science level, and much more work is needed before we are capable of xenotransplantation. I want that work to continue and to expand. To that end, I am committed to creating a research oversight system that is capable of efficiently, consistently, and effectively overseeing chimera research. This is crucial to shoring up public trust and interest in the research. The proposed project as an important step toward creating an effective oversight system so that scientists around the country and around the world are not unduly hindered in their ability to learn new things using chimeric organisms.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,



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Date: September 29, 2017
Subject: Your project 'Actionalble Ethics Oversight for Human-Animal Chimera Research

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Dear Drs. Maschke and Hyun,

As Ethics Committee Chairperson for the International Society for Stem Cell Research (ISSCR) I am pleased to endorse your project "Actionable Ethics Oversight for Human-Animal Chimera Research." Your bioethics research team and your expert working group are staffed with notably qualified individuals who are committed to and capable of addressing the expanding complexities of human-animal chimera research.

Although the ISSCR has recently updated its stem cell research guidelines, including guidelines for chimera research, there is a pressing need for further guidance for researchers and institutional oversight regulators in this rapidly advancing field, especially in light of the now widespread use of genome editing tools. An empirically-based approach such as yours which seeks to identify further applicable ethical standards for chimera research is precisely what the research community needs at this point. In my current joint project on the ethics of organoid technology with the Hubrecht Institute (prof Hans Clevers) we encounter similar ethical and regulatory challenges due to the hybrid character of organoids. I therefore think your project may inspire similar debates in bioethics.

I am pleased that the ISSCR guidelines and the ISSCR Ethics Committee advisory report on chimera research will serve as useful starting points for your proposed project. Dr. Insoo Hyun has been closely involved in these aforementioned ISSCR efforts, so I know your proposed project will continue to build on that previous work in a very fruitful manner. Please let me know if the ISSCR Ethics Committee could be of any help as you move forward with your project in the future.

Sincerely,

Annelien Bredenoord, PhD

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Date: 01 October 2017
Reference: HC/PW/019
Subject: project "Actionable Ethics Oversight for Human-Animal Chimera Research

Dear Drs. Maschke and Hyun,

As stem cell scientist and past-president of the Royal Netherlands Academy of Arts and Sciences, I believe your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research" is well poised to provide necessary additional guidance for institutional regulators and researchers working in this crucial area of stem cell science.

Although a general set of international guidelines exists for the ethical conduct of human-animal stem cell chimera research, promulgated by the International Society for Stem Cell Research (ISSCR), chimera research is likely to expand in evermore complex directions given the potential additional uses of human naïve pluripotent stem cells, organoids, and genome editing tools. Such rapid developments pose new ethical challenges for institutions and scientists, and more specific professional guidance will become necessary in the near future. For example, if human-animal chimera models can be engineered to incorporate greater amounts of human biological materials, particularly in their central nervous systems, then their scientific utility will surely increase, but perhaps in direct proportion to the moral ambiguities these scientific models may create. What does humanization of an animal model mean for regulators? What are its ethical limits, and how do researchers know if they have crossed important ethical boundaries? These are important questions.

I am pleased to endorse your research team's comprehensive approach to ethics oversight. As you know, human-animal chimera research is a vital area of stem cell science that transcends national borders. Having a clear and actionable plan for ethics oversight will help facilitate international scientific collaborations. I very much welcome your plan to gather insights from regulators and chimera researchers in the U.S., as it is essential for any further ethical recommendations in this area to address the concerns of those actually responsible for conducting the research. I wish you the best of luck in pursuing this important endeavor.

Sincerely,

Hans Clevers, MD PhD
Professor of Molecular Genetics

Research Development &
Administration

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September 22, 2017

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research. " I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am Director of Oregon Health and Science University's Research Integrity Office. In this role, I manage the OHSU's oversight of gene editing research, embryonic stem cell research, and human-animal chimera research. In the course of my work, I have reviewed existing guidance as well as scholarship addressing oversight of human-animal chimera research, and found it to be of little assistance in developing oversight approaches or frameworks. Your proposed project will close an important knowledge gap by addressing conceptual and ethical questions raised by human-animal chimera research so that clear and operationalizable guidance can be developed.

As you may also know, OHSU dissolved its ESCRO and developed an ongoing review system for oversight of many of the ethical issues that arise in this area. In some ways, this oversight approach is an experiment in governance, and I would look forward to sharing experiences and insights with you and your colleagues about this approach to oversight, learning about oversight approaches used at other research institutions, and developing recommendations to address oversight of human-animal chimera research.

My experience in developing an ad-hoc committee to review ethical issues surrounding gene editing research in embryonic stem cells at OHSU may be of interest to the working group as they explore the human-animal chimera areas of research, and mechanisms of review. Through relationships developed during this special review process, I have agreed to discuss ethical issues of human embryonic stem cell research as a guest lecturer in a bioethics course at Oregon State University. I also serve as a board member for the Northwest Association of Biomedical Research, whose mission includes focus on promoting the public's trust in biomedical research and its ethical conduct.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Kara Manning Drolet, Ph.D.

UNIVERSITY OF CALIFORNIA, SAN DIEGO UCSD

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Dear Drs. Maschke and Hyun,

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As you know, I am Dr. Larry Goldstein, Director of Sanford Consortium for Regenerative Medicine at UCSD and Distinguished Professor of Cellular & Molecular Biology and Neurosciences, where my lab uses hIPSC derived neurons, astrocytes and microglia to study the molecular basis for Alzheimer's disease and other neurodegenerative diseases. Use of human-animal chimeras is a newly developing and exciting branch of our projects and we will be able to use this technology in our future studies.

In my experience, oversight of the work that I do, and human-animal chimera research in general, can be challenging for institutions to oversee and difficult for scientists to predict. One of my concerns about this confusion is that it could end up inappropriately restricting important science.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Lawrence S. B. Goldstein, PhD
Distinguished Professor of Cellular & Molecular Medicine
Distinguished Professor of Neurosciences

Stanford Law School

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September 26, 2017

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Dear Drs. Maschke and Hyun:

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings; to contribute actively to discussion and deliberation of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight at all project meetings; and to help develop the project's analysis and recommendations.

As you know, I am the Deane F. and Kate Edelman Johnson Professor of Law and Professor, by courtesy, of Genetics at Stanford University, where I have specialized in the ethical, legal, and social implications of new biomedical technologies, particularly those related to genetics, neuroscience, and stem cell research. I direct Stanford's Center for Law and the Biosciences and the Stanford Program in Neuroscience and Society as well as chair the Steering Committee for the Stanford Center for Biomedical Ethics. I chair California's Human Stem Cell Research Advisory Committee and am co-chair of the Neuroethics Division of the NIH BRAIN Initiative's Multi-Council Working Group (as well as being a member of the Working Group). I am also a member of the Committee on Science, Technology, and Law of the National Academies and a member of the Neuroscience Forum of the National Academy of Medicine

I have published several articles and book chapters on ethical and policy issues in human-animal chimera research. And I feel strongly that the research (or, better, chimeras as a research tool) generally should proceed, yet I also think that some kinds of chimeras require

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careful thought—and thoughtful care. This is particularly true of chimeras where non-human animals have human contributions to their gonads, brains, or outward appearance. There is some guidance available – a July 2005 *Science* piece from a Johns Hopkins's organized group on chimeras involving humans and non-human primates, the NAS stem cell guidelines, and the ISSCR guidelines – but institutions and scientists are still unsure how to proceed. I also worry that public understanding of this kind of research is lacking, which could impede the science.

I am happy to commit to come to a work group meeting to talk about my research and views, and to engage with you and other Working Group members in addressing various issues related to human-animal chimera research.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Henry T. Greely

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Dear Drs. Maschke and Hyun,

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As you know, I am currently Associate Professor, Section Chief of Experimental Surgery and Imaging Support, Chief IACUC Veterinarian, and Director of Education, Department of Veterinary Medicine and Surgery, The University of Texas MD Anderson Cancer Center. I have experience managing large, complex animal programs, including research programs involving genetically altered mice and nonhuman primates. Some of my recent collaborations include evaluation of irreversible electroporation as an adjunct therapy for the treatment of osteomyelitis in a rabbit model and for ablation of spinal tumors in a canine model; strategies for reversal of radiation induced sterility in a nonhuman primate model; development of a novel inferior vena cava filter in a swine model; assessment of the rabbit as a model for osteoradionecrosis; and evaluation of novel topical therapies for chronic wounds in a swine model. I also oversee training laboratories for physicians and other trainees using a variety of animal models.

My interest in this project stems primarily, however, from my comprehensive knowledge of the regulatory and compliance processes related to animal research and an in-depth

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understanding of the process research institutions undergo for accreditation by AAALAC International, a private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and assessment programs. I currently serve as a member of AAALAC's International Council on Accreditation.

Rapid advances in human stem cell science and genetic engineering techniques are enabling researchers to more extensively and precisely insert human cells (and self-organizing mini-organ structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of vertebrate animals. These scientific advances are revealing the conceptual, ethical, and procedural limitations of existing ethics guidance for human-animal chimera research and its oversight. While national and international guidelines exist for Embryonic Stem Cell Research Oversight (ESCRO) committee members specifically about reviewing chimera protocols, there is no analog in the IACUC world. As IACUCs are tasked with reviewing an increasing number of protocols that involve the creation and use of chimeric organisms, and that involve larger animals such as pigs, sheep, or non-human primates, committee members will need training and guidance on chimera-specific issues. The project is therefore timely, and its outputs will be utilized by animal care and use programs across the country.

I am also pleased that this project will bring together chairs and members of ESCRO committees and chairs and members of IACUCs. Though members of these committees sometimes review the same protocols, they rarely talk to each other. The roles and scope of both committees will be clarified as this project critically analyzes what type of oversight system works best for this type of research.

I have extensive experience with IACUC review (18 years) as well as with IBC and a variety of other safety committees. My service to AAALAC, International (14 years) has kept me on the forefront of advances in program oversight and methods to enhance animal welfare in the conduct of quality research.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Lori R Hill

Lori R. Hill, DVM, DACLAM

PRIM&R
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

September 24, 2017

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Department of Bioethics
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Cleveland, OH 44106

Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am currently Executive Director of PRIM&R, Public Responsibility in Medicine & Research. Founded in 1974, PRIM&R advances the highest ethical standards in the conduct of biomedical, behavioral, and social science research. We accomplish this mission through education, membership services, professional certification, public policy initiatives, and community building. The aims of the proposed project align with PRIM&R's mission in that it will develop clear and actionable guidelines for ensuring that research involving human-non-human chimeras adheres to the highest ethical standards.

In addition to PRIM&R's organizational resources, described below, I will bring to the Working Group expertise in philosophical analysis, in-depth knowledge of both non-human and human research oversight, experience developing and delivering educational modules and resources for members of research oversight committees, and a commitment to shoring up public trust in the research—and research oversight—enterprise.

This project will bridge a gap between philosophical theorizing about moral status and species boundaries and practically determining what we owe to chimeric organisms. It will address conceptual and ethical questions raised by human-animal chimera research so that clear and operationalizable guidance can be developed. This is extremely important to PRIM&R's membership, which includes chairs, members, directors, and staff of Institutional Animal Care and Use Committees (IACUCs), who tasked with approving research protocols that propose the use of chimeras in biomedical research.

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PRIM&R members and non-members use our Knowledge Center and educational programs and resources to obtain further training on topics related to biomedical research involving non-human animals. We do not yet provide resources on issues specific to chimera creation, though I expect a demand for them as chimera research expands, owing to advances in genome editing technology and stem cell research. PRIM&R regularly hosts in-person and online webinars, short courses, and workshops on various topics in research oversight. Participation in these events often leads to practice changes at participants' home institutions. Prior to becoming Executive Director, I served as PRIM&R's Director of Education and was directly engaged in creating these courses and resources.

I see an opportunity through this project to develop educational resources for oversight committee members as well as the general public pertaining to chimera research and research oversight. I have this expertise and would be happy to contribute PRIM&R's resources to your dissemination plan. I also envision hosting a pre-conference workshop at one of our annual IACUC conferences to provide continuing education on ethical and oversight issues related to human-animal chimeras. Any resources we create would then be archived in PRIM&R's Knowledge Center and made publicly available.

Finally, as a moral philosopher who has spent the last 12 years writing, speaking, teaching, and thinking about research ethics, bioethics, and other issues in applied ethics—first as a philosophy professor, and then in my role as an educator at PRIM&R—I will bring to the working group my experience with rigorous conceptual analysis and ethical theorizing, on the one hand, combined with an understanding of how those concepts and principles can and should be translated into practical guidance, on the other.

I look forward to engaging with you and the other Working Group members to address the difficult and important conceptual, normative, and oversight questions raised by human-animal chimeras.

Sincerely,

Elisa A. Hurley, PhD
Executive Director
PRIM&R

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September 29, 2017

Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am Professor of Genetics at the University of Alabama at Birmingham and serve many roles involving oversight of biomedical research using genetically modified animal models including Director of the Transgenic & Genetically Engineered Models (TGEMs) facility, member of the Institutional Biosafety Committee (IBC), and Chair of the Institutional Animal Care and Use Committee (IACUC). My laboratory uses genetically modified animal models to study numerous physiological and behavioral processes. Training in the melanocortin receptor (GPCRs) field creating knockout mouse models broadened my interests towards molecular mechanisms by which CNS melanocortin receptors regulate feeding, energy balance, thermoregulation, inflammation, and learning and memory. More recently, we have focused on 1) mechanisms by which primary cilium localized on hypothalamic neurons regulate energy balance, and 2) humanized models of Neurofibromatosis Type 1 and developing therapeutic interventions.

My interest in this project stems from experience on UAB's IACUC and IBC, as well as our move to use human induced pluripotent stem cells as a research tool. Rapid advances in human stem cell science and genetic engineering techniques are enabling researchers to more extensively and precisely insert human cells (and self-organizing mini-organ structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of vertebrate animals. These scientific advances are revealing the conceptual, ethical, and procedural limitations of existing ethics guidance for human-animal chimera research and its oversight. While national and international guidelines exist for Embryonic Stem Cell Research Oversight (ESCRO) committee members specifically about reviewing chimera protocols, institutional IBC and IACUC committees struggle to develop their own policies and interpret federal regulations that often are unclear. As IBCs and IACUCs are tasked with reviewing an increasing number of protocols that involve the creation and use of chimeric organisms, and that involve larger animals such as pigs, sheep, or non-human primates, committee members will need training and guidance on chimera-specific issues. This project is therefore very timely, and I expect will be well received with resulting outputs utilized by most all biomedical research institutions.

I am also pleased that this project will bring together chairs and members of ESCRO committees and chairs and members of IACUC committees. Though we sometimes review the same protocols, we rarely talk to each other. The roles and scope of both committees will be clarified as this project critically analyzes what type of governance system works best for this type of research. Importantly, I have participated in an online group of IACUC chairs from several large institutions for the last several years and found that our ability to ask for input for situations frequently not addressed (or clear) in federal regulations has been extremely helpful in making decisions regarding developing policies at UAB. I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Bob Kesterson, Ph.D.
Professor
Director, Transgenic & Genetically Engineered Models (TGEMs)
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McGill | Faculty of Medicine | Faculté de médecine

September 28, 2017

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Dear Drs. Maschke and Hyun:

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As you know, I am Professor of Biomedical Ethics / Social Studies of Medicine at McGill, where I am also interim director of the Biomedical Ethics Unit. I formerly chaired the ISSCR ethics committee and co-directed the revision of the society's Guidelines on human embryo research and clinical translation. I also have a large research program investigating the ethics of animal research in drug development, and presented ISSCR's position on human-animal chimera research to the NIH during its temporary hold on such research.

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It is clear to me that there are many unsettled questions regarding the ethics and oversight of human-animal research, and I heartily endorse this effort to bring greater clarity and order to this research frontier. I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Jonathan Kimmelman, PhD
Associate Professor

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Division of Public Health Sciences
Department of Social Sciences and Health Policy

26 September 2017

Nancy M. P. King, JD
Professor, Social Sciences and Health Policy
and Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine
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Karen J. Maschke, PhD
Research Scholar
The Hastings Center
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Insoo Hyun, PhD
Department of Bioethics
Case Western Reserve University
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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present about the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am Professor of Social Science and Health Policy at Wake Forest School of Medicine, where I also have an appointment in the Institute for Regenerative Medicine. In addition, I co-direct the Center for Bioethics, Health, and Society at Wake Forest University. I have researched and published on legal and policy issues in stem cell research, gene transfer research and gene editing, and regenerative medicine. In particular, my work has addressed issues arising from research with human embryonic stem cells, embryonic stem cell oversight committees (ESCROs), genome editing of embryos, and regenerative medicine technologies that focus on organ transplantation and regeneration, including chimerism.

As research in regenerative medicine and genome editing expands rapidly, it has become increasingly clear that the ethics and policy issues around animal-human chimera research are conceptually ambiguous and much in need of further consideration. Existing guidelines are insufficient to keep pace with the development of research in this area; thus, scientists, research institutions, and funders are uncertain about how to proceed and in need of further guidance.

I believe that my past and current scholarly activities can assist your project's Working Group in its consideration of the current and future status of ESCROs and the many different areas of research that include human-animal chimeras. In addition, I am a current member of the DHHS Secretary's Advisory Committee for Human Research Protections, which works closely with the Office for Human Research Protections in providing guidance to the Secretary, and I am a former member of the Recombinant DNA Advisory Committee; finally, I have long worked on issues relating to IBCs and IACUCs. As you are well aware, all of these oversight bodies touch on various aspects of the complex issues relating to chimera research.

In sum, the challenges raised by human-animal chimera research are complex and multifaceted, and this project is therefore both necessary and timely. I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Nancy M. P. King, JD

CIRM
CALIFORNIA'S STEM CELL AGENCY

September 21, 2017

Karen J. Maschke, PhD
Research Scholar
The Hastings Center
21 Malcolm Gordon Road
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Insoo Hyun, PhD
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Dear Drs. Maschke and Hyun:

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research. " I understand that as a Working Group member, I will be asked to present my experiences with the development of institutional oversight policies governing human-animal chimera research funded by the California Institute for Regenerative Medicine at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As the Senior Officer to the CIRM Standards Working Group, I manage the development and evaluation of oversight regulations governing all CIRM-funded research, including studies involving human-animal chimeras. Many questions have come up over the years about the oversight of research involving transplantation of human stem and progenitor cells to non-human animals. The landscape is uneven, varying from institution to institution. This variance has the potential to impede research.

More refined guidance offering a clear description of the concerns that human-animal chimera research raises, or offering clear decisions points for oversight are needed. Your proposed project is therefore very timely, and will help provide needed clarity in this dynamic area particularly as pre-clinical studies evaluating the safety and efficacy of cell-based therapeutic are increasing important to the field of regenerative medicine.

I look forward to sharing these experiences and procedures with the Working Group in the effort to develop efficacious approaches to the oversight of human-animal chimera research.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Geoffrey Lomax Dr.PH.

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September 25, 2017

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am the Director of the Embryonic Stem Cell Research Oversight ("ESCRO") Committee at Harvard University. In this role, I manage the oversight of all research involving human embryonic stem cell derivation and use at Harvard University, including some of the University's research involving human-animal chimeras. Oversight of chimera research is a continuing challenge for ethics committees like ours, particularly when the research involves injecting human cells into the brains or nervous systems of animals. It can be difficult to know how to measure or assess humanization in human-animal chimeras, creating uncertainty for oversight committees and researchers alike.

Because ESCROs are unregulated bodies, it is important that they can work together to create predictable, actionable, and understandable practices around research like animal-human chimera research. As part of your project, I would look forward to hearing how other ESCROs

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and institutions are approaching these issues and to working with you and other members of the Working Group to develop reasonable approaches.

Within my broader role in the Office of the Vice Provost for Research at Harvard, I convene stakeholders from across the University on a wide range of research oversight issues and work with various stakeholders and ethics committees to develop rational research oversight policies and procedures. For certain ethical issues that arise with respect to emerging research advancments, we convene broader groups of national and international experts to inform and guide our policy development. I look forward to sharing best practices in this area, as well as gleaning insight from other ESCROs on this important issue of ethics oversight for human-animal chimera research.

As a former state public health policymaker and co-chair of the National Academies of Sciences Interstate Alliance on Stem Cell Research, I recognize the value of engaging stakeholders and sharing experiences and ideas to address nuanced bioethical questions. I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Melissa J. Lopes, J.D.
Senior Research Compliance Officer, Office of the Vice Provost for Research
Director, Harvard ESCRO

PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

P. Pearl O'Rourke, M.D.
Director, Human Research Affairs

09/25/2017

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am Director of Human Research Affairs at Partners HealthCare Systems in Boston and an Associate Professor of Pediatrics at Harvard Medical School. In my role as Director of Human Research Affairs, I am responsible for the systems that support the regulatory and ethical oversight of human research and the responsible conduct of research. In that role, I have been involved in our oversight of research involving the creation of human-animal chimeras. In terms of guidance for assisting with that oversight, existing guidelines are not very helpful, and oversight committees struggle with what to do.

While I certainly understand the idea of humanizing an animal, and have given this area of research considerable thought and attention, I am not clear on what humanization means in terms of the protocols we are asked to advise on and to assess. For instance, if the presence of human cells in an animal embryo or in an animal brain is important for assessing humanization,

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P. Pearl O'Rourke, M.D.
Director, Human Research Affairs

how many cells mark the relevant oversight threshold? Given the pace of scientific research in this area, especially since the introduction of new gene editing techniques and advances in transplantation related research, the "once we see it, we will know it" approach does not seem wise to me.

I want to offer you my support for your project. I am particularly impressed by your plan to include representatives from animal welfare and IACUC communities. I would look forward to sharing my experiences and research with the Working Group and to working with you to create clear and useful approaches to oversight of research involving animal-human chimeras. I have had the opportunity to serve on a number of working groups that had focused on challenging issues – and in each have found the experience extremely valuable. Even when a precise "answer" remains elusive, the robust discussion and evaluation of options improve the field.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

P. Pearl O'Rourke, M.D.

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September 26, 2017

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RE: *Working Group - Actionable Ethics Oversight for Human-Animal Chimera Research*

Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human - non-human animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human - non-human animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am Associate Director of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research (Broad Stem Cell Research Center (BSCRC)) at the University of California, Los Angeles (UCLA). In that role, I have been deeply involved with the creation of oversight mechanisms for human- non-human animal chimera research, including policies and procedures for the Human Pluripotent Stem Cell Research Oversight Committee. Prior to joining the BSCRC, I worked for more than 10 years in UCLA's Office for Protection of Research Subjects as Associate Director-Human Subject Research, responsible for five Institutional Review Boards (IRBs) and their review of the ethical and legal conduct of human subjects research, creation of a campus-wide education and certification program, membership on Independent Safety Monitoring Boards, and informed consent monitoring. I have also published and presented in the area of human pluripotent stem cell research and human research subject protection.

In my experience, the ethical and policy issues for human - non-human animal chimera research challenge the traditional oversight strategies for academic research institutions. Part of the struggle stems, in my view, from a lack of clarity about the philosophical issues: What exactly is the nature of the concern driving oversight in this area? Are we concerned about creating

something that is more human than we want it to be—and if so, in what ways might it be more human? One of my concerns about this confusion is that it could end up unduly restricting important science without concomitant benefits or protections.

I am particularly impressed that your proposed project will address conceptual issues, include people who focus on non-human animal welfare, and that you are using a workshop approach so that different oversight approaches can be considered. The science is moving very fast in areas involving human - non-human animal chimeras, and this is an optimal time to be open to thinking about whether we should be doing things differently in this area. I look forward to sharing my experiences and research with the Working Group and to working with you to create clear and useful approaches to oversight of research involving non-human animal - human chimeras.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Steven Peckman
Associate Director

UNIVERSITY AT ALBANY
State University of New York

Department of Philosophy

September 29, 2017

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my research as it relates to the philosophical issues raised by human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

I am Assistant Professor of Philosophy at the University of Albany, SUNY. My areas of specialization include philosophy of biology and bioethics, and my research focuses on conceptual and ethical issues arising from recent advances in genetics and biotechnology. Topics I have written about include genetic engineering, humanized mice, and human-nonhuman chimeras.

In the course of my research, it has become increasingly clear to me that there is an abundance of indeterminacy surrounding the conceptual and ethical issues involving human-nonhuman chimeras and that the philosophical tools for addressing these issues are in need of further development. Let me offer a couple of examples.

Although human-nonhuman chimeras have been the focus of ethical controversies for more than a decade, little has been said about the relationship between the origin of the transferred cells of chimeras and the morally relevant capacities to which they may give rise. Consider, for example, a pair of developing mouse fetuses. Suppose the first receives a brain stem cell transplant from a human and the second receives a brain stem cell transplant from a dolphin. Suppose further that both mice acquire "human-like" characteristics (e.g., increased intelligence) because of the transfer. Should the distinct origins of the cells, even though they give rise to seemingly identical characteristics, affect the moral status of the two mice? Currently, public policy in the United States recommends treating the two mice differently. While a local Institutional Animal Care and Use Committee (IACUC) must review both proposals to check for animal welfare issues, only the mouse receiving cells from a human is subject to an additional layer of review by a local Embryonic Stem Cell Research Oversight (ESCRO) committee. But should the distinct origins of cellular material matter when it comes to making moral distinctions? The answer is not clear, since the question has not been explicitly addressed in the literature on human-nonhuman chimeras.

Another important issue involving human-nonhuman chimeras concerns the difficulty of making judgments in the face of scientific uncertainty. When human-nonhuman chimeras are created, it's difficult to say whether they are similar enough to their human counterparts to serve as effective models of human characteristics. Yet getting the judgment correct in this situation is crucial, since the "humanization" of

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the host species raises sticky ethical issues that might be overlooked by researchers on the basis that humanizing nonhuman animals promises better research models. But that judgment is not obvious. I've argued that viewing the characteristics one hopes to model as a mechanism can help ground judgments of similarity. If target characteristics are viewed in this way, similarity relations between mechanisms can justify our inferences from model to target. Even so, this approach has limits. For example, if we view something like human disease as a mechanism, and if the parts and boundaries of the mechanism are preserved in the host organism (an incredibly difficult task, as I point out in my work), we have some reason to believe that the host can simulate human disease. However, the inference is weak without the right context. It turns out that even identical mechanisms may not justify the inference that what is true of one mechanism in one organism will be true of the same mechanism in another organism. The fact that context can have such a significant impact on the anticipated human characteristics shows that even the mechanistic approach to biological inference, an approach that has become increasingly popular, has limits. These limits must be taken into consideration when creating public policy recommendations about the possible "humanization" of non-human organisms.

Both of the above examples from my own work fit under the broader set of problems identified by the PIs: That existing research guidelines for human-nonhuman chimeras lack clarity about what humanization means, how to measure it, and when it is and is not problematic. I believe my philosophical work will be valuable to the Working Group and I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative, and oversight questions.

Sincerely,

Monika Piotrowska, Ph.D.

NEW YORK UNIVERSITY

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September 21, 2017

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Associate Professor
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Case Western Reserve University
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Cleveland, OH 44106

Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present philosophical research on chimera use in biomedical research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-nonhuman chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am currently Clinical Assistant Professor of Environmental Studies, Affiliated Professor of Bioethics, Medical Ethics, and Philosophy, and Director of the Animal Studies M.A. Program at New York University. My scholarship in these fields explores sentience, agency, and moral status in human and nonhuman animals, the ethics of using animals in food, research, and other industries, and the relevance of domesticated, liminal, and wild nonhuman animals to global challenges such as climate change. I am keenly interested in the conceptual and ethical issues that arise in the creation and use of human-nonhuman chimeras.

I will contribute to the Working Group by helping fellow members understand the philosophical issues surrounding the moral status of nonhumans, including chimeras, and challenging them to think critically about the justifications for creating chimeras. I look forward to translating philosophical literature on "humanizing" nonhumans, the nature and value of species boundaries, the relevance of individual capacities and species membership to moral status, and the like into actionable policy and oversight recommendations. Your proposed project will close an important knowledge gap by addressing conceptual and ethical questions raised by human-nonhuman chimera research so that clear and operationalizable guidance can be developed.

My scholarship in animal studies is motivated in part by a commitment to animal activism, advocacy, and philanthropy. I see effective oversight and clear guidelines for oversight committee members as one, though not the only, way to protect animals in biomedical research. To that end, I am committed to co-developing with Working Group members guidelines and recommendations that protect chimeras and promote their welfare.

In addition to my current position at New York University, I previously worked in the Department of Bioethics at the National Institutes of Health, where I was able to take IACUC training, observe IACUC meetings, and speak with people engaging in nonhuman subjects research as well as in education, consultation, and oversight regarding this research. I also work with several nonprofits that promote animal welfare and animal studies, so I have experience not only with the perspectives of people engaging in nonhuman subjects research and oversight but also with the perspectives of people advocating for changes to this research and oversight. I would love to draw from all these experiences to help ensure that all relevant and valuable perspectives are considered as part of this Working Group.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, ethical, and policy questions.

Sincerely,

Jeff Sebo
Clinical Assistant Professor of Environmental Studies
Affiliated Professor of Bioethics, Medical Ethics, and Philosophy
Director of the Animal Studies M.A. Program
New York University

Christopher J Stodgell, PhD
Associate Professor, Obstetrics & Gynecology
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UR MEDICINE
MEDICINE of THE HIGHEST ORDER

September 20, 2017

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am currently Associate Professor in the School of Medicine and Dentistry of the University of Rochester. Most relevant to this proposal, I am Chair of the University Committee on Animal Resources (UCAR), or IACUC at the University of Rochester.

The goal of my research is to understand the environmental and genetic etiologies of developmental disorders, such as autism spectrum disorders. To this end, I utilize animal models in my research and appreciate how human-non-human animal chimeras could be used to answer certain scientific questions. Furthermore, my experience as a member and current chair of the Congressionally Directed Medical Research Program's Autism Research Panel, I am reviewing an increasing number of research proposals that use tissue and genes from human origin in non-human species with the goal of better understanding the neurobiology of autism spectrum disorders

My interest in this project stems primarily, however, from my experience on Rochester's UCAR. Rapid advances in human stem cell science and genetic engineering techniques

are enabling researchers to more extensively and precisely insert human cells (and self-organizing mini-organ structures derived from human stem cells) into any stage of embryonic, fetal, and post-natal development of

vertebrate animals. These scientific advances are revealing the conceptual, ethical, and procedural limitations of existing ethics guidance for human-animal chimera research and its oversight. While national and international guidelines exist for Embryonic Stem Cell Research Oversight (ESCRO) committee members specifically about reviewing chimera protocols, there is no analog in the IACUC world. As IACUCs are tasked with reviewing an increasing number of protocols that involve the creation and use of chimeric organisms, and that involve larger animals such as pigs, sheep, or non-human primates, committee members will need training and guidance on chimera-specific issues. The project is therefore timely, and its outputs will be utilized by animal care and use programs across the country.

I am also pleased that this project will bring together chairs and members of ESCRO committees and chairs and members of IACUC committees. Though we sometimes review the same protocols, we rarely talk to each other. The roles and scope of both committees will be clarified as this project critically analyzes what type of governance system works best for this type of research.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

THE UNIVERSITY of WISCONSIN MADISON

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research. " I understand that as a Working Group member, I will be asked to present my philosophical research on non-human animals and chimera use in biomedical research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am an Associate Professor (with tenure) at the University of Wisconsin, Madison. I have a joint appointment in the Department of Medical History and Bioethics and the Philosophy Department, and affiliate appointments in the Department of Medical Sciences in the School of Veterinary Medicine, in the Department of Agricultural and Applied Economics in the College of Agricultural and Life Sciences, and in the Gaylord Nelson Institute for Environmental Studies. I received my Ph.D. in ethics from the Massachusetts Institute of Technology. My research focuses on ethical and policy issues arising from modern biotechnology, both biomedical and agricultural. I have broad interests in applied ethics, ethical theory, metaethics, and political philosophy. Recent work focuses on the ethics of animal use, including the creation and use of human-non-human chimeras. I wrote the Stanford Encyclopedia of Philosophy's entry on Human/Non-Human Chimeras – the go-to resource, written for a general readership, to learn about philosophical, conceptual, and ethical issues

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surrounding chimera creation and use. I have also published more specific papers on human-non-human chimeras in the *Kennedy Institute of Ethics Journal* and inn the *Journal of Law, Medicine, and Ethics*.

I will contribute to the Working Group by helping fellow members understand the philosophical issues surrounding the moral status of non-human animals, including chimeras, and challenging Working Group members to think critically about these conceptual issues. I look forward to translating philosophical literature on "humanizing" non-human animals, the relevance of cognition to moral status, species boundaries, and the like into actionable policy and oversight recommendations. Your proposed project will close an important knowledge gap between philosophical theorizing and the practice of research oversight by addressing conceptual and ethical questions raised by human-animal chimera research so that clear and operationalizable guidance can be developed.

In addition to my scholarship, I have also served on the UW Health Sciences Institutional Review Board, the UW Hospital Ethics Committee, UW's Biotechnology Advisory Committee, the Animal Care and Use Committee for UW's College of Letters and Sciences, and UW's Stem Cell Research Oversight Committee. I have presented on chimeras to PRIM&R and to the *National Academy of Sciences.* I also recently gave a presentation on how to improve the translation of animal ethics research into animal research practice and oversight. These various experiences also provide insight into oversight challenges, and I look forward to contributing as well to discussions about governance and oversight of chimera research.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

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Department of Philosophy
University of Wisconsin, Madison

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Lorenz Studer, MD
Director, SKI Center for Stem Cell Biology
Member, Developmental Biology Program

September 30, 2017

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Dear Drs. Maschke and Hyun,

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am the director of the Center for Stem Cell Biology at the Memorial Sloan Kettering Cancer Center. My laboratory uses human pluripotent stem cells (hPSCs) as a tool for modeling and treating human diseases of the nervous system. Our studies involve transplantation of human cells into mouse, rat and – in some instances - non-human primate brains. Some of those studies are motivated by our work geared towards the first clinical trial of using hPSC-derived dopamine neurons in Parkinson's disease. Our more basic research questions also commonly involve the transplantation of human cells into animals including studies that address the mechanisms controlling the timing of human development.

There is a great need to develop novel guidelines for human-animal chimera research. It will be important to critically discuss and address some of the common concerns such as the extent of human chimerism acceptable for both neuronal and glial cell types, strategies under development to prevent or promote extent of human chimerism in the CNS and any special considerations for studies in large animals including non-human primates. With the rapid progress in human pluripotent stem cell technologies and our ability to produce customized human neurons on demand, the need for such an effort is greater than ever.

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I have participated in the past on various committees and panels that have deliberated ethical questions related to human stem cell science and human animal chimera research including as participant at workshops at the National Institutes of Health and at the National Academy of Sciences. I have also served as a member of the International Society for Stem Cell Research (ISSCR) working group that published the recently updated "Guidelines for Stem Cell Research and Clinical Translation". Such experience, combined with the many relevant research interests in my own lab, should offer an interesting perspective for the other members of the working group.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,

Lorenz Studer, MD

The Rockefeller University
SCIENCE FOR THE BENEFIT OF HUMANITY

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September 25, 2017

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Dear Drs. Maschke and Hyun:

I am pleased to accept your invitation to join the Working Group for your proposed project "Actionable Ethics Oversight for Human-Animal Chimera Research." I understand that as a Working Group member, I will be asked to present my experiences with the oversight of human-animal chimera research at one of the project's meetings, actively contribute to discussion and deliberation at all project meetings of conceptual, ethical, and policy challenges raised by human-animal chimera research and its oversight, and provide input into the development of the project's analysis and recommendations.

As you know, I am Associate Vice-President for Research Support at The Rockefeller University. As part of that role, I am involved in a number of research compliance issues, including the oversight of human pluripotent stem cell research conducted at The Rockefeller University, and through the Tri-Institutional Stem Cell Initiative (Tri-SCI), with the research conducted at Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine. In particular, I have been deeply involved with the development of policies and procedures for the oversight of embryonic stem cell research as well as on-going efforts aimed at developing best practices for that oversight. This includes leading the IRB, SCRO and ESCRO Workshops at the World Stem Cell Summit in 2013, 2014 and 2015 and participating in the working group for Harvard's "The Ethics of Embryo Research and the Future of the 14 Day Rule Symposium" in November 2016. I have also conducted research on oversight issues in embryonic stem cell research, which has been published in *Nature* and *Cell*.

In the course of my work, I have paid very close attention to guidelines for and scholarship addressing the oversight of human-animal chimera research. This is a challenging area for institutions, oversight committees, and scientists, due to widespread uncertainty about the nature of the concerns, thresholds, and optimal oversight approaches. I am particularly impressed that your proposed project will address conceptual issues, that you are including people who focus on animal welfare, and that you are using a workshop approach so

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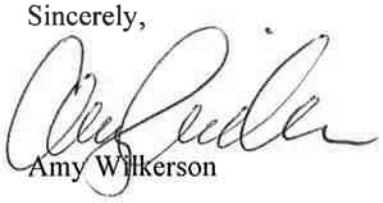
that different oversight approaches can be considered. The science is moving very fast in areas involving human-animal chimeras, and this is an optimal time to be open to thinking about whether we should be doing things differently in this area. I look forward to sharing my experiences and research with the Working Group and to working with you to create clear and useful approaches to oversight of research involving animal-human chimeras.

At The Rockefeller University, I work on and in support of a number of research oversight committees. This includes chairing the University's Institutional Biosafety Committee and the Tri-SCI Administrators Group (which staffs the TriSCI ESCRO Committee). I also serve as a member of the University's Institutional Animal Care and Use Committee, the University Safety Committee, the University's Laboratory Safety Committee, and the University's BL3 Oversight Committee. Through my twenty-plus years of experience in these areas, I have learned how important clear guidance and on-going education of committee members and the scientists whose work is reviewed is to ensuring that responsible and worthwhile science can be conducted. I have also learned – in large measure from establishing and staffing the TriSCI ESCRO Committee – how crucial it is that the guidelines be actionable. I greatly appreciate that your proposed work aims to address both of these areas.

I look forward to engaging with you and the other Working Group members to address these difficult and important conceptual, normative and oversight questions.

Sincerely,



Amy Wilkerson