DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected With HIV

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

SUMMARY: The U.S. Department of Health and Human Services (HHS), through the National Institutes of Health (NIH), announces the publication of Final Safeguards and Research Criteria for transplantation of HIV-positive donor organs in HIV-positive recipients. All such transplants must occur under an institutional review board (IRB)-approved research protocol that is compliant with federal regulations governing human subjects' research. The goal of this research is to increase knowledge about the safety, efficacy, and effectiveness of solid organ transplantation (SOT) utilizing HIV-positive donors in HIV-positive recipients.

A summary of public comments on the previously published Draft Safeguards and Research Criteria and HHS' responses follow, as well as the Final Safeguards and Research Criteria.

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SUPPLEMENTARY INFORMATION: HHS initially published the *Draft Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV, subsequently referred to as the ''Draft Safeguards and Research Criteria,''* in the **Federal Register** on June 18, 2015, for a 60-day public comment period ending August 17, 2015. In the months leading up to the draft publication, HHS presented the research criteria at national meetings of transplantation and HIV medicine professionals and received their input. Several teleconferences were hosted with transplantation community stakeholders from the private, nonprofit, and government sectors.

HHS received comments from a total of 13 individuals/entities on the Draft Safeguards and Research Criteria. Comments were submitted by transplant centers, Organ Procurement Organizations (OPOs), the Organ Procurement and Transplantation Network (OPTN), United Network of Organ Sharing (UNOS), HIV and transplantation professional societies, and a municipal agency. Overall, these comments were supportive of the HOPE Act and the Draft Safeguards and Research Criteria. Many commenters made useful suggestions that provided clarity and were incorporated into the Final Safeguards and Research Criteria. While the comments will not be addressed individually in this response document, questions, comments, and suggestions about specific aspects of the Draft Safeguards and Research Criteria are addressed by topic below.

HOPE Act: Scope

The HOPE Act permits HIV-positive to HIV-positive organ transplantation under IRB-approved research protocols conforming to the Final Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV, which were developed as directed in the HOPE Act. Patients receiving HIV-positive kidneys from deceased HIV-positive donors in South Africa (Muller, 2015) had survival rates of 84 percent and 74 percent at 1 and 5 years, respectively; however, there is presently no evidence for the safety, efficacy, and effectiveness of HIV-positive to HIV-positive transplantation in North America. The Final Safeguards and Research Criteria are meant to support the acquisition of new clinical knowledge and mechanistic insights about HIV-positive to HIV-positive organ transplantation in the United States. The results of this research will be evaluated by the Secretary of HHS and the OPTN to determine whether and how the OPTN standards for organ transplantation shall be revised to address HIV-positive organ donors.

One commenter raised concerns about the negative impact of adverse outcomes at transplant centers conducting research in HIV-positive to HIV-positive transplants on transplant program-specific reports. This commenter proposed ''that transplants performed with HIV-positive donor to HIV-positive recipients are not included in the center specific reports. The risk of transplanting these patients is unknown, and there is no risk adjustment for it on the center specific reports. There will potentially be a strong disincentive for centers to do these patients leading to fewer patients receiving life-saving organ transplants.'' Clearly this is an important issue but one that is beyond the authorities delegated to the NIH to enable implementation of the HOPE Act (*i.e.,* to develop safeguards and research criteria).

Living Donors

Several commenters stated that HIV-infected living donors may be at long-term risk for renal and/or liver disease and therefore their centers would not use HIV-infected living donors. Another commenter felt it was premature to embark on living HIV-positive donors without prior experience with deceased HIV-positive donors and recommended a staged approach. The Hope Act (2013) does not include any language addressing the use of living HIV-infected donors.

The long-term risks of living organ donation to the donor might be greater for those infected with HIV than for those who are not. At the same time, the desire to donate an organ, (*e.g.,* to save or prolong a life) is strong, and evaluation of the risks and benefits of such a decision is personal and unique to a given donor/recipient pair. Evidence for the safety of organ donation by an HIV-infected individual will only be generated by clinical research. HHS has included living donors in these Safeguards and Research Criteria so that, if investigators choose to pursue this line of research, that research can be conducted with appropriate informed consent, safeguards, and rigor.

The decision to participate in HIV-positive to HIV-positive clinical research is made freely, based on informed consent in the absence of coercion. The health care team must provide a rigorous, transparent education and informed consent process that describes alternatives, risks, potential benefits, unknowns, and the need for long-term follow-up. These discussions must address how research-related injuries are managed and paid for, and must specifically include the present uncertainties about the outcomes for both HIV-positive living donors and the recipients of HIV-positive organs. Participation of knowledgeable, independent advocates for both the HIV-positive recipient and the HIV-positive donor is required by these Safeguards and Research Criteria.

Independent Advocates

Some commenters strongly supported the requirement for independent advocates for both HIV-positive recipients and prospective HIV-positive living donors. Others viewed this as unnecessary given the expertise of the principal investigator and study team and current OPTN standards. With

respect to informed consent, the role of the independent advocate complements that of the investigator and does not replace it. The investigator is assumed to have the expertise necessary to discuss risks, benefits, expectations, and alternatives. The advocate is an additional knowledgeable person who is neither a member of the research team nor the patient's health care provider, whose role is to provide information, answer questions, and provide assurance of equal access to health care regardless of the patient's decisions regarding research participation. For example, the advocate can assure that the transplant candidate is aware that he or she has the right to be offered and to accept an HIV-*negative* deceased donor organ should one become available, and can assure the prospective living donor of confidentiality and support should he or she determine that donation is not in his or her own best interest.

Transplant Hospital Experience

Several commenters from academic institutions, professional societies, and the OPTN indicated that the requirements for physicians' and surgeons' prior experience in HIV-negative to HIV-positive organ transplant were excessive and would result in few centers being able to participate in the research allowed under the HOPE Act. In response to the wide consensus on this issue, we have accepted the specific suggestion of the American Society of Transplant Surgeons (ASTS). Section 3 of the Final Safeguards and Research Criteria describe collective team experience, rather than individual experience.

Immunologic Criteria (CD4+ T-Cell Counts, HIV Viral Load)

Several commenters expressed concerns about the usefulness and relevance of requiring a minimum CD4+ T-cell count/percentage in the donor. They argued that the CD4+ T lymphocyte count will not predict allograft function, and that, among HIV-positive to HIV-positive transplants in South Africa, excellent outcomes were observed in recipients of kidneys from donors with CD4+ T-cell counts well below 200. These commenters urged flexibility and the elimination of this minimum immunologic criterion. In response to these comments, Section 1 of the Final Safeguards and Research Criteria was revised to indicate that, although collection of CD4+ T cell counts and percentages during the donor evaluation is required, no minimum criterion is imposed for organ acceptance. Some commenters preferred excluding any donors with detectable plasma viral load due to the risk of transmitted drug resistance. Unfortunately, it will not be possible in all cases to mitigate the risk of transmitting viral resistance by setting viral load limits and/or assessing antiretroviral resistance profiles in the time available for donor evaluation. It is expected that in many cases, potential donors will have adequate medical history available to inform the transplantation team's assessment and maximally reduce the risk of transmitting resistant virus. For these reasons, the Final Safeguards and Research Criteria do not stipulate a limit on the allowable viral load in a donor. The transplant team should only transplant the organ if the team is confident they can define a post-transplant antiretroviral regimen that will be safe, tolerable, and effective. Concerns about transmitted drug resistance must be included in the recipient informed consent process for the research study. In addition, at the time of an organ offer, the recipient informed consent must address the transplant team's assessment of risk specific to the characteristics of the offered organ.

Biospecimens

Several commenters emphasized the importance of a pre-transplant donor organ biopsy. The final updated research criteria include a requirement for performance of a pre-implantation ''back-table'' biopsy for post-transplantation patient management and future scientific and mechanistic studies. Although there are no further specimen requirements, we strongly encourage the inclusion of serial biospecimens (*e.g.,* allograft tissue, urine, serum, and cells) in the individual research protocols. These specimens will be a valuable resource to the community in studies relating to superinfection risks, for example. Failure to collect such specimens, particularly in organ donors, would be a regrettable lost opportunity.

Required Outcomes

Several commenters expressed concerns about data collection, quality, and reporting. The HOPE Act requires the Secretary of HHS to review the results of research conducted under the Act. One purpose of the criteria presented in the Final Safeguards and Research Criteria is to ensure that all investigators conducting research in HIV-positive to HIV-positive transplantation collect similar data elements. This standardization will facilitate the subsequent review mandated in the HOPE Act.

Conclusion Regarding Comments Received

HHS appreciates the time and effort taken by commenters to respond to the Request for Comments. The comments represented the deliberative efforts of truly dedicated individuals and organizations in transplantation and HIV medicine. All the responses were helpful in revising the draft Human Immunodeficiency Virus (HIV) Organ Policy Equity (HOPE) Act Safeguards and Research Criteria for Transplantation of Organs Infected with HIV.

The Final Safeguards and Research Criteria for transplantation of HIV-positive (HIV+) donor organs in HIV-positive (HIV+) recipients are as follows:

ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome.
APOL1	Apolipoprotein 1.
ART	Antiretroviral Therapy.
CD4	Cluster of Differentiation 4.
CMS	Centers for Medicare & Medicaid Services.
CNS	Central Nervous System.
dL	Deciliter.
FDA	U.S. Food and Drug Administration.
FIPSE	Spanish Foundation for AIDS Research.
GESIDA	Spanish AIDS Study Group.
HAART	Highly Active Antiretroviral Therapy.
HBV	Hepatitis B Virus.
HCT/Ps	Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).
HCV	Hepatitis C Virus.

ABBREVIATIONS—Continued

HIV	Human Immunodeficiency Virus.
HOPE Act	HIV Organ Policy Equity Act.
INR	International Normalized Ratio.
IRB	Institutional Review Board.
mL	Milliliter.
NIH	National Institutes of Health.
NNRTI	Non-Nucleoside (or Non-Nucleotide) Reverse Transcriptase Inhibitor.
NRTI	Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitor.
OI	Opportunistic Infection.
OPO	Organ Procurement Organization.
OPTN	Organ Procurement and Transplantation Network.
PCR	Polymerase Chain Reaction.
PML	Progressive Multifocal Leukoencephalopathy.
RNA	Ribonucleic Acid.
SOPs	Standard Operating Procedures.
SOT	Solid Organ Transplantation.
SRTR	Scientific Registry of Transplant Recipients.
UNOS	United Network for Organ Sharing.
μL	Microliter.

DEFINITIONS

ABO compatible	People who have one blood type (A, B, AB, or O) form proteins (antibodies) that cause their immune system to react against other blood types. This is important when a patient needs to receive blood (transfusion) or have an organ transplant. The blood types must be matched to avoid an ABO incompatibility reaction. ABO compatible is when the blood types are matched.
Antiretroviral therapy (ART) resistance.	When an HIV strain develops drug resistance and/or genetic mutations associated with drug resistance.
Types/classes of HIV/AIDS antiretroviral drugs (current at publication).	(1) Entry inhibitors. (2) Fusion inhibitors. (3) Nucleoside reverse transcriptase inhibitors (NRTIs). (4) Non-nucleoside reverse transcriptase inhibitors (NNRTIs). (5) Integrase inhibitors. (6) Protease inhibitors. (7) Multi-class combination products.
HIV strain	Distinct genetic variants of the HIV retrovirus, conferring characteristics such as susceptibility or resistance to ART medications.
HIV-negative	Not testing positive for HIV by serology and/or nucleic acid testing using FDA-licensed, approved or cleared test devices.
HIV-positive	HIV-infected by serology and/or nucleic acid testing using FDA-licensed, approved, or cleared test devices.
HIV undetectable viral load	(The conventional definition at the time of the publication of this research criteria document, based on current clinical technology/practice): HIV ribonucleic acid (RNA) below 50 copies with current technology.
Opportunistic infection	Infections that are more frequent or more severe because of immunosuppression in HIV-infected persons (Kaplan, 1995a, 1995b; Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents, 2015).
Suppressed viral load	HIV RNA below 50 copies with current technology at time of publication of this research criteria document.
Viral detection threshold	HIV RNA below 50 copies with current technology at time of publication of this research criteria document.

Executive Summary

The HOPE Act requires the HHS Secretary (the Secretary) to develop and publish criteria for research involving transplantation of human immunodeficiency virus-infected donor organs in HIV-positive recipients. A summary of the criteria for conducting clinical research in HIV-positive to HIV-positive organ transplantation is included in the chart below, and the criteria are set forth in six broad categories (Donor Eligibility, Recipient Eligibility, Transplant Hospital Criteria, Organ Procurement Organization (OPO) Responsibilities, Prevention of Inadvertent Transmission of HIV, and Study Design/Required Outcome Measures). These criteria are in addition to current policies and regulations governing organ transplantation and human subjects' research. The goals of these criteria are, first, to ensure that research using organs from HIV-positive donors is conducted under conditions protecting the safety of research participants and the general public; and second, to ensure that the results of this research provide a basis for evaluating the safety of solid organ transplantation (SOT) from HIV-positive donors to HIV-positive recipients.

Category	Criteria
Donor Eligibility:	
All HIV-positive deceased donors.	No evidence of invasive opportunistic complications of HIV infection. Pre-implant donor organ biopsy. Viral load: no requirement.

Category	Criteria
Deceased donor with known history of HIV infection and prior antiretroviral therapy (ART).	The study team must describe the anticipated post-transplant antiretroviral regimen(s) to be prescribed for the recipient and justify its conclusion that the regimen will be safe, tolerable, and effective.
HIV-positive living donor	Well-controlled HIV infection defined as: • CD4+ T-cell count ≥500/μL for the 6-month period before donation. • HIV–1 RNA <50 copies/mL. • No evidence of invasive opportunistic complications of HIV infection. Pre-implant donor organ biopsy.
Recipient Eligibility	CD4+ T-cell count ≥200/μL (kidney). CD4+ T-cell count ≥100 μL (liver) within 16 weeks prior to transplant and no history of opportunistic infection (OI); or ≥200 μL if history of OI is present. HIV–1 RNA <50 copies/mL and on a stable antiretroviral regimen. No evidence of active opportunistic complications of HIV infection. No history of primary central nervous system (CNS) lymphoma or progressive multifocal leukoencephalopathy (PML).
Transplant Hospital Criteria	Transplant hospital with established program for care of HIV-positive subjects. HIV program expertise on the transplant team. Experience with HIV-negative to HIV-positive organ transplantation. Standard operating procedures (SOPs) and training for the organ procurement, implanting/operative, and postoperative care teams for handling HIV-infected subjects, organs, and tissues. Institutional review board (IRB)-approved research protocol in HIV-positive to HIV-positive transplantation. Institutional biohazard plan outlining measures to prevent and manage inadvertent exposure to and/or transmission of HIV. Provide each living HIV-positive donor and HIV-positive recipient with an ''independent advocate''. Policies and SOPs governing the necessary knowledge, experience, skills, and training for independent advocates.
OPO Responsibilities	SOPs and staff training procedures for working with deceased HIV-positive donors and their families in pertinent history taking; medical chart abstraction; the consent process; and handling blood, tissues, organs, and biospecimens. Biohazard plan to prevent and manage HIV exposure and/or transmission.
Prevention of Inadvertent Transmission of HIV.	Each participating Transplant Program and OPO shall develop an institutional biohazard plan for handling organs from HIV-positive donors that is designed to prevent and/or manage inadvertent transmission or exposure to HIV. Procedures must be in place to ensure that human cells, tissues, and cellular and tissue-based products (HCT/Ps) are not recovered from HIV-positive donors for implantation, transplantation, infusion, or transfer into a human recipient; however, HCT/Ps from a donor determined to be ineligible may be made available for nonclinical purposes.
Required Outcome Measures:	
Wait List Candidates	HIV status. CD4+ T-cell counts. Co-infection (hepatitis C virus [HCV], hepatitis B virus [HBV]). HIV viral load. ART resistance. Removal from wait list (death or other reason). Time on wait list.
Donors (all)	Type (Living or deceased). HIV status (HIV-infected [HIV-positive] new diagnosis, HIV-positive known diagnosis). CD4+ T-cell count. Co-infection (HCV, HBV). HIV viral load. ART resistance.
Living Donors	Progression to renal insufficiency in kidney donors. Progression to hepatic insufficiency in liver donors. Change in ART regimen as a result of organ dysfunction. Progression to acquired immunodeficiency syndrome (AIDS). Failure to suppress viral replication (persistent HIV viremia). Death.
Transplant Recipients	Rejection rate (annual up to 5 years). Progression to AIDS. New OI. Failure to suppress viral replication (persistent HIV viremia). HIV-associated organ failure. Malignancy. Graft failure. Mismatched ART resistance versus donor. Death.

The HOPE Act research criteria focus on liver and kidney transplantation, where there is substantial experience with HIV-negative to HIV-positive transplantation. The intent is not to exclude the possibility of HIV-positive to HIV-positive transplantation of other organs; however, transplant organ-specific teams must gain experience

with HIV-negative to HIV-positive transplantation before embarking on the more complex and less well-defined issues with HIV-positive to HIV-positive transplantation. The minimum combined experience required of the transplant physician and HIV physician on the team is five organ-specific cases over 4 years.

The HOPE Act requires the Secretary and the Organ Procurement and Transplantation Network (OPTN) to review the results of the scientific research conducted under these criteria to determine whether the results warrant further revisions to the OPTN's standards of quality. Under the HOPE Act, the Secretary may in the future determine that participation in research under such criteria is no longer required for HIV-positive to HIV-positive transplants.

Background

Public Law 113–51, The HOPE Act, requires the HHS Secretary (the Secretary) to, among other things, ''develop and publish criteria for conduct of research relating to transplantation of organs from donors infected with human immunodeficiency virus (HIV) into individuals who are infected with HIV before receiving such organs.'' (See Public Health Service Act section 377E(a) [codified at 42 U.S.C. 274f–5]). In addition, pursuant to section 377E(c) of the HOPE Act, the Secretary is required, in conjunction with the OPTN, to review the results of that research to determine whether revisions should be made to the standards of quality adopted under section 372(b)(2)(E) of the Public Health Service Act (OPTN standards for the acquisition and transportation of donated organs) and the regulations governing the operation of the OPTN (42 CFR 121.6).

The authority vested in the Secretary under section 377E(a) to develop and publish research criteria was delegated to the Director, National Institutes of Health (NIH), and these research criteria are the subject of this document. They are meant to ensure first, that research using organs from HIV-positive donors is conducted under conditions protecting the safety of research participants and the general public; and second, that the results of this research provide a basis for evaluating the safety of transplantation of organs from HIV-positive donors to HIV-positive recipients.

Process

This document was authored by representatives of the NIH and Centers for Disease Control and Prevention. Additional input from representatives of other federal agencies, including the Health Resources and Services Administration, Centers for Medicare & Medicaid Services (CMS), and the Food and Drug Administration (FDA), was solicited. In addition, perspectives and input were solicited from community stakeholders.

Introduction

The advent of effective antiretroviral therapy (ART) in the mid-1990s for treatment of individuals infected with HIV transformed a rapidly fatal disease into a well-controlled chronic illness. Currently, the life expectancy of individuals infected with HIV and receiving ART early in the course of their disease approaches that of individuals without HIV infection (Wada, 2013, 2014). In this era of greater longevity, liver failure, end-stage renal disease, and cardiovascular disease have emerged as important causes of morbidity and mortality in patients with HIV infection (Neuhaus, 2010).

Organ transplantation prolongs survival and improves quality of life for individuals with end-stage organ disease (Matas, 2014; Kim, 2014). Until recently, however, organ transplantation was unavailable to those infected with HIV due to concerns that pharmacologic immunosuppression to prevent organ rejection would hasten the progression from HIV infection to AIDS, concerns about disease transmission, and reluctance to allocate organs to a population whose outcome was unpredictable (Blumberg, 2009, 2013a, 2013b; Mgbako, 2013; Taege, 2013). Nevertheless, a few transplant programs accepted HIV-positive patients on their transplant waiting lists and accumulated data showing kidney or liver transplantation could be done safely in these patients (Roland, 2002, 2003a, 2003b, 2003c; Blumberg, 2009; Stock, 2010; Yoon, 2011; Terrault, 2012). Subsequently, a prospective, multicenter clinical trial of kidney and liver transplantation in 275 patients demonstrated that, among HIV-positive kidney and liver transplant recipients, patient and graft survival rates were acceptable and within the range of outcomes currently achieved among non-infected transplant recipients. However, the rate of kidney rejection was unexpectedly high, demonstrating that the immune dysregulation resulting from HIV infection, HCV co-infection, and antirejection drugs is complex and incompletely understood. Some of the challenges encountered in that study remain relevant for clinical sites offering organ transplantation to HIV-positive individuals today (*e.g.,* management of drug interactions and toxicities when combining complex medical regimens, management of combined morbidities of two or more active diseases, and the need for ongoing collaboration among medical professionals from different specialties) (Frassetto, 2007, 2014; Locke, 2014). Despite the complexities, this study and others (Ragni, 1999; Frassetto, 2009; Huprikar, 2009; Stock, 2010; Touzot, 2010; Cooper, 2011; Duclos-Vallee, 2011; Reeves-Daniel, 2011; Fox, 2012; Terrault, 2012; Grossi, 2012; Gomez, 2013; Harbell, 2013) demonstrate that kidney and liver transplantation are appropriate in HIV-positive individuals with liver or kidney failure, although gaps in knowledge and many research questions remain. There is much less experience with heart (Calabrese, 2003; Bisleri, 2003; Pelletier, 2004; Uriel, 2009, 2014; Castel, 2011a, 2011b; Durante-Mangoni, 2011 and 2014) and lung (Mehta, 2000; Humbert, 2006; Petrosillo, 2006; Bertani, 2009; Kern, 2014a, 2014b) transplantation in HIV-positive recipients, or mechanical circulatory assistance (Brucato, 2004; Fieno, 2009; Mehmood, 2009; Sims, 2011) as a bridge to transplantation, although case reports and small case series suggest acceptable short-term outcomes are possible.

Prior to the passage of the HOPE Act, U.S. law required that all U.S. transplants for HIV-positive recipients utilize organs from HIV-uninfected donors. (See 42 U.S.C. 273(b)(3)(C), 274(b) and 18 U.S.C. 1122, all prior to amendment by the HOPE Act). The potential for increasing the pool of available organ donors for all recipients by allowing the use of organs from donors infected with HIV for transplantation into recipients infected with HIV (hereinafter referred to as ''HIV-positive to HIV-positive transplantation'') is recognized (Boyarsky, 2011, 2015; Mgbako, 2013; Mascolini, 2014; Kucirka, 2015; Richterman, 2015). It is estimated that an additional 500 organ donors per year might be available if HIV-positive individuals were accepted as organ donors for HIV-positive recipients (Boyarsky, 2011). The published experience with HIV-positive to HIV-positive SOT at this time comes from Muller et al from the University of Cape Town in South Africa. Initially, Muller et al (2010) reported 100 percent patient and graft survival in a four-patient pilot study. Subsequently, the same group reported an additional 10 HIV-positive to HIV-positive renal transplants (Muller, 2012). All patients were restarted on ART early postoperatively in the immunosuppressive setting of T-

cell-depleting induction therapy, tacrolimus, mycophenolate mofetil, and prednisone. One to 4 years after transplantation, outcomes remained excellent and all patients had undetectable viral loads (Muller, 2012). The cumulative University of Cape Town experience of 27 HIV-positive to HIV-positive transplant procedures was recently summarized in the New England Journal of Medicine (Muller, 2015). The 1- and 5-year death-censored graft survival was 93 and 84 percent, respectively, and 1- and 5-year patient survival was 83 and 74 percent, respectively. Of note, the South African HIV-positive deceased donors were ART-naïve, without history of opportunistic infection or proteinuria, and had normal pre-transplant renal biopsies. While renal function has remained normal in the recipients, three have had routine post-transplant renal biopsies demonstrating new changes typical of early HIV-associated nephropathy that were not present in baseline biopsy specimens. The long-term significance of these findings remains unknown and awaits longer follow-up. All patients had undetectable plasma HIV viral loads after transplantation. Graft rejection rates were 8 percent at 1 year and 22 percent at 3 years.

This document presents criteria for conducting research in HIV-positive to HIV-positive organ transplantation in the United States. The criteria are grouped into six broad categories: Donor Eligibility, Recipient Eligibility, Transplant Hospital Criteria, OPO Responsibilities, Prevention of Inadvertent Transmission of HIV, and Study Design/Required Outcome Measures. These research criteria do not describe all of the necessary components of a research protocol for HIV-positive to HIV-positive transplantation, such as the specific medication regimens, pre-transplant induction (if any), maintenance immunosuppression after transplantation, or control of HIV infection. These protocol elements and others will be determined by an investigator's specific research questions and the expertise of those conducting the research. Rather, the criteria address the minimum safety and data requirements of clinical research in HIV-positive to HIV-positive transplantation. As mandated by the HOPE Act, the Secretary, together with the OPTN, is charged with reviewing the results of scientific research conducted under these criteria to determine whether the OPTN's standards of quality should be further modified and whether some HIV-positive to HIV-positive transplants should proceed outside the auspices of research conducted under such criteria.

This document focuses on liver and kidney transplantation, as it is only in liver and kidney transplantation that there is substantial experience with transplantation from HIV-negative donors to HIV-positive recipients (Sawinski, 2015; Locke, 2015a, 2015b; Miro, 2015). The intent is not to exclude the possibility of HIV-positive to HIV-positive transplantation of other organs such as the heart or lung in the future; however, transplant teams must gain experience with HIV-negative to HIV-positive transplantation of a specific organ before taking on the more complex and less well-defined issues of HIV-positive to HIV-positive transplantation of that organ. Centers developing research protocols for HIV-positive to HIV-positive transplantation of organs other than kidney or liver must have a study team with demonstrated experience in HIV-negative to HIV-positive transplants, as noted in Section 3.1(ii), for the organ transplant(s) proposed in the research protocol. Specific criteria for the transplantation of organs other than the liver and kidney have not been provided in this document because no evidence base exists to support such recommendations. The study team developing a research protocol for HIV-positive to HIV-positive non-renal, non-liver transplantation must develop and justify specific criteria for review and approval by their IRB, based on the relevant experiences of the study team and others.

These criteria are in addition to, not in place of, current policies and regulations governing organ transplantation and human subjects' research. Accordingly, to emphasize the specific requirements unique to the investigational transplantation of organs from HIV-positive donors into HIV-positive recipients, the research criteria set forth here do not address related requirements that exist in federal regulations or OPTN bylaws or policies including, but not limited to, obligations imposed on OPTN transplant hospitals and transplant programs concerning informed consent of transplant recipients and living donors, the equitable allocation of organs, and organ offers. The regulations governing the operation of OPTN are codified at 42 CFR part 121 and OPTN policies and bylaws can be found at *http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf.*

Under these research criteria, all HIV-positive to HIV-positive transplantation must occur under an IRB-approved research protocol and shall comply with any other existing laws, policies, and regulations governing the conduct of human subjects' research (see Public Law 113–51 and, *e.g.,* 45 CFR part 46, as applicable). In addition, a transplant program conducting research in HIV-positive to HIV-positive transplantation under these research criteria must provide each living donor and recipient with an independent advocate.

Although the criteria set forth in this document outline the minimum safety requirements for research involving HIV-positive to HIV-positive transplantation, it is expected that investigators will develop more specific eligibility criteria based on their individual research questions and protocols. In addition, it is likely, that researchers will wish to collect research specimens (blood, urine, tissue) in addition to those specified in the Research Criteria.

1 Donor Eligibility

HIV-positive living donors and HIV-positive deceased donors of organs for transplantation into an HIV-positive recipient must fulfill applicable clinical criteria in place for HIV-uninfected organ donors.

There is substantial concern about the consequences of transplanting an organ from an HIV-positive donor to a recipient infected with a strain of HIV that differs from the donor's in terms of its responsiveness to antiretroviral therapy (ART). The likelihood and impact of HIV superinfection in this context are unknown. Adverse consequences could range from transient loss of viral suppression, necessitating a change in antiretroviral regimen to a worst-case scenario in which the new infecting strain of HIV is unresponsive to available antiretroviral treatment and the recipient progresses to AIDS (Redd, 2013). Information relevant to understanding the known or potential extent of antiretroviral resistance in the strain of HIV infecting the organ donor may be incomplete for many reasons:

- There may be inadequate virus in donor specimens for antiretroviral resistance testing;
- If the specimen is adequate, there may not be enough time within the decision-making evaluation window to fully assess antiretroviral resistance before the clinical deterioration of the donor, organ procurement, and implantation;
- The donor's history of antiretroviral treatment may be unknown or incomplete;

• Results from prior antiretroviral resistance testing may be unavailable.

These issues might be especially challenging when considering organ donation from deceased donors whose HIV infection is first identified during donor evaluation. As of 2011, an estimated 1 in 6 U.S. adults living with HIV infection were undiagnosed (Prevention, 2013) and an estimated 16 percent of newly diagnosed, untreated individuals were infected with virus resistant to at least one class of antiretroviral drug (Kim, 2013; Megens, 2013).

It is anticipated that the risk of transmission of resistant HIV strains may be lower from deceased donors with a well-documented history of antiretroviral treatment, undetectable virus at demise, and robust and persistent undetectable viral load for at least 1 year prior to death. However, to impose this as an eligibility criterion would limit the pool of suitable donors and severely limit the ability to study transplantation of HIV-positive organs under the HOPE Act. In addition, it will not be possible in all cases to obtain viral loads and/or antiretroviral resistance profiles in the time available for donor evaluation. Transplant teams evaluating a donor must review all available donor and recipient information and be able to propose an antiretroviral regimen that will be equally or more safe, tolerable, and effective for the recipient after transplantation as the regimen in place in the recipient before transplantation. For instance, a donor who only achieves viral suppression with a regimen known to be intolerable to the recipient must not be accepted. If there is doubt about the ability to suppress viral replication after transplantation, the transplant must not move forward.

Donors co-infected with hepatitis are not excluded from HIV-positive to HIV-positive transplant; however, careful consideration must be given when evaluating a donor co-infected with HBV and/or HCV (Terrault, 2012; Miro, 2012; Moreno, 2012; Sherman, 2014; Chen, 2014). Although HCV therapeutic strategies are rapidly evolving (Liang, 2013), it is possible that mixed genotype HCV infections may influence post-transplant treatment of HCV in the recipient. Prior antiretroviral treatment of the donor and/or recipient with agents active against HBV (*i.e.,* lamivudine, emtricitabine, adefovir, and tenofovir) has the potential for inducing or uncovering archived HBV drug resistance in the recipient (Dieterich, 2007; Soriano, 2009; Pais, 2010).

In the case of a living HIV-positive organ donor, the risk of future end-stage liver or kidney failure in the donor must be carefully assessed as it is in other at-risk populations currently eligible to donate an organ. For example, kidney disease in HIV-positive patients has been associated with the apolipoprotein 1 (APOL1) coding variants that confer a very high risk of susceptibility and are almost exclusively found in patients of African descent (Freedman, 2013; Genovese, 2010). Living donation of a kidney from a donor having such a variant may be associated with an unacceptable risk of subsequent kidney disease to both the donor and the recipient (Freedman, 2015; Reeves-Daniel, 2011; Parsa, 2013; Riella, 2015).

The consent process for an HIV-positive living organ donor must include and document provision to the donor of information regarding: (1) The possibility that the loss of organ function resulting from donation could preclude the use of certain antiretroviral drugs in the future; (2) the risk of kidney or liver failure in the future; (3) the possibility of transmission of occult opportunistic infections to the recipient; and (4) the absence of U.S. experience in HIV-positive to HIV-positive organ transplantation, and thus the unpredictable nature of donor and recipient outcomes (Mgbako, 2013).

HIV-positive transplant candidates who are listed for a transplant in the context of a research study of HIV-positive to HIV-positive transplantation must have the same opportunity as other transplant candidates to receive an organ from an HIV-negative donor, should one become available for them.

1.1 HIV-Positive Donor Eligibility Criteria

The HIV-specific donor eligibility criteria for deceased donors and for living donors are listed (also refer to Table 1). Co-infection with HBV and/or HCV is not an exclusion criterion, although research that includes co-infected donors must address any additional eligibility criteria within their research protocol.

1.1.1 HIV-Positive Deceased Donors

When evaluating HIV-positive deceased donors, it is understood that limited medical history may be available and/or known at the time of the donor evaluation. The OPO must make reasonable efforts to obtain prior medical history so that a transplant center team may best determine the suitability of the potential donor based on the information available. A complete history of antiretroviral regimens and a history of viral load tests and resistance testing are especially valuable for evaluating the likelihood of donor HIV resistance to antiretroviral regimens. A history of OIs or cancers is also of high importance, due to the increased risk for both attributable to HIV, and the additional difficulty of treating some infections and neoplasms in a post-transplant setting. It is possible that deceased donors with lower CD4+ T-cell counts may pose an increased risk of harboring transmissible diseases (*e.g.,* opportunistic infections or neoplasms) that may be difficult to detect during organ harvest and transplantation; teams conducting transplants under the HOPE Act are urged to assess donors with low CD4+ T-cell counts (*e.g.,* ≤200/μL) with special caution and to promptly inform IRBs and protocol sponsors of known or suspected disease transmission events.

Minimum eligibility criteria for all HIV-positive deceased donors:

i. Documented HIV infection using an FDA-licensed, approved, or cleared test device(s).

ii. No evidence of invasive opportunistic complications of HIV infection.

iii. Pre-implant donor organ biopsy to be stored, at a minimum, for the duration of the study (or at least 5 years); additional specimens may be obtained to support specific research goals.

Additional eligibility criteria for HIV-positive deceased donors with a known history of HIV and prior treatment with ART:

i. The study team must describe the anticipated post-transplant antiretroviral regimen(s) to be prescribed for the recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

1.1.2 HIV-Positive Living Donors

Minimum eligibility criteria for HIV-positive living donors:

i. Documented HIV infection using an FDA-licensed, approved, or cleared test device.

ii. Well-controlled HIV infection, as evidenced by:

a. CD4+ T-cell count ≥500/μL for the 6-month period preceding donation.

b. Fewer than 50 copies/mL of HIV–1 RNA detectable by ultrasensitive or real-time polymerase chain reaction (PCR) assay.

iii. A complete history of ART regimens and ART resistance.

iv. The study team must be able to predict a safe, tolerable, and effective regimen to be prescribed for the recipient based on the donor's current ART regimen as well as the donor's history of ART resistance.

v. No evidence of invasive opportunistic complications of HIV infection.

vi. A liver biopsy (in liver donors) or a kidney biopsy (in kidney donors) showing no evidence of a disease process that would put the donor at increased risk of progressing to end-stage organ failure after donation, or that would present a risk of poor graft function to the recipient.

2 Recipient Eligibility

A key consideration when evaluating potential HIV-positive transplant candidates is the ability to suppress HIV viral load post-transplant. This includes a thorough assessment by the transplant team of the candidate recipient's prescribed antiretroviral medications, HIV RNA levels while on medications, adherence to HIV treatment, and any available HIV resistance testing; a similar evaluation of the donor must also be carried out. A transplant should only take place if, after evaluating both recipient and donor, the team is confident they can define a post-transplant antiretroviral regimen that will be safe, tolerable, and effective. If there is any doubt on the part of the transplant team about the ability to suppress viral replication post-transplant, the transplant should not move forward. Concerns about transmitted drug resistance must be included in the recipient informed consent process for the research study. At the time of an organ offer, the recipient informed consent must address the transplant team's assessment of risk specific to the organ they are being offered.

2.1 HIV-Positive Recipient Eligibility Criteria

The following HIV-specific criteria must be met when screening for an HIV-positive to HIV-positive organ transplant (also refer to Table 1):

i. CD4+ T-cell count ≥200/μL (kidney) and ≥100/μL (liver) within 16 weeks prior to transplant; any patient with history of OI must have a CD4 positive T-cell count ≥200/uL.

ii. HIV RNA less than 50 copies/mL and on a stable antiretroviral regimen.*

iii. No evidence of active opportunistic complications of HIV infection.

iv. No history of primary CNS lymphoma or progressive PML.

v. Concurrence by the study team that, based on medical history and ART, viral suppression can be achieved in the recipient post-transplant.

*Patients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen for the patient once organ function is restored after transplantation.

TABLE 1—SUMMARY OF DONOR AND RECIPIENT ELIGIBILITY CRITERIA FOR HIV-POSITIVE SERO-CONCORDANT ORGAN TRANSPLANT PAIRS UNDER THE HOPE ACT

HIV-Related variables	Deceased donor	Living donor	HIV-Positive recipient
Current CD4+ T-cell count (T lymphocytes/μL)	No requirement	≥500 for 6 months prior to organ donation.	If no history of OI • ≥200 If history of OI • ≥200 (kidney) • ≥100 (liver) CD4+ T-cell count measured within 16 weeks of transplantation
Plasma HIV RNA viral load (copies/mL).	No requirement**	<50	<50*
Opportunistic infection	No invasive OI	No invasive OI	Currently, • No active OI Historically, no • CNS lymphoma • PML

*Organ recipients who are unable to tolerate ART due to organ failure or who have only recently started ART may have detectable viral load and still be considered eligible if the study team is confident there will be a safe, tolerable, and effective antiretroviral regimen to be used by the recipient once organ function is restored after transplantation.

**In deceased donors with a known history of HIV infection and prior treatment with ART, the study team must describe the anticipated post-transplant antiretroviral regimen(s) to be used by the organ recipient and justify their conclusion that the proposed regimen will be safe, tolerable, and effective.

3 Transplant Hospital Criteria

Expertise in the management of individuals with HIV infection is essential for this research. A transplant hospital participating in HIV-positive to HIV-positive transplantation must include experts in the field of transplantation as well as experts in the management of HIV infection working collaboratively as a part of a study team.

3.1 Specific Transplant Hospital Criteria

i. An established program for the care of individuals infected with HIV.

ii. In order for a transplant hospital to initiate HIV-positive to HIV-positive transplantation, there must be a study team consisting of (at a minimum) a transplant surgeon, a transplant physician, and an HIV physician. The transplant physician and HIV physician collectively must have experience with at least 5 HIV-negative to HIV-positive transplants with the designated organ(s) over the last 4 years. This constitutes the minimal experience necessary, and the IRB must evaluate key personnel (*i.e.,* transplant surgeon, transplant physician, and HIV physician) in the context of total expertise and experience with respect to HIV and/or organ transplantation (confirm and document HIV-negative to HIV-positive transplant experience of the team).

iii. Defined SOPs and training for the hospital personnel involved in procurement and/or implantation regarding the following issues:

a. Donor evaluation
b. Organ recovery
c. Handling, processing, packaging, shipping, and transporting of blood, lymph nodes, tissues, and organs to and/or within the transplant hospital
d. Transplant procedure

iv. Transplant hospitals with an IRB-approved research protocol in HIV-positive to HIV-positive transplantation

must inform the OPTN of additional organ-specific acceptance criteria for organs from HIV-positive donors.

v. Transplant hospitals with an IRB-approved research protocol in HIV-positive to HIV-positive transplantation with HIV-positive candidates on the wait list willing to accept an HIV-positive organ must specify any additional acceptance criteria to the OPO.

vi. The transplant hospital must verify the HIV status of both the donor and the recipient.

vii. Defined SOPs and training regarding an institutional biohazard plan, which outlines the measures taken to prevent and manage inadvertent exposure and/or transmission of HIV.

viii. Defined policies and SOPs for governing the necessary knowledge, experience, skills, and training for independent advocates.

3.2 Independent Advocates

A transplant program conducting research in HIV-positive to HIV-positive transplantation under these research criteria must provide each HIV-positive living donor and recipient with an independent advocate.

In the setting of a living donor transplant, there must be two independent advocates, one for the donor and another for the recipient. Each advocate must be independent of the research team and must have knowledge and experience with both HIV infection and organ transplantation.

At a minimum, transplant hospitals conducting research in HIV-positive to HIV-positive transplantation shall develop policies and procedures addressing the role, knowledge, and experience of independent advocates in the setting of HIV infection, transplantation, medical ethics, informed consent, and the potential impact of external pressure on the HIV-positive recipient's decision, and HIV-positive living donor's decision (if applicable) about whether to enter the HIV-positive to HIV-positive transplant research study.

3.2.1 Independent HIV-Positive Recipient Advocate

Transplant programs performing HIV-positive to HIV-positive transplants must designate and provide each HIV-positive recipient and prospective HIV-positive recipient with an independent advocate who is responsible for protecting and promoting the rights and interests of the HIV-positive recipient (or prospective recipient). The independent advocate for the HIV-positive recipient must:

i. Promote and protect the interests of the HIV-positive recipient (including with respect to having access to a suitable HIV-negative organ if it becomes available) and take steps to ensure that the HIV-positive recipient's decision is informed and free from coercion.

ii. Review whether the potential HIV-positive recipient has received information regarding the results of SOT in general and transplantation in HIV-positive recipients in particular and the unknown risks associated with HIV-positive to HIV-positive transplant.

iii. Demonstrate knowledge of HIV infection and transplantation.

3.2.2 Independent HIV-Positive Living Donor Advocate

Transplant programs performing HIV-positive donor transplantations must designate and provide each living HIV-positive donor and living prospective HIV-positive donor with an independent advocate who is responsible for promoting and protecting the rights and interests of the HIV-positive donor (or prospective donor). More specifically, the independent advocate for the HIV-positive living donor must:

i. Promote and protect the interests of the HIV-positive donor (including with respect to having ample opportunity to withdraw consent from donation) and take steps to ensure that the HIV-positive donor's decision is informed and free from external pressure.

ii. Review whether the potential HIV-positive donor has received information regarding (a) risks of organ donation in general, as well as the additional potential risks that are the specific to the HIV-positive donor, including accelerated organ failure, and limitations of future use of specific antiretroviral agents; and (b) the unknown outcome of HIV-positive to HIV-positive organ transplantation.

iii. Demonstrate knowledge of HIV infection and transplantation.

4 OPO Responsibilities

Clinical research in HIV-positive to HIV-positive organ transplantation requires a partnership between OPOs and transplant programs. OPOs participating in the evaluation and allocation of HIV-positive organs to centers conducting research in HIV-positive to HIV-positive transplantation must adhere to the following criteria:

i. Develop SOPs and staff training procedures to effectively work with the family and other sources of medical history for HIV-positive donors in assessing medical and behavioral risks; HIV clinic and pharmacy medical record abstraction; obtaining research consent from next of kin of HIV-positive donors; performing physical examination of HIV-positive donors; collecting blood, tissue, and other biospecimens (*e.g.,* urine, bronchoalveolar lavage, spleen, lymph nodes, and biopsy material); and handling, processing, storing, labeling, and shipping of the biospecimens.

ii. Conduct training in obtaining relevant and pertinent HIV-positive history, duration of HIV infection, opportunistic illnesses and their therapy, risk factors for HIV, CD4+ T-cell counts (lows and highs), HIV resistance, ART medication history use and response, history of ART resistance, present ART, HIV viral loads, and HIV genotype and tropism, when known.

iii. Develop a biohazard plan to prevent and manage exposure to or transmission of HIV.

These criteria are in addition to, not in place of, current Organ Procurement and Transplantation Network (OPTN) policies and bylaws, state or local laws, and federal regulations governing organ transplantation and research that pertains to OPOs.

5 Prevention of Inadvertent Transmission of HIV

Although the use of HIV-positive organs may help alleviate transplant shortages and reduce patient waiting list times, there also are patient safety concerns to consider. Prevention or management of inadvertent transmission of HIV or exposure of an HIV-negative recipient to organs or tissues from an HIV-positive donor due to identification error is paramount (Ison, 2009, 2011a, 2011b). The transplant community, with regulatory oversight at multiple levels, has been able to achieve a high level of safety through routine procedures and clinical practice. The precautions taken with ABO compatible donor-recipient pairs and HCV-infected donor organs in HCV-infected recipients (Morales, 2010; Kucirka, 2010; Mandal, 2000; Tector, 2006) are existing models. However, vulnerabilities still exist, and mishaps still occur. For instance, the risks of error during manual transcription of information are well documented.

Each transplant hospital shall have an institutional biohazard plan for handling of HIV-positive organs—to include, for example, organ quarantine measures, electronic information capture on infectious disease testing results, communication protocols between OPOs and transplant hospitals—that is designed to prevent and/or manage inadvertent transmission of or exposure to HIV.

Tissues (*e.g.,* cornea, blood vessels, or cartilage) not associated with the organ to be transplanted and organs are often recovered from organ donors. The FDA regulates human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are intended for implantation, transplantation, infusion, or transfer into a human recipient under the authority of section 361 of the Public Health Service Act and the implementing regulations in 21 CFR part 1271. Under 21 CFR part 1271, persons with risk factors for, or clinical evidence of, relevant communicable diseases, or whose test results are positive or reactive for relevant communicable diseases (including HIV) are ineligible to donate HCT/Ps. Procedures must be in place to ensure that HCT/Ps are not recovered from HIV-positive donors for implantation, transplantation, infusion, or transfer into a human recipient; however, HCT/Ps from a donor who has been determined to be ineligible may be made available for nonclinical purposes.

6 Study Design/Required Outcome Measures

There is a wide range of clinical and immunologic questions that might be addressed in the context of research in HIV-positive to HIV-positive transplantation. These include, for example, questions related to HIV superinfection; incidence and severity of OIs (including transmission of occult OIs from donor to recipient); immunologic mechanisms contributing to the increased rate of kidney rejection observed in HIV-positive recipients; quality of life for recipients of HIV-positive to HIV-positive transplantation; outcomes of living HIV-positive donors; and a host of others. The questions will be determined by the investigators who design research protocols for studying HIV-positive to HIV-positive transplantation. However, to ensure that all studies of HIV-positive to HIV-positive transplantation can contribute to evaluation of the safety of the procedure, the following key donor and recipient characteristics and outcome measures must be incorporated into the design of all clinical trials of HIV-positive to HIV-positive transplantation.

6.1 Wait List Candidates

- HIV status
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load
- ART resistance
- Removal from wait list (death or other reason)
- Time on wait list

6.2 Donors (all)

- Type (living or deceased)
- HIV status (HIV-positive new diagnosis, HIV-positive known diagnosis)
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load
- ART resistance
- Pre-transplant donor allograft biopsy

6.3 Living Donors (6, 12, and 24 Months Following Organ Donation)

- Progression to renal insufficiency in kidney donors:
  - Proteinuria defined as urinary protein excretion >150 mg/day or urine protein/creatinine ratio >0.2
  - eGFR <60 mL/minute/1.73m^2
- Progression to hepatic insufficiency in liver donors (INR >1.5 and/or total bilirubin >2.0)
- Change in ART regimen as a result of decreased organ function
- Progression to AIDS
- Failure to suppress viral replication (persistent viremia)
- Death

6.4 Transplant Recipients

- Rejection rate (annual up to 5 years)
- Progression to AIDS
- New OIs
- Failure to suppress viral replication (persistent viremia)
- HIV-associated organ failure
- Malignancy
- Graft failure
- Mismatched ART resistance versus donor
- Death

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Dated: November 20, 2015.

Francis S. Collins,

Director, National Institutes of Health.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: Center for Scientific Review Special Emphasis Panel; Member Conflict: Reproductive Biology.

Date: December 8, 2015.

Time: 1:00 p.m. to 4:00 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6701 Rockledge Drive, Bethesda, MD 20892, (Virtual Meeting).

Contact Person: Michael Knecht, Ph.D., Scientific Review Officer, Center for Scientific Review, National Institutes of