described in section II of this document, please identify the topic you are addressing. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov*.

V. Transcripts

As soon as a transcript is available, it will be accessible at *http://www.regulations.gov*. It may also be viewed in person at the Division of Dockets Management (see **ADDRESSES**). A transcript will also be available in either hardcopy or on CD–ROM, after submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (ELEM–1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857. A link to the transcripts will also be available approximately 45 days after the public workshop on the Internet at *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htm*. (Select this public workshop from the posted events list.)

Dated: June 12, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015–14983 Filed 6–17–15; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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, Department of Health and Human Services.

ACTION: Notice of availability and request for comments.

SUMMARY: The HOPE Act requires the Secretary of Health and Human Services (the Secretary) to develop and publish criteria for research involving transplantation of HIV-infected (HIV+) donor organs in HIV+ recipients. The goals of these criteria are, first, to ensure that research using organs from HIV+ 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 solid organ transplantation (SOT) from HIV+ donors to HIV+ recipients. The National Institutes of Health (NIH), U.S. Department of Health and Human Services, invites the public to submit comments regarding the proposed HOPE Act criteria.

DATES: To ensure that comments will be considered, comments must be received no later than 5:00 p.m. on August 17, 2015.

ADDRESSES: Comments may be submitted by any of the following methods:

- *Email: HOPEAct@mail.nih.gov.*
- *Fax:* 301–451–5671.
- *Regular Mail:* Dr. Jonah Odim, 5601 Fishers Lane, Room 6B21, MSC 9827, Bethesda, MD 20892–9827.
- *Hand Delivery, Overnight Mail, FedEx, and UPS:* Dr. Jonah Odim, 5601 Fishers Lane, Room 6B21, MSC 9827, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dr. Jonah Odim, 240–627–3540.

SUPPLEMENTARY INFORMATION: There is little evidence base for HIV+ to HIV+ organ transplantation, and it is only in liver and kidney transplantation that there is substantial experience with transplantation of organs from HIV-uninfected (HIV−) donors to HIV+ recipients. The criteria for conducting clinical research in HIV+ to HIV+ organ transplantation 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) and are summarized in the table below. 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+ 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 SOT from HIV+ donors to HIV+ recipients.

Category	Criteria
Donor Eligibility:	
Deceased donor with known history of HIV infection.	Cluster of differentiation 4 (CD4)+ T-cell count ≥200/microliter (μL) or ≥14%. HIV–1 ribonucleic acid (RNA) <50 copies/milliliter (mL); No history of viral load >1000 copies/mL in the prior 12 months. No active opportunistic infection (OI).
Deceased donor with newly diagnosed HIV infection.	CD4+ T-cell count ≥200/μL or ≥14%. Viral load: no requirement. No active OI.
Living HIV+ donor	Well-controlled HIV infection. CD4+ T-cell count (lifetime nadir) ≥200/μL. CD4+ T-cell count ≥500/μL for the 6-month period before donation. HIV–1 RNA <50 copies/mL. No OI. Pre-transplant donor allograft biopsy showing no evidence of disease that would increase the risk of post-transplant organ failure or poor graft function.
Recipient (HIV+) Eligibility	CD4+ T-cell count ≥200/μL (kidney). CD4+ T-cell count ≥100μL (liver) within 16 weeks prior to transplant; or ≥200μL with history of OI HIV–1 RNA <50 copies/mL and on a stable antiretroviral regimen. No active OI or neoplasm. No history of chronic cryptosporidiosis, primary central nervous system (CNS) lymphoma, or progressive multifocal leukoencephalopathy (PML).

Category	Criteria
Transplant Hospital Criteria	Transplant hospital with established program for care of HIV+ subjects. HIV program expertise on the transplant team. Experience with HIV− to HIV+ 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+ to HIV+ transplantation. Institutional biohazard plan outlining measures to prevent and manage inadvertent exposure and/or transmission of HIV. Provide each living HIV+ donor and HIV+ 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+ donors and their family 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 HIV Transmission.	Each participating Transplant Program and OPO shall develop an institutional biohazard plan for handling of HIV+ organs 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+ 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+ new diagnosis, HIV+ known diagnosis). CD4+ T-cell count. Co-infection (HCV, HBV). HIV viral load. ART resistance.
Living Donors	Progression to renal insufficiency in kidney donors (serum creatinine >2 mg/deciliter (dL), serum creatinine level twice the pre-donation creatinine level, or proteinuria). Progression to hepatic insufficiency in living donors (international normalized ratio (INR) >1.5 and/or total bilirubin >2.0). 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 (Years 1 and 2). 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.

Instructions for Submitting Comments: Comments are invited on but not limited to: (1) Donor and recipient eligibility criteria; (2) the inclusion of living HIV+ donors; (3) other viral co-infections in the donor and/or recipient (*e.g.,* HBV and/or HCV) (4) transplant hospital criteria; (5) OPO responsibilities; (6) minimal required outcome measures under the HOPE Act; and (7) whether the proposed collection of these minimal outcome measures is sufficient to assess the safety of HIV+ to HIV+ transplant as outlined in the HOPE Act. Do not include personal information that you do not want publicly disclosed.

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	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.
HIV	Human Immunodeficiency Virus.
HIV−	HIV-uninfected.
HIV+	HIV-infected.
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 Reverse Transcriptase Inhibitor.

NRTI	Nucleoside 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.

Background

Public Law 113–51, The HOPE Act, requires the Secretary of Health and Human Services (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 organ.'' (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+ 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 SOT from HIV+ donors to HIV+ 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 subjects 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 rejection would hasten progression from HIV infection to AIDS, concerns about disease transmission, and reluctance to allocate organs to a population whose outcome was unpredictable (Blumberg, 2009, 2013; Mgbako, 2013; Taege, 2013). Nevertheless, a few transplant programs accepted HIV+ 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; Blumberg, 2009; Stock, 2010; Yoon, 2011; Terrault, 2012). Subsequently, a prospective, multi-center clinical trial of kidney and liver transplantation in 275 patients demonstrated that among HIV+ 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 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+ 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; 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+ individuals with liver or kidney failure, though 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, 2014) transplantation in HIV+ 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+ recipients utilize organs from HIV − uninfected (HIV −) donors. See 42 U.S.C. 273(b)(3)(C), 274(b); 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+ to HIV+ transplantation'') is recognized (Boyarsky, 2011; Mgbako, 2013; Mascolini, 2014). It is estimated that an additional 500 organ donors per year might be available if HIV+ individuals were accepted as organ donors for HIV+ recipients (Boyarsky, 2011). The only published experience with HIV+ to HIV+ SOT at this time is an early pilot report from South Africa (Muller, 2010) with 100 percent patient and graft survival in 4 patients. In a follow-up report from the same group, an additional 10 HIV+ to HIV+ renal transplants were performed (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 four years post-transplantation, outcomes remained excellent and all patients had undetectable viral loads (Muller, 2012).

This document presents criteria for conducting research in HIV+ to HIV+ SOT. 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+ to HIV+ transplantation, such as the specific medication regimens, pre-transplant induction (if any), maintenance immunosuppression after transplantation, or control of HIV infection. These considerations, 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+ to HIV+ 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+ to HIV+ 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 − donors to HIV+ recipients. The intent is not to exclude the possibility of HIV+ to HIV+ transplantation of other organs such as heart or lung in the future; however, transplant teams should gain experience with HIV − to HIV+ transplantation of a specific organ before taking on the more complex and less well-defined issues of HIV+ to HIV+ transplantation of that organ. Centers developing research protocols for HIV+ to HIV+ non-renal, non-liver transplantation must have a study team with demonstrated experience in HIV − to HIV+ 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 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+ to HIV+ non-renal, non-liver transplantation will need to 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 research. Accordingly, to emphasize the specific requirements unique to the transplantation of organs from HIV+ donors into HIV+ recipients in research, the research criteria set forth here do not address related requirements that may 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 can be found at *http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf.*

Under these research criteria, all HIV+ to HIV+ 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+ to HIV+ transplantation under these research criteria must provide each living donor and recipient with an ''Independent Advocate'' (as defined in CMS regulations at 42 CFR 482.98(d)).

1 Donor Eligibility

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

There is substantial concern about the consequences of transplanting an organ from an HIV+ donor to a recipient infected with a strain of HIV that differs from the donor's in terms of its responsiveness to 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; there may be inadequate virus in donor specimens for antiretroviral resistance testing; if the specimen is adequate there may be a limited time, or decision-making window, to assess antiretroviral resistance before the organ must be implanted; the donor's history of antiretroviral treatment may be unknown; and results of any 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 matching donors and recipients infected with strains of HIV that have the same antiretroviral resistance pattern and whose infections are effectively controlled with comparable antiretroviral regimens will pose the lowest risk of harm to the recipient. However, such a stringent transplant eligibility criterion would limit the pool of suitable donors and constrain capacity to study transplantation of HIV+ organs under the HOPE Act. Transplant teams evaluating a donor should review all available donor and recipient information and be able to propose an antiretroviral regimen that will be equally or more effective, safe, and tolerable for the recipient after transplantation as the regimen in place before transplantation. If there is substantial doubt about the ability to suppress viral replication after transplantation, a different donor should be sought.

Donors co-infected with hepatitis are not excluded from HIV+ to HIV+ 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 (Fofana, 2014; 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 and tenofovir) has the potential for revealing HBV drug resistance in the recipient (Dieterich, 2007; Soriano, 2009; Pais, 2010).

In the case of a living HIV+ 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+ patients has been associated with variants in the apolipoprotein 1 (APOL1) coding variants that confer a very high risk of susceptibility, and are almost exclusively found in patients of African

descent (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 (Reeves-Daniel, 2011).

These criteria require that the consent process for an HIV+ 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 ART drugs in the future; (2) the risk of kidney or liver failure in the setting of HIV infection in the future; (3) the possibility of transmission of occult OIs to the recipient; and (4) the absence of U.S. experience in HIV+ to HIV+ organ transplantation, and thus the unpredictable nature of donor and recipient outcomes (Mgbako, 2013).

HIV+ transplant candidates who are listed for a transplant in the context of a research study of HIV+ to HIV+ 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 Donor (HIV+) Eligibility Criteria

The HIV-specific donor eligibility criteria specified below apply when screening HIV+ deceased and HIV+ living donors (also refer to Table 1). Co-infection with HBV and/or HCV is not an exclusion criterion, although researchers that include the co-infected donor must address any additional eligibility criterion within their research protocol.

1.1.1 Deceased Donors

When evaluating HIV+ deceased donors, it is understood that limited medical history may be available and/or known at the time of the donor evaluation. The transplant team must make all reasonable efforts possible to obtain prior medical history to determine the suitability of the potential donor. 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 ART regimens. In addition, 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.

Minimum eligibility criteria for all HIV+ deceased donors:

i. Documented HIV infection using licensed test devices and with established confirmatory criteria.

ii. No known history of a CD4+ T-cell count <200/μL.

Minimum eligibility criteria for deceased donors with a known history of HIV infection:

i. Documented HIV infection using licensed test devices and with established confirmatory criteria.

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

a. CD4+ T-cell count ≥200/μL or ≥14 percent.

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

c. No known history of a viral load > 1000 copies/mL in the prior 12 months.

iii. The study team must be able to predict a tolerable regimen in the recipient based on the current regimen suppressing virus in the donor as well as the donor's history of ART resistance.

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

Minimum eligibility criteria for deceased donors newly diagnosed with HIV infection at the time of evaluation for organ donation:

i. Documented HIV infection using licensed test devices and with established confirmatory criteria.

ii. CD4+ T-cell count ≥200/μL or ≥14 percent.

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

1.1.2 Living Donors Infected With HIV

Minimum eligibility criteria for living donors infected with HIV:

i. Documented HIV infection using licensed test devices and with established confirmatory criteria.

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

a. Lifetime nadir of ≥200 CD4+ T cells/μL.

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

c. Fewer than 50 copies/mL of HIV–1 RNA detectable by ultrasensitive or real-time PCR assay.

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

iv. The study team must be able to predict a tolerable regimen in the recipient based on the current regimen suppressing virus in the donor as well as the donor's history of ART resistance.

v. No evidence of active 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+ transplant candidates is the ability to suppress HIV viral load post-transplant. This includes a thorough assessment by the transplant team of the patient's prescribed antiretroviral medications, HIV RNA levels while on medications, adherence to HIV treatment, and any available HIV resistance testing. The transplant team must be able to devise a post-transplant medication regimen that is both tolerable and effective in suppressing HIV. If there is any significant doubt on the part of the transplant team about the ability to suppress viral replication post-transplant, the patient should not be enrolled in a study of HIV+ to HIV+ organ transplantation.

2.1 Recipient Eligibility Criteria

The following HIV-specific criteria must be met when screening for a HIV+ to HIV+ 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+ T-cell count ≥200/μL.

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

iii. No active OI or neoplasm.

iv. No history of chronic cryptosporidiosis, 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 an effective antiretroviral regimen for the patient once organ function is restored after transplantation.

TABLE 1—SUMMARY OF DONOR (D) AND RECIPIENT (R) ELIGIBILITY CRITERIA FOR HIV+ SERO-CONCORDANT ORGAN TRANSPLANT PAIRS (D/R) UNDER THE HOPE ACT

HIV-related variables	Deceased donor		Living donor	HIV+ recipient
	New HIV infection diagnosis	History of HIV infection		
Current CD4+ T-cell count (T lymphocytes/μL).	≥200 or ≥14%	≥200 or ≥14%	≥500 for six months prior to organ harvest.	If history of OI, • ≥200. If no 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 AND No measurement >1000 over preceding 12 months.	<50	<50 *
Opportunistic infection	No active OI	No active OI	Currently, ... • No active OI. ..... Historically, no, ... • Chronic cryptosporidiosis.. • CNS lymphoma. ..... • PML..	

* 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 an effective antiretroviral regimen for the patient once organ function is restored after transplantation.

3 Transplant Hospital Criteria

Expertise in the management of individuals with HIV infection is essential for this research. A transplant hospital participating in HIV+ to HIV+ 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+ to HIV+ transplantation, there must be a study team consisting of (at a minimum) a transplant surgeon, a transplant physician, and an HIV physician, each of whom have experience with at least 5 HIV − to HIV+ transplants with the designated organ(s) over the last four years. This constitutes the minimal experience necessary, and the IRB should evaluate key personnel (transplant surgeon, transplant physician, and HIV physician) in the context of total expertise and experience with respect to HIV and/or organ transplantation.

iii. Defined SOPs and training for the procurement team and implanting team 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+ to HIV+ transplantation must report to the OPTN organ-specific acceptance criteria for organs from HIV+ donors.

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

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

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+ to HIV+ transplantation under these research criteria must provide each living donor and recipient with an ''Independent Advocate'' (as defined in CMS regulations at 42 CFR 482.98(d).

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

At a minimum, transplant hospitals conducting research in HIV+ to HIV+ 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+ recipient's decision, and HIV+ living donor's decision (if applicable) about whether to enter the HIV+ to HIV+ transplant research study.

3.2.1 Independent HIV+ Recipient Advocate

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

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

ii. Review whether the potential HIV+ recipient has received information regarding the results of SOT in general and transplantation in HIV-infected recipients in particular; and the unquantifiable risks of transmission of HIV, OIs, ART resistance, and accelerated kidney, liver, and cardiovascular disease in HIV+ recipients of HIV+ donor organs.

iii. Demonstrate knowledge of HIV infection and transplantation.

3.2.2 Independent HIV+ Living Donor Advocate

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

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

ii. Review whether the potential HIV+ 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+ donor, including accelerated organ failure, and limitations of future use of specific antiretroviral agents; and (b) the unknown outcome of HIV+ to HIV+ organ transplantation.

iii. Demonstrate knowledge of HIV infection and transplantation.

4 OPO Responsibilities

Clinical research in HIV+ to HIV+ organ transplantation requires a partnership between OPOs and transplant programs. OPOs participating in research of HIV+ to HIV+ organ transplantation must adhere to the following criteria:

i. Develop SOPs and staff training procedures to effectively work with the family and friends of HIV+ subjects in history taking, medical record abstraction, HIV clinic and pharmacy medical record telephone abstraction, obtaining research consent from next of kin to HIV+ subjects, performing physical examination of HIV+ subjects, collecting blood, tissue, and other biospecimens (*e.g.,* urine, bronchoalveolar lavage, spleen, lymph nodes, and biopsy material), handling, processing, storing, and shipping.

ii. Conduct training in obtaining relevant and pertinent HIV+ history, duration of HIV infection, opportunistic infections 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.

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 policies 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 or exposure of an HIV-recipient to organs or tissues from an HIV+ donor due to identification error is paramount (Ison, 2011). 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 develop an institutional biohazard plan for handling of HIV+ organs (*e.g.,* 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+ to HIV+ 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+ recipients; quality of life for recipients of HIV+ to HIV+ transplantation; outcomes of living HIV+ donors; and a host of others. The questions will be determined by the investigators who design research protocols for studying HIV+ to HIV+ transplantation. However, to ensure that all studies of HIV+ to HIV+ 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+ to HIV+ 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+ new diagnosis, HIV+ known diagnosis)
- CD4+ T-cell count
- Co-infection (HCV, HBV)
- HIV viral load
- ART resistance

6.3 Living Donors (12 months following organ donation)

- Progression to renal insufficiency in kidney donors (serum creatinine > 2 mg/dL, serum creatinine level twice the pre-donation creatinine level, or proteinuria).

- 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 (Years 1 and 2)
- 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: June 12, 2015

Francis S. Collins,

Director, National Institutes of Health.

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BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration

Mandatory Guidelines for Federal Workplace Drug Testing Programs; Request for Information Regarding Specific Issues Related to the Use of the Hair Specimen for Drug Testing

AGENCY: Substance Abuse and Mental Health Services Administration (SAMHSA), Department of Health and Human Services (DHHS).

ACTION: Request for information.

SUMMARY: This document is a request for information regarding specific aspects of the regulatory policies and standards that may be applied to the Mandatory Guidelines for Federal Workplace Drug Testing Programs (hair specimen). The original comment close date was June 29, 2015. We are extending the date to July 29, 2015 to allow for additional comments.

DATES: Comment Close Date: To be assured consideration, comments must be received at one of the addresses provided below on or before July 29, 2015.

ADDRESSES: Because of staff and resource limitations, we cannot accept comments by facsimile (FAX) transmission. You may submit comments in one of four ways (please choose only one of the ways listed):

Electronically: You may submit electronic comments to *http://www.regulations.gov*. Follow ''Submit a comment'' instructions.

By regular mail: You may mail written comments to the following address only: Substance Abuse and Mental Health Services Administration, Attention: Division of Workplace Programs, 1 Choke Cherry Road, Room 7–1029, Rockville, MD 20857. Please allow sufficient time for mailed comments to be received before the close of the comment period.

By express or overnight mail: You may send written comments to the following address only: Substance Abuse and Mental Health Services Administration, Attention: Division of Workplace Programs, 1 Choke Cherry Road, Room 7–1029, Rockville, MD 20850.

By hand or courier: Alternatively, you may deliver (by hand or courier) your written comments only to the following address prior to the close of the comment period:

For delivery in Rockville, MD: Substance Abuse and Mental Health Services Administration, Attention: Division of Workplace Programs, 1 Choke Cherry Road, Room 7–1029, Rockville, MD 20850. To deliver your comments to the Rockville address, call telephone number (240) 276–2600 in advance to schedule your delivery with one of our staff members. Because access to the interior of the Substance Abuse and Mental Health Services Administration Building is not readily available to persons without federal government identification, commenters are encouraged to either schedule your drop off or leave your comments with the security guard in the main lobby of the building.

FOR FURTHER INFORMATION CONTACT: Sean Belouin, Division of Workplace Programs, Center for Substance Abuse Prevention (CSAP), SAMHSA, 1 Choke Cherry Road, Room 7–1029, Rockville, Maryland 20857, (240) 276–2716 (phone), (240) 276–2610 (Fax), or email at *sean.belouin@samhsa.hhs.gov*.

SUPPLEMENTARY INFORMATION: Inspection of Public Comments: All comments received before the close of the comment period are available for viewing by the public, including any personally identifiable or confidential business information that is included in a comment. We post all comments received before the close of the comment period on the following Web site as soon as possible after they have been received: *http://www.regulations.gov*. Follow the search instructions on that Web site to view public comments. Comments received by the deadline will also be available for public inspection at the Substance Abuse and Mental Health Services Administration, Division of Workplace Programs, 1 Choke Cherry Road, Rockville, MD 20850, Monday through Friday of each week from 8:30 a.m. to 4 p.m. To schedule an appointment to view public comments, phone (240) 276–2716.

I. *Background:* The Department of Health and Human Services (HHS) establishes the standards for Federal Workplace Drug Testing Programs under the authority of Section 503 of Public Law 100–71, 5 U.S.C. Section 7301, and Executive Order No. 12564. As required, HHS published the Mandatory Guidelines for Federal Workplace Drug Testing Programs (Guidelines) in the **Federal Register** on April 11, 1988 [53 FR 11979]. SAMHSA subsequently revised the Guidelines on June 9, 1994 [59 FR 29908], September 30, 1997 [62 FR 51118], November 13, 1998 [63 FR 63483], April 13, 2004 [69 FR 19644], and on November 25, 2008 [73 FR 71858]. On May 15, 2015, HHS published a notice of proposed revisions