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Deceased Donor Intervention Research: A Survey of Transplant Surgeons, Organ Procurement Professionals, and Institutional Review Board Members

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Innovative deceased donor intervention strategies have the potential to increase the number and quality of transplantable organs. Yet there is confusion over regulatory and legal requirements, as well as ethical considerations. We surveyed transplant surgeons (n = 294), organ procurement organization (OPO) professionals (n = 83), and institutional review board (IRB) members (n = 317) and found wide variations in their perceptions about research classification, risk assessment for donors and organ transplant recipients, regulatory oversight requirements, and informed consent in the context of deceased donor intervention research. For instance, when presented with different research scenarios, IRB members were more likely than transplant surgeons and OPO professionals to feel that study review and oversight were necessary by the IRBs at the investigator, donor, and transplant center hospitals. Survey findings underscore the need to clarify ethical, legal, and regulatory requirements and their application to deceased donor intervention research to accelerate the pace of scientific discovery and facilitate more transplants.

Abbreviations: IRB, institutional review board; OPO, organ procurement organization; OPTN, Organ Procurement and Transplantation Network; PHI, personal health information; UNOS, United Network for Organ Sharing

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Introduction

The number of deceased donor organs has not kept pace with the growing demand for transplantation in the United States (1), despite many novel efforts to expand the organ supply (2–5). Innovative donor intervention strategies focus on achieving and maintaining optimal circulatory, metabolic, and hemodynamic function to facilitate procurement of organs for transplantation. Together with technological advances to better preserve organs and mitigate organ injury, identifying effective donor intervention strategies has potential to increase the number and quality of transplantable organs from deceased donors (6–10). For instance, some studies have demonstrated that improvement in organ quality and more transplantable organs per donor can be achieved with more aggressive donor intervention (9,11,12). While findings from donor intervention research are encouraging, there is considerable opportunity for growth in this line of scientific investigation.

The design and implementation of prospective, randomized controlled donor intervention trials is complex and necessitates collaborative agreements among investigators, organ procurement organizations (OPOs), and transplant centers to efficiently assess the impact of such interventions on organ quality, the number of organs recovered and transplanted, and organ recipient outcomes. Additionally, the myriad regulatory, legal, and ethical issues pertaining to deceased donor intervention research introduce daunting conceptual and logistical challenges (10,13,14). Many questions have been raised that warrant further clarification and discussion in the donation, transplantation, and research oversight communities: Who can or should authorize donor intervention research? Should transplant candidates be informed of donor research and, if so, how and when should this occur? What are the risks to transplant recipients of organs from donors who were part of interventional studies? What regulatory bodies, if any, should review and provide oversight of deceased donor intervention research (14–16)?

Optimizing deceased donor organ quality and quantity through innovative donor research necessitates that stakeholders—scientists, donation professionals, transplant professionals, governmental agencies, experts in human research protections, and the general public—reach consensus on these complex issues. However, the perceptions of these stakeholders regarding donor intervention research are unknown. Understanding these perceptions may be helpful in developing a pathway to perform donor intervention trials that provides balance among all stakeholders, but yet is within the current legal and ethical framework of organ donation and human research protection, and maintains public trust in organ donation processes. Therefore, we surveyed transplant surgeons, OPO professionals, and institutional review board (IRB) members about deceased donor intervention research. Each constituency may see donor research through a different lens. OPO professionals are generally nonscientists with expertise in the donation process including authorization, donor management, and procurement, but without any training in human subjects research. The primary mission for OPO professionals is increasing the availability of transplantable organs. Transplant surgeons have scientific expertise, with some level of instruction on human subject research, and seek organs that yield the best possible outcomes for their patients. IRB members may lack knowledge about donation and transplantation, but have considerable expertise about federal regulations pertaining to human subjects research. Similarities and differences in their perspectives may help to shape future dialogue about deceased donor intervention research.

Methods

We designed an online survey (Qualtrics, Provo, UT) to assess views about conducting deceased donor intervention research. Questions were developed to reflect the regulatory, legal, and ethical issues described in the literature summarizing this line of research (10,13–15). The initial survey was reviewed by transplant surgeons (n = 2), OPO professionals (n = 2), IRB members (n = 2), and a public health expert (n = 1) and, based on their feedback, modifications were made to improve readability/clarity and to reduce duplication. The final survey included three brief research scenarios, each followed by questions with forced-choice responses assessing views about research classification, perceived risk, regulatory requirements, and informed consent. An opportunity for open-ended comments was provided at the end of the survey. The three research scenarios were selected because they each introduce unique ethical and regulatory elements. The first scenario describes a randomized controlled trial involving deceased donors only, with no data collection from living recipients. The second scenario amends the trial to now include the retrieval of standard clinical data about organ recipients. The third scenario describes a new randomized controlled trial with deceased donors that includes the collection of organ recipient data that extend beyond routine clinical care.

We identified 100 medical centers in the United States that performed the most solid organ transplants in 2013 (http://optn.transplant.hrsa.gov/). We felt that high-volume centers were most likely to be (or to become) involved in donor intervention research and to perform regulatory reviews of such research. We identified as many transplant surgeons and IRB members as possible at these 100 centers via search of online directories. Next, we identified the executive team members of the 58 OPOs in the United States using available online resources.

Between May and October 2014, we emailed a study invitation to all transplant surgeons (n = 538), IRB members (n = 1229), and OPO professionals (n = 138) for whom we found valid email addresses, providing a secure hyperlink to complete the survey online. Because we were unable to locate the email addresses of all OPO executive team members, we asked those for whom we had valid email addresses to forward the study invitation to other team members. Reminder emails were sent 2 and 6 weeks later. Beth Israel Deaconess Medical Center's Committee on Clinical Investigations certified the exempt status of the study.

Survey responses were exported into PASW 17.0 (IBM, Inc., Chicago, IL) for coding and statistical analysis. Data are expressed as the number and percentage of respondents with specific item responses. Chi-square tests examined for differences between transplant surgeons, OPO professionals, and IRB members, as well as for response differences by sociodemographic characteristics. If cell sizes did not meet requirements for chi-square tests, Fisher's exact test was used. Due to the high number of statistical tests performed, statistical significance was set at $p < 0.01$.

Results

Survey response rate

We sent 1905 email invitations, although the number of OPO professionals who received forwarded emails is unknown. Ninety-five emails (5%) were undeliverable. We received 732 responses, of which 694 usable surveys were collected. The difference (n = 38) were submissions that did not contain any responses. The response rate was higher for transplant surgeons (n = 294, 55%) than for IRB members (n = 317, 26%) ($p < 0.001$). Surveys were received from 83 OPO professionals. When respondents (n = 21) indicated more than one role (e.g. transplant surgeon and IRB member), we selected a primary role using the following priority classification: transplant surgeon first, OPO professional second, IRB member third.

Respondent characteristics

All 11 United Network for Organ Sharing (UNOS) regions were represented. The majority of transplant surgeons and OPO professionals but only half of IRB members had >5 years experience. Few (13%) transplant surgeons had been directly involved in deceased donor intervention research. In contrast, most (71%) OPO professionals had participated in such research (Table 1).

Research scenario no. 1

Thyroid hormone is medication that is currently used in deceased organ donors. Dr. Finnigan hypothesizes that there is an optimal pharmacologic dose of an FDA-approved thyroid hormone that will increase the successful ''procurement and utilization of hearts for transplantation.'' To test this hypothesis, Dr. Finnigan designs a multisite randomized controlled trial in which adults with irreversible neurological determination of death (i.e. brain dead) at

Table 1: Survey respondent characteristics (N = 694)

	N	(%)
Transplant surgeons, n = 294		
Transplant experience, yrs		
0–5	52	(18%)
6–10	119	(40%)
>10	123	(42%)
PI or co-investigator on deceased donor intervention or organ preservation study (past or present)	38	(13%)
OPO professionals, n = 83		
OPO experience, yrs		
0–5	4	(5%)
6–10	17	(20%)
>10	62	(75%)
Led or participated in deceased donor intervention or organ preservation study (past or present)	59	(71%)
IRB members, n = 317		
IRB experience, yrs		
0–5	162	(51%)
6–10	89	(28%)
>10	66	(21%)
Primary role		
Member	250	(79%)
Administrator	67	(21%)

IRB, institutional review board; OPO, organ procurement organization; PI, principal investigator.

10 hospitals in the United States will be administered one of three different doses of the thyroid hormone. The primary outcomes are procurement of the heart (yes, no) and utilization of the heart (transplanted, not transplanted). The thyroid hormone does not have any known clinical benefit for the potential organ donor. The potential organ donors have documentation of donor designation, including authorization for research, through the department of motor vehicles registry from their state of residence.

As reported in Table 2, while most respondents (64%) considered this study to be human subjects research, responses varied by professional role. IRB members (82%) were most likely to consider the study to be human subjects research, followed next by transplant surgeons (58%) and then OPO professionals (19%) ($p < 0.001$). More than half (58%) considered the study to be of no risk to the deceased donor, although 37% classified it as minimal risk. While respondent types did not differ in their assessment of risk level to study donors, they did vary in their assessment of risk to potential recipients of the study donor's heart ($p < 0.001$) and other organs ($p < 0.001$). OPO professionals were more likely than transplant surgeons and IRB members to conclude that there was no risk for recipients of the study donor's heart and other organs.

Most IRB members (93%) and transplant surgeons (73%) indicated that the study requires review by the investigator's IRB, although only 35% of OPO professionals deemed this necessary ($p < 0.001$). IRB members also were more likely than transplant surgeons and OPO professionals to feel that the study requires IRB review at the donor hospitals ($p < 0.001$) and at centers where the heart and other organs are transplanted ($p < 0.001$).

Transplant surgeons (36%) and IRB members (45%) were more likely than OPO professionals (8%) to indicate that informed consent (or authorization) for the study should be obtained from the donor's next-of-kin ($p < 0.001$). IRB members felt more strongly than transplant surgeons and OPO professionals that transplant candidates who are offered the heart ($p < 0.001$) and other organs ($p < 0.001$) from study donors should be informed about the study.

Research scenario no. 2

Dr. Finnigan decides to add a secondary outcome measure to the study. Specifically, she will ask the heart transplant recipient's surgeon to send her the following recipient data annually for 3 years after transplantation: laboratory data obtained by the transplant program as part of routine clinical care, ejection fraction, number and timing of acute rejection episodes, and patient survival status.

Compared to OPO professionals (14%), more transplant surgeons (67%) and IRB members (86%) considered the risk level to heart transplant recipients to be at least minimal ($p < 0.001$). Most transplant surgeons (87%) and IRB members (97%) felt that the protocol amendment requires review by the investigator's IRB, compared to only 33% of OPO professionals ($p < 0.001$). Similar group differences were observed for whether IRB review was required at centers where the study heart is transplanted (transplant surgeons = 60%, IRB members = 72%, OPO professionals = 17%, $p < 0.001$).

Most transplant surgeons (78%) and IRB members (91%) felt it is necessary for heart transplant recipients to provide informed consent for the data elements to be shared with the investigator, whereas only 14% of OPO professionals felt this was necessary ($p < 0.001$). For those who thought informed consent from the recipient was necessary, two-thirds (67%) felt that consent should be obtained at the time the donor heart is offered (i.e. before surgery) and the majority (85%) felt that the transplant candidate should still be offered the heart even if they refused study participation.

Research scenario no. 3

In a separate study, Dr. Finnigan discovers a new agent that works through the innate immune system. In animal studies, she finds that it improves donor liver function and survival after transplant. To test this agent in humans, Dr. Finnigan designs a multisite randomized controlled trial in which adults with irreversible neurological determination of death (i.e. brain dead) will be given this agent prior to organ recovery. The trial is designed in an effort to obtain FDA approval. As part of the FDA application process, Dr. Finnigan discloses that in the animal studies, some of

Table 2: Transplant surgeon, OPO professional, and IRB member responses to research scenario no. 1, n (%)

	Total sample (N = 694)	Transplant surgeons (n = 294)	OPO professionals (n = 83)	IRB members (n = 317)	p-value
Consider study to be human subjects research (yes)	447 (64%)	171 (58%)	16 (19%)	260 (82%)	<0.001
Assessment of risk level to study donors					
None	405 (58%)	156 (53%)	56 (68%)	193 (61%)	
Minimal	254 (37%)	123 (42%)	26 (31%)	105 (33%)	
Moderate	20 (3%)	9 (3%)	1 (1%)	10 (3%)	
High	15 (2%)	6 (2%)	0 (0%)	9 (3%)	0.12
Assessment of risk level to potential recipient of study donor's heart					
None	166 (24%)	85 (29%)	52 (63%)	29 (9%)	
Minimal	345 (50%)	176 (60%)	30 (36%)	139 (44%)	
Moderate	152 (22%)	21 (7%)	1 (1%)	130 (41%)	
High	30 (4%)	11 (4%)	0 (0%)	19 (6%)	<0.001
Assessment of risk level to potential recipient of study donor's other organs (e.g. lungs, kidneys, liver, pancreas)					
None	178 (26%)	89 (30%)	58 (70%)	31 (10%)	
Minimal	351 (51%)	183 (62%)	24 (29%)	144 (45%)	
Moderate	135 (19%)	12 (4%)	1 (1%)	122 (38%)	
High	25 (4%)	7 (2%)	0 (0%)	18 (6%)	<0.001
Study requires review by Dr. Finnigan's IRB (yes)	538 (78%)	215 (73%)	29 (35%)	294 (93%)	<0.001
Study requires review by IRB at each hospital in which potential donors may be involved (yes)	242 (35%)	47 (16%)	2 (2%)	193 (61%)	<0.001
Study requires review by IRB at hospital where a study donor's heart is transplanted (yes)	217 (31%)	79 (27%)	11 (13%)	127 (40%)	<0.001
Study requires review by IRB at hospital where a study donor's other organs (e.g. lungs, kidneys, liver, pancreas) are transplanted (yes)	193 (28%)	58 (20%)	10 (12%)	125 (39%)	<0.001
Informed consent (or authorization) from donor's next-of-kin is necessary (yes)	255 (37%)	105 (36%)	7 (8%)	143 (45%)	<0.001
Transplant patient who is offered heart from a study donor should be informed about study (yes)	443 (64%)	129 (44%)	23 (28%)	291 (92%)	<0.001
If ''yes'':					
Surgeon tells patient, no formal consent process needed	80 (18%)	26 (20%)	2 (9%)	52 (18%)	
Surgeon tells patient, documents patient's verbal consent to proceed with transplant	91 (21%)	45 (35%)	2 (9%)	44 (15%)	
Surgeon tells patient, obtains patient's written consent to proceed with transplant	268 (60%)	58 (45%)	19 (82%)	191 (66%)	<0.001
Transplant patient who is offered organ other than heart from a study donor should be informed about study (yes)	381 (55%)	117 (40%)	14 (17%)	250 (79%)	<0.001
If ''yes'':					
Surgeon tells patient, no formal consent process needed	70 (18%)	26 (22%)	1 (7%)	43 (17%)	
Surgeon tells patient, documents patient's verbal consent to proceed with transplant	79 (21%)	44 (38%)	2 (14%)	33 (15%)	
Surgeon tells patient, obtains patient's written consent to proceed with transplant	229 (60%)	47 (40%)	11 (79%)	171 (68%)	<0.001

Note: Not all percentages for each question add up to 100 due to missing responses.
IRB, institutional review board; OPO, organ procurement organization.

the donors developed metabolic acidosis and the recipients of their livers had biochemical evidence of coagulation dysfunction, but neither seemed to impact the survival or long-term function of the liver. In the planned human study, the intended primary outcomes are the utilization of the liver (transplanted, not transplanted) and posttransplant liver function as measured by a series of blood tests in the liver transplant recipients. These blood tests would be in addition to those routinely collected as part of usual posttransplant care. The potential organ donors have documentation of donor designation, including authorization for research, through the department of motor vehicles registry from their state of residence.

As reported in Table 3, most transplant surgeons (93%) and IRB members (94%) consider Research Scenario no. 3 to be human subjects research, compared to only 39% of OPO professionals ($p < 0.001$). Most respondents (71%) assessed the risk level to study donors to be at least minimal. Transplant surgeons and OPO professionals were more likely than IRB members to consider the study to be of moderate risk to donors, whereas IRB members were much more likely to assess it as a minimal risk study. The three groups did not differ significantly on their perception of risk to potential recipients of the study donor's liver or other organs.

Most transplant surgeons (93%) and IRB members (97%) indicated that the study requires review by the investigator's IRB, compared to only 59% of OPO professionals ($p < 0.001$). Two thirds (69%) of IRB members also thought the study requires IRB approval at each donor hospital, compared to 32% of transplant surgeons and 5% of OPO professionals ($p = 0.002$). Both transplant surgeons and IRB members were more likely than OPO professionals to feel that the study requires IRB approval at the hospitals receiving organs from study donors. Most respondents reported that transplant patients offered any organ from a study donor should be informed about the study; the majority felt that written consent should be obtained prior to transplantation.

Timing of consent

We asked respondents about two different strategies for informing transplant candidates about deceased donor research more generally (i.e. not specific to one of the Research Scenarios). Most respondents ($n = 601/694$, 87%) indicated that transplant candidates should be informed at the time they are added to the waiting list that there are deceased donor studies being conducted that could enhance the quality and quantity of organs for transplantation, but that these studies may pose some potential risk to recipients. Also, most respondents (613/694, 88%) felt that at the time of organ offer, transplant candidates should be informed if the deceased donor was part of a research study. Among these respondents, there was clear consensus (i.e. >95% agreed with each statement) that candidates should be told (1) the specific purpose and nature of the study, (2) the risk assessment as it pertains to future graft functioning, (3) any potential impact on the transplant recipient's health and mortality, and (4) any study findings relevant to transplant outcomes.

Finally, no statistically significant relationships were found between individual survey responses and respondent characteristics, including years of experience, participation in deceased donor research, or UNOS region (all p-values >0.05).

Discussion

This study highlights similarities and differences in perceptions of transplant surgeons, OPO professionals, and IRB members about research classification, risk assessment for donors and transplant recipients, regulatory requirements, and informed consent in the context of deceased donor intervention research. Study findings strongly underscore the need to clarify ethical, legal, and regulatory requirements and their application to deceased donor research.

The U.S. Department of Health and Human Services, under the Common Rule, excludes deceased individuals from its definition of human subjects research (17). Furthermore, IRBs, which are responsible for ensuring compliance with the Common Rule and the protection of human research subjects, have no regulatory authority over deceased donors. Research Scenario No. 1, a multisite randomized trial evaluating the dosing effects of thyroid medication administered to deceased donors on the procurement and transplantation of hearts, does not meet regulatory criteria for human subjects research and therefore does not require IRB review at donor or recipient hospitals based on federal regulations. OPO professionals were more likely than transplant surgeons and IRB members to recognize that this study does not require IRB review. Most IRB members felt that the study should be reviewed by each donor hospital's IRB. While such review is not required by federal regulations, we acknowledge that there should be some mechanism to ensure that the donor hospital administration is aware of the research being conducted. IRB members, and transplant surgeons to a lesser extent, may feel that IRB review at donor and recipient hospitals is appropriate even if not required as it provides a level of risk assessment, conflict-of-interest evaluation, and administrative oversight where currently none exists. It is perhaps for this reason that some hospitals currently have expansive policies that require IRB review of all research protocols, including those involving deceased individuals.

It is not until the collection of transplant recipient data is added to the study protocol in Research Scenario No. 2 that federal regulations about the conduct of human subjects research are triggered. IRB members and transplant surgeons are likely to have more experience than OPO

Table 3: Transplant surgeon, OPO professional, and IRB member responses to research scenario no. 3, n (%)

	Total sample (N = 694)	Transplant surgeons (n = 294)	OPO professionals (n = 83)	IRB members (n = 317)	p-value
Consider study to be human subjects research (yes)	603 (87%)	273 (93%)	32 (39%)	298 (94%)	<0.001
Assessment of risk level to study donors					
None	202 (29%)	112 (38%)	24 (29%)	66 (21%)	
Minimal	327 (47%)	88 (30%)	36 (43%)	203 (64%)	
Moderate	133 (19%)	79 (27%)	23 (28%)	31 (10%)	
High	24 (3%)	11 (4%)	0 (0%)	13 (4%)	<0.001
Assessment of risk level to potential recipient of study donor's liver					
None	6 (1%)	6 (2%)	0 (0%)	0 (0%)	
Minimal	146 (21%)	68 (23%)	34 (41%)	44 (14%)	
Moderate	432 (62%)	188 (64%)	47 (57%)	197 (62%)	
High	104 (15%)	26 (9%)	2 (2%)	76 (24%)	0.42
Assessment of risk level to potential recipient of study donor's other organs (e.g. heart, lungs, kidneys, pancreas)					
None	20 (3%)	6 (2%)	1 (1%)	13 (4%)	
Minimal	221 (32%)	117 (40%)	49 (59%)	55 (17%)	
Moderate	351 (51%)	150 (51%)	30 (36%)	171 (54%)	
High	98 (14%)	20 (7%)	2 (2%)	76 (24%)	0.67
Study requires review by Dr. Finnigan's IRB (yes)	631 (91%)	273 (93%)	49 (59%)	309 (97%)	<0.001
Study requires review by IRB at each hospital in which potential donors may be involved (yes)	316 (46%)	94 (32%)	4 (5%)	218 (69%)	0.002
Study requires review by IRB at hospital where a study donor's liver is transplanted (yes)	500 (72%)	209 (71%)	41 (49%)	250 (79%)	<0.001
Study requires review by IRB at hospital where a study donor's other organs (e.g. heart, lungs, kidneys, pancreas) are transplanted (yes)	383 (55%)	155 (53%)	32 (39%)	196 (62%)	<0.001
Informed consent (or authorization) from donor's next-of-kin is necessary (yes)	298 (43%)	144 (49%)	18 (22%)	136 (43%)	<0.001
Transplant patient who is offered liver from a study donor should be informed about study (yes)	676 (97%)	282 (96%)	81 (98%)	313 (99%)	0.09
If ''yes'':					
Surgeon tells patient, no formal consent process needed	45 (7%)	20 (7%)	16 (20%)	9 (3%)	
Surgeon tells patient, documents patient's verbal consent to proceed with transplant	55 (8%)	28 (10%)	5 (6%)	21 (7%)	
Surgeon tells patient, obtains patient's written consent to proceed with transplant	569 (84%)	230 (82%)	58 (73%)	281 (90%)	<0.001
Transplant patient who is offered organ other than liver from a study donor should be informed about study (yes)	576 (83%)	229 (78%)	55 (66%)	292 (92%)	<0.001
If ''yes'':					
Surgeon tells patient, no formal consent process needed	39 (7%)	14 (6%)	5 (9%)	20 (7%)	
Surgeon tells patient, documents patient's verbal consent to proceed with transplant	75 (13%)	34 (15%)	9 (16%)	32 (11%)	
Surgeon tells patient, obtains patient's written consent to proceed with transplant	457 (79%)	178 (78%)	40 (73%)	239 (82%)	0.52
Study should be performed only if liver will not be used for transplantation (yes)	80 (12%)	53 (9%)	5 (6%)	22 (7%)	<0.001
Study should be performed only if other organs will not be used for transplantation (yes)	85 (12%)	21 (7%)	4 (5%)	60 (19%)	<0.001

Note: Not all percentages for each question add up to 100 due to missing responses
IRB, institutional review board; OPO, organ procurement organization.

professionals with studies in which medical record or laboratory data are collected from living patients and, therefore, understand that IRB review and approval are required under federal law at both the investigator's IRB and the IRBs at centers where transplant recipient data will be accessed. Unlike transplant surgeons and IRB members, OPO professionals vary in their roles, training, and responsibilities and, therefore, may not have regular exposure to randomized controlled trials nor be familiar with regulations guiding the collection of research data from living individuals. To the degree that OPO professionals will be engaged in or provide oversight for deceased donor research that includes human subjects, training in human subjects research protections (e.g. Collaborative Institutional Training Initiative Program) should be compulsory in the same way that it is for all other clinical investigators.

Faced with these research scenarios, it is clear that the perception of regulatory requirements may present a formidable barrier to conducting donor intervention research. In Research Scenarios Nos. 2 and 3, for instance, investigators must seek IRB approval at their own institution and at hospitals in which organs from study donors are transplanted, which necessitates the preparation and submission of numerous IRB applications (many more if donor hospital IRB review is deemed necessary). With increased organ sharing regionally and nationally, centers transplanting organs from research donors cannot possibly be identified in advance of procurement and allocation, thus further delaying IRB review, approval, and study implementation at these sites. Our data show that IRB members have differing opinions about the risks inherent in these research protocols as well as about donor next-of-kin authorization and informed consent requirements, which could lead to disparate conclusions and (un) necessary modifications before a study is approved (18). Finally, whether IRB review is necessary at centers where organs other than those under direct study are being transplanted represents another gray area requiring clarification. Data from recipients of nonstudy organs (i.e. ''bystander'' organs) may not be part of the study protocol per se, but surveillance may be deemed necessary to assess any unanticipated adverse effects of the donor intervention on these organs and their recipients. Whether this surveillance falls into the category of research or oversight remains to be clarified.

Research Scenarios Nos. 1 and 3 involve administration of a drug to individuals who are dead; therefore, there is no risk to these donors. However, one third of respondents for Research Scenario No. 1 and more than two thirds for Research Scenario No. 3 perceived at least minimal risks to the study donors. Both the determination of at least minimal risk and the variability in risk assessment across the two scenarios are difficult to explain. Some respondents may have felt that the ''risk'' is to the donor's anatomical gift if the study intervention could cause the donated organ(s) to no longer be viable for transplantation. Failure to honor the deceased's intention of an organ gift for transplantation may erode public trust that donated organs will be prioritized for transplantation. This concern can be attenuated by ensuring that authorization for organ gifting includes the use of organs for both transplantation and research (15). While this measure of transparency will not eliminate the risk, policies can be developed ensuring that only research protocols with minimal risk of rendering an organ unsuitable for transplantation are approved.

Some respondents may have been concerned about the loss of privacy for donors. However, unlike the human subjects research regulation that only covers living individuals, the privacy of a patient's health information is protected after death. The U.S. Health Insurance Portability and Accountability Act (HIPAA) (19) prohibits covered entities (e.g. donor and transplant hospitals) from using/disclosing personal health information (PHI) for 50 years after death unless there is authorization from a legal representative or an exception applies. However, HIPAA allows for the waiver of authorization for use/disclosure of PHI if it is for research on health information about the deceased, the targeted individual has died, and the use/disclosure of PHI is for research purposes only. Because these conditions likely apply in most donor intervention studies and OPOs are not covered entities under HIPAA, concerns about privacy requirements should not represent a barrier to pursuing donor intervention research.

As highlighted by others (13–15), donor intervention research raises several issues pertinent to authorization, informed decision-making, and informed consent. In our survey, we stipulated that the decedent had documented their donation intentions and provided authorization for research. The majority of OPO professionals, therefore, did not feel that additional next-of-kin authorization for research was necessary. On the other hand, comparatively more transplant surgeons and IRB members felt that the family (or legal next-of-kin) should be asked to provide consent or authorization for the deceased to be part of the intervention trial. In the United States, research on the deceased donor's body and/or organs is permitted without additional next-of-kin authorization under the Uniform Anatomical Gift Act (UAGA) (20), if the deceased previously authorized such research. Indeed, the family cannot override the deceased's documented decision. Only in the absence of the deceased's documented decision must authorization be obtained from next-of-kin for research to be conducted. Also, it is important to emphasize that the UAGA, which governs authorization for deceased donation including permission for research on the decedent's body or donated organ(s), follows a gift law framework, in legal contrast to the standard informed consent elements that are necessary for research with living individuals (21).

Deceased donor intervention research, while intended to increase the number of organs available for transplantation,

may have unintended downstream risks that require careful consideration. For instance, what are the risks of donor research on transplant candidates, transplant recipients of study organs, and transplant recipients of ''bystander'' organs? We found no clear consensus on how much risk is incurred by transplant recipients in our research scenarios. Research Scenario No. 3 involves use of an experimental agent with the donor that is not FDA approved and additional (beyond usual care) laboratory tests for the liver recipient. While all three respondent types were in agreement that there was some risk to transplant recipients of study and ''bystander'' organs, many OPO professionals considered these risks to be minimal whereas IRB members considered them to be moderate to high. These differences in risk level assessment are not entirely surprising, since intuitive judgments in determinations of risk are prone to cognitive bias (22,23). IRB members are less familiar with donor intervention research, so they can be expected to attribute more risk to these research protocols, even if they pose less risk than protocols in areas more familiar to IRB members (23,24).

Most IRB members felt that transplant candidates who are offered any organ from study donors should be informed about the donor research before accepting the organ for transplantation, regardless of perceived risk to the recipient. On the other hand, transplant surgeons and OPO professionals felt more strongly about informing transplant candidates of higher risk studies such as the one depicted in Research Scenario No. 3. The consensus opinion in this scenario was that transplant surgeons should tell the patient about the donor study at the time of organ allocation and obtain written informed consent before proceeding with transplantation. The precise information that should be communicated to patients is open to discussion, but there is consensus among respondents that, at a minimum, patients should be informed about the specific purpose and nature of the study, the risk assessment as it pertains to future graft functioning, any potential impact on the transplant recipient's health and mortality, and any study findings relevant to transplant outcomes. While written informed consent may represent the ''gold standard,'' further consideration of the most appropriate consent process under these circumstances is necessary to avoid unintended consequences to transplant candidates, other wait-listed patients, and society. Whether a patient who has waited years for a lifesaving transplant can reasonably be expected to make an informed decision at the time of organ allocation represents a potential ethical quandary. Our survey findings suggest that a two-tiered consent process should be considered: first, patients should be informed at the time they are added to the waiting list that there are deceased donor intervention studies being conducted and, second, informed about any specific studies involving the organ being offered at time of transplantation. Finally, it is important to resolve other questions going forward, e.g. is it permissible (and ethical) for a wait-listed transplant candidate to accept an organ from a study donor and then decide not to participate in research designed to evaluate the benefits and adverse outcomes associated with that organ?

This study has limitations that may affect interpretation of the data. One limitation is the potential for response bias, e.g. those who completed the survey had stronger opinions about the topic and they may not represent the larger population of transplant surgeons, OPO professionals, and IRB members. Similarly, our decision to recruit surgeons and IRB members from hospitals with the highest transplant volume may have biased responses toward those with more experience or knowledge of deceased donor research. To optimize participation, we designed a survey that was brief and, consequently, did not capture the full range of donor research being done in the field, nor did we ask all possible questions of ethical, regulatory, and clinical significance. The survey response rate was moderately low, particularly among IRB members, which limits the generalizability of our findings. Finally, future research should solicit the attitudes and opinions of additional stakeholders, including other transplant and OPO professionals, transplant candidates/recipients, donor families, ethicists, and the general public.

In conclusion, our survey findings highlight differing opinions from knowledgeable professionals about how best to define deceased donor intervention research, assess its risks, obtain authorization for it and the subsequent transplantation of associated organs, and provide appropriate oversight. It may be that the traditional IRB structure and processes are not the most optimal oversight mechanism for this type of research. A recently published randomized controlled trial serves as an exemplar for scientific discovery through deceased donor research that is performed in a manner consistent with ethical and regulatory standards (25) A review of its supplementary appendices also amplifies how daunting the challenges can be in conducting deceased donor intervention research. To that end, the Health Resources and Services Administration formed a collaborative group to consider the barriers to performing donor intervention research. The committee has been charged with making recommendations that would best balance the need for (1) a more efficient review process with scientific expertise, consistency, and equity; (2) facilitating the deceased's donation intentions; (3) protecting the interests of transplant candidates and recipients; and (4) preserving public trust in deceased donation and transplantation. Our study findings amplify the need for this committee to recommend strategies that simultaneously remove barriers to deceased donor intervention research and accelerate the pace of scientific discovery to facilitate more transplants.

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References

1. Israni AK, Zaun DA, Rosendale JD, Snyder JJ, Kasiske BL. OPTN/SRTR 2013 Annual Data Report: Deceased organ donation. Am J Transplant 2015; 15 Suppl 2: 1–13.
2. Melcher ML, Blosser C, Baxter-Lowe LA, et al. Dynamic challenges inhibiting optimal adoption of kidney paired donation: Findings of a consensus conference. Am J Transplant 2013; 13: 851–860.
3. Childress JF, Liverman CT, eds. *Organ donation: Opportunities for action*. Washington, DC: The National Academies Press; 2006.
4. Howard DH, Siminoff LA, McBride V, Lin M. Does quality improvement work? Evaluation of the Organ Donation Breakthrough Collaborative. Health Serv Res 2007; 42: 2160–2173.
5. Saidi RF, Elias N, Kawai T, et al. Outcome of kidney transplantation using expanded criteria donors and donation after cardiac death kidneys: Realities and costs. Am J Transplant 2007; 7: 2769–2774.
6. Kotsch K, Ulrich F, Reutzel-Selke A, et al. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: A prospective randomized controlled trial. Ann Surg 2008; 248: 1042–1050.
7. Schnuelle P, Gottmann U, Hoeger S, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: A randomized controlled trial. JAMA 2009; 302: 1067–1075.
8. Al-Khafaji A, Elder M, Lebovitz DJ, et al. Protocolized fluid therapy in brain-dead donors: The multicenter randomized MOnIToR trial. Intensive Care Med 2015; 41: 418–426.
9. Salim A, Velmahos GC, Brown C, Belzberg H, Demetriades D. Aggressive organ donor management significantly increases the number of organs available for transplantation. J Trauma 2005; 58: 991–994.
10. Dikdan GS, Mora-Esteves C, Koneru B. Review of randomized clinical trials of donor management and organ preservation in deceased donors: Opportunities and issues. Transplantation 2012; 94: 425–441.
11. DuBose J, Salim A. Aggressive organ donor management protocol. J Intensive Care Med 2008; 23: 367–375.
12. Rosendale JD, Kauffman HM, McBride MA, et al. Aggressive pharmacologic donor management results in more transplanted organs. Transplantation 2003; 75: 482–487.
13. Feng S. Donor intervention and organ preservation: Where is the science and what are the obstacles? Am J Transplant 2010; 10: 1155–1162.
14. Abt PL, Marsh CL, Dunn TB, et al. Challenges to research and innovation to optimize deceased donor organ quality and quantity. Am J Transplant 2013; 13: 1400–1444.
15. Glazier AK, Heffernan K, Rodrigue JR. A framework for conducting deceased donor research in the U.S. Transplantation. In press.
16. Rey MM, Ware LB, Matthay MA, et al. Informed consent in research to improve the number and quality of deceased donor organs. Crit Care Med 2011; 39: 280–283.
17. Department of Health and Human Services, Public Welfare, Part 46. Code of Federal Regulations, Title 45, Protection of Human Subjects. [cited 2015 May 19]. Available from: http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf
18. Abbott L, Grady C. A systematic review of the empirical literature evaluating IRBs: What we know and what we still need to learn. J Empir Res Hum Res Ethics 2011; 6: 3–19.
19. Department of Health and Human Services, Office of the Secretary, Parts 160 and 164. Code of Federal Regulations, Title 45, Standards for Privacy of Individually Identifiable Health Information. [cited 2015 April 16]. Available from: http://www.hhs.gov/ocr/privacy/hipaa/administrative/privacyrule/prdecember2000all8parts.pdf
20. National Conference of Commissioners on Uniform State Laws Revised Uniform Anatomical Gift Act, 2006. [cited 2015 March 23]. Available from: http://www.uniformlaws.org/shared/docs/anatomical_gift/uaga_final_aug09.pdf
21. Glazier AK. The principles of gift law and the regulation of organ donation. Transpl Int 2011; 24: 368–372.
22. Slovic P. Perception of risk. Science 1987; 236: 280–285.
23. Pritchard IA. How do IRB members make decisions? A review and research agenda. J Empir Res Hum Res Ethics 2011; 6: 31–46.
24. Rid A, Emanuel EJ, Wendler D. Evaluating the risks of clinical research. JAMA 2010; 304: 1472–1479.
25. Niemann CU, Feiner J, Swain S, et al. Therapeutic hypothermia in deceased organ donors and kidney-graft function. N Engl J Med 2015; 373: 405–414.