A Framework for Conducting Deceased Donor Research in the United States

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Abstract: There are a number of regulatory barriers both perceived and real that have hampered widespread clinical research in the field of donation and transplantation. This article sets forth a framework clarifying the existing legal requirements and their application to the conduct of research on deceased donors and donor organs within the United States. Recommendations are focused on resolving some of the ambiguity surrounding deceased donor authorization for research, Health Insurance Portability and Accountability Act requirements and the role of institutional review board oversight. The successful conduct of clinical research in the field of donation and transplantation requires an understanding of these regulatory nuances as well as identification of important ethical principles to consider. Facilitation of these concepts will ultimately provide support for innovative research designed to increase the availability of organs for transplantation. Further work identifying the optimal infrastructure for overview of clinical research in the field should be given priority.

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The need for innovation to the field of transplantation has brought focus to the legal and ethical considerations of research involving deceased organ and tissue donors.[1] Professional confusion over how to apply well-understood principles for living human research subjects in the context of deceased donation has led to inconsistent practices and has been cited as a barrier to conducting clinical research.[2] This has been particularly complicated within the United States given the legal and regulatory landscape. In response, U.S. leaders of the organ donation and transplantation communities have convened a multidisciplinary task group to clarify and establish consensus on the appropriate involvement of deceased donors in clinical research. The group also identified the need for centralized review and oversight of large scale, multi-institutional donor intervention trials given the complexities that come with conducting clinical research in the context of organ allocation.[3] As a result of this work, the conduct of research on deceased donors and donor organs has been mapped to existing U.S. legal and regulatory frameworks. The analysis resolves some of the questions regarding what constitutes legally appropriate and ethical authorization to involve deceased donors in research, the application of privacy laws and the oversight and review of deceased donor research. For purposes of this analysis, only donors that have been declared deceased based on brain death criteria are considered. The potential to conduct donor intervention research before death declaration on donors after circulatory determination of death has been excluded to focus the issues on research involving decedents and organs from the decedents. Also, although we recognize the relevance of these issues to other regions of the world, we focus exclusively on the United States because other countries may have legal, ethical, and regulatory frameworks that are quite different.

GENERAL REGULATORY FRAMEWORK FOR DECEASED DONOR CLINICAL RESEARCH

The conduct of human subjects research within the United States is primarily governed by the Federal Policy for the Protection of Human Subjects. Published in 1991, the Federal Policy has been codified in separate regulations by 15 departments and agencies, including the Department of Health and Human Services (HHS). The HHS regulations, referred to herein as "the Common Rule," apply to any institution that is engaged in HHS funded or supported human subjects research.[4] The Common Rule also applies to institutions conducting privately or commercially funded human subjects research if they have voluntarily elected to apply the regulations to all research regardless of funding through the terms of their Federalwide Assurance with the federal government.[4] The

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Food and Drug Administration (FDA) has a similar but not identical set of regulations for research investigating the safety and efficacy of products under the FDA's jurisdiction (drugs, devices, or biologics) before such products are approved to the market.[5]

The Common Rule defines human subjects research as collecting data by interacting or intervening with, or collecting individually identifiable information about, living human subjects in a systematic way with the purpose of obtaining generalizable knowledge. The FDA regulations focus more specifically on "clinical investigations" of regulated products in human beings (and sometimes, with respect to investigational devices, in human tissue). Research that triggers the Common Rule or FDA requirements must be approved by an institutional review board (IRB) constituted in accordance with the regulations, and each participant must provide informed consent that includes specific elements (unless an IRB waives them under limited circumstances). However, "human subject" is specifically defined under the Common Rule as "a living individual."[4] The FDA regulations also imply that human subjects are living individuals (whether enrolled as a healthy control or due to a specific disease profile).[5] Therefore, in the context of donation and transplantation, the human subject protection regulations clearly do not apply to deceased donors or donated organs.

Accordingly, in the United States, IRBs have no legally mandated regulatory purview over deceased donors or donor organs (there are no "human subjects" to protect) nor do the Common Rule and FDA informed consent protections make sense in the deceased donor context. The goal of the informed consent process under the human subject protection regulations is to ensure that the subject, or an appropriate legally authorized representative, understands the potential risks of participating, the alternative treatment options to participation, and any possible benefits before agreeing to participate in the research. These protections are particularly important in human subjects research because the goal of the research activity is generalizable knowledge to benefit advancement of medical science achieved through a standardized protocol rather than individualized treatment to benefit a specific patient. In contrast, there are no physical risks or benefits to the deceased donor from research involving the decedents' remains. Participating in the research cannot "harm" the deceased donor as it can in the living human subject, with the exception of privacy considerations that are managed under a distinct regulatory framework in the United States. Instead, the potential harm that could result from research on the deceased donor or the decedent's organs, if any, may be to the potential transplant recipient. Although this is a serious concern, it is effectively managed by the review, approval, and consent process on the recipient side and does not implicate the deceased donor directly. One could consider the potential harm of research to the deceased donor as possible interference with the donor's intent to gift an organ for transplantation. As discussed below, this can be addressed by ensuring appropriate authorization for the gift to be used both for transplantation and research purposes. The concept of potential harms to donation or the public trust (rather than to the donor) is also an important ethical concern but warrants different types of protections that the direct individual harms that are typically evaluated when considering human subjects research.

DONOR AUTHORIZATION FOR RESEARCH: WHAT TYPE OF LEGAL PERMISSION IS REQUIRED TO CONDUCT RESEARCH ON A DECEASED DONOR OR DONOR ORGAN THAT IS INTENDED FOR TRANSPLANTATION?

Clinical Research Protocols that Include Donor Management or Ex Vivo Interventions on Donor Organs Constitute "Research"

The widely accepted definition of "research," particularly within US regulatory frameworks governing human subjects research and the privacy of health information, is a systematic investigation designed to develop or contribute to generalizable knowledge. Clinical research protocols implementing donor management techniques or ex vivo organ interventions therefore likely constitute "research." This is because the protocols are designed to allow for systematic investigation for the purpose of contributing to generalizable knowledge in the field of transplantation. The results are intended for publication and widespread dissemination. The fact that the organs may also be intended for transplantation does not alter this analysis; there is a dual purpose of research in addition to the purpose of transplantation. This is similar to "therapeutic" clinical trials in which interventions are conducted on patients where there may be a simultaneous treatment and research purpose at play. However, in the context of deceased organ donor research, the ultimate "treatment" recipient is distinct from the deceased organ donor on whom, or organ on which, the research intervention is trained. Furthermore, the decedent, under the law, is not considered a "human subject" enrolled in the research.

The laws that govern deceased donation, for example, the Uniform Anatomical Gift Act (UAGA) in the United States, infrequently define "research" use of an anatomical gift. Given the prevailing definition of research, an intervention on the deceased donor's body during management or on an organ ex vivo pursuant to a research protocol with the goal of disseminating the results will most likely be considered a "research" use of the anatomical gift under the laws that govern deceased donation. This is the case even though the primary aim of the recovery is to transplant suitable organs. The legal question is what type of authorization is required for an anatomical gift to be used for the dual and concurrent purposes of transplantation and research.

Use of an Anatomical Gift for a Research Purpose Is Governed by the UAGA

The UAGA—a state statutory law—governs the consent process for use of deceased donor organs in the United States[6] The UAGA permits all or part of the human body to be gifted for 3 specific purposes: transplantation (or therapy), research, and education.[6] Any research on the deceased donor's body or donated organs or tissues that will be conducted postmortem falls under the UAGA and authorization for such use must comply with the UAGA.

Under the UAGA, an adult can make a legally recognized gift of organs to be donated at death and used for any of the 3 permitted purposes.[6] No further authorization is required from family (nor can next of kin override the gift at the time of the donor's death).[6] In the absence of an individual having made his or her own decision before death, next of kin, after a statutorily imposed priority order, can authorize

donation (for transplant, research or education) at the time of the donor's death.[6]

Authorizing organ donation under the UAGA for research does not follow informed consent principles nor does it include the specific informed consent elements required under FDA and HHS regulations applicable to human subjects research.[7] Instead, the UAGA follows a gift law framework. This significant legal distinction is supported by the fact that as compared to the living human subject, the deceased donor does not experience risks or benefits to participating in research. Under the UAGA, an anatomical gift can be made in manner that authorizes use of donated organs and tissues for any permitted purposes or it can be specific (eg, just transplantation). Whether "research use" is authorized will therefore depend on how the gift was made. An anatomical gift may specifically authorize a particular purpose like transplantation and research or not specify a purpose at all. Most donor registries, such as those run through the Registry of Motor Vehicles, provide an opportunity for individuals to make a general donor designation, but do not specify a purpose.

The UAGA of each state delineates how an anatomical gift may be used if the document authorizing the gift does not specify a purpose. The UAGA generally provides that in such instances the gifted organs and tissues may be used for transplantation as the priority.[6] However, there are some states that also allow for the research use of organs and tissues when the document of gift does not specify a purpose. In conducting research on deceased donors or donor organs and tissues, it is important to review the applicable state UAGA law to determine whether general donor registration includes authorization for research use on the gifted organs and tissues.[8] If the donor registry in a particular state does not include authorization for research (or the potential donor is not registered), authorization for research use of gifted organs and tissues can be obtained from the appropriate surrogate. Specific research protocols need not be delineated—general authorization for research is sufficient to meet the legal requirements of the UAGA. Most organ procurement organizations (OPOs) document this as a simple research check box on the donation authorization form.

As identified above, in donor management and ex vivo organ clinical protocols, there is a dual and concurrent purpose of both transplantation and research. Although this is a grey area in the law, both purposes (transplantation and research) should be authorized to comply with the UAGA and ensure that the gift is used consistent with the donor's intent. This is also consistent with the ethical directive to maintain the public's trust in the donation system and provide appropriate transparency as to how donated organs are used. As a matter of practice this can be achieved by confirming that a donor's authorization in a registry or an authorization form signed by an appropriate surrogate includes research use of gifted organs and tissues.

It is important to recognize the donor's right under the UAGA to direct how the anatomical gift can be used. An organ specifically gifted only for transplantation purposes cannot be used for research without violating the UAGA (which includes criminal penalties for certain intentional violations).[6] The OPO and the transplant team, as custodians of the gift are responsible for ensuring that the organs are used only for the purposes authorized. There is also a responsibility to ensure that the recovery of any additional tissues (like spleen or blood) that are required solely for research purposes are authorized by the donor or donor's surrogate. The UAGA requires permission for "what" is recovered (specific organs, tissues or specimens of any kind) as well as permission for the "why" (transplant, research, education).

Use of Identifiable Donor Data for Research Purposes Must be Consistent With Privacy Laws

Although the human subject protection regulations do not apply directly to the decedent or organ involved in deceased donor research, privacy laws such as the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996 and its implementing regulations may be cited as an obstacle to deceased donor research because of additional authorization requirements for the use of a decedent's health information in research. However, HIPAA does not provide a meaningful obstacle to deceased donor research.

The HIPAA applies to "Covered Entities" (health care providers, health plans, and health care clearinghouses) and their uses and disclosures of protected health information (PHI).[9] The PHI includes individually identifiable information related to the past, present, or future treatment of an individual. Although OPOs generally do not qualify as Covered Entities (and are therefore not directly subject to HIPAA's requirements), the hospitals at which donated organs and tissues are surgically recovered, and also where they are transplanted, are covered by HIPAA.

In general, absent a specific exception or individual authorization, HIPAA prohibits the use and disclosure of an individual's PHI while living and for 50 years after the individual's death.[9] For decedents, authorization can be given by the individual legally authorized to act on behalf of the estate.[9] The HIPAA expressly permits the use and disclosure of PHI for clinical donation and transplantation purposes without authorization.[10] For research uses, HIPAA requires authorization by an individual or a decedent's legally authorized representative unless one of several research-related exceptions is met. There is an exception under HIPAA for research on decedents' information that is likely to apply in the deceased donor research context. If the researcher can meet the following criteria, the Covered Entity may use or disclose a decedent's PHI for research purposes without authorization: (i) use or disclosure is sought solely for research on PHI of decedents; (ii) the individuals at issue have died; and (iii) the PHI is necessary for the research purposes.[11] Another possible option would be for an IRB or privacy board to grant a waiver of authorization or alteration of the consent process for purposes of the research. Waivers are permissible where (i) the research presents no more than minimal risk to the privacy of individuals, based on certain regulatory criteria; (ii) the research could not practicably be conducted without the waiver or alteration; and (iii) the research could not practicably be conducted without access to and use of the PHI.[11] An IRB can serve this function even if the underlying research does not qualify as human subjects research and would not otherwise be before the IRB. Other research-related exceptions available under HIPAA may also be relevant depending on the specific circumstances of a given protocol.

Proposed Approach to Deceased Donor Permission for Research

- Clinical research protocols involving interventions on the deceased donor from whom organs will be recovered for

transplantation or directly on the donor organs themselves before transplantation constitute both a research and transplantation use of the gifted materials. Accordingly, use of donated organs and tissues for both purposes should be authorized consistent with the applicable state UAGA law.
- Authorization for an anatomical gift to be used for a research purpose can be obtained through a surrogate or confirmed through first-person authorization. Specific state UAGA laws should be consulted to determine if donor registration includes authorization for research use.
- Deceased donors on whom, and donor organs on which, research interventions are conducted are not "human subjects" under U.S. human subject protection laws; therefore, informed consent of the kind normally required for human subjects research participation is not required.
- As an important component of public trust and transparency, donor families should be informed about the conduct of any research measures planned in connection with organ recovery, including postmortem donor management interventions or ex vivo interventions.
- Use of identifiable donor data requires a basis under applicable privacy laws; in the United States, an applicable regulatory exception under HIPAA or authorization by the decedent's legally authorized representative that meets HIPAA's requirements will be necessary.

REVIEW AND APPROVAL OF DONOR INTERVENTION RESEARCH: SHOULD DONOR INTERVENTION RESEARCH BE REVIEWED AND APPROVED BY THE OPO?

There is no specific legal requirement that OPOs review and approve research, and although it is being considered, it is currently not an accreditation standard. Because the OPO is responsible for confirming or obtaining donor authorization, communicating with donor families, managing deceased donors and recovering organs, it is a common practice for OPOs to review and approve research that involves donor or donor organ interventions.

Although it is simple for OPOs to review local protocols, larger-scale multicenter clinical trials that involve donor or donor organ interventions, particularly those that straddle the transplantation, would more effectively be reviewed at a regional or national level. This would provide a more consistent level of evaluation and appropriate consideration of the potential issues, as well as identification of potential efficiency for certain systemic and logistical challenges.

The steering principles for reviewing and approving deceased donor research should be focused on ensuring the research has scientific merit, protections are in place to reduce the likelihood that transplantation could be compromised and that donor authorization and privacy considerations have been adequately addressed. Additional review of the research guided by ethical considerations of potential impact on organ allocation and utilization, public trust, and transparency should be evaluated.[2]

Proposed Approach to OPO Review and Approval of Deceased Donor Research

- OPOs should have written research policies that ensure donor and donor organ interventions are consistently reviewed and approved. The following elements should be in a research policy:

  ○ Transplantation as priority
  ○ Process for review including application and evaluation
    ▪ the probable benefits of the research to transplant stakeholders
    ▪ the importance of the knowledge that may reasonably be expected to result from the research
    ▪ the potential impact from the research on public trust and transparency in the donation system
    ▪ whether interventions will occur at or outside of the donor hospital
    ▪ the adequacy of privacy protections under applicable regulations

  • Requirement of authorization for research use (either by the donor or a surrogate)
  • Requirement of IRB approval from transplant researcher's affiliated institution if applicable (ie, if the recipient is determined to be a "human subject"). This should include considerations of the following:

    ▪ risks of the research on wait-listed transplant candidates
    ▪ risks of the research on transplant recipients receiving study organs
    ▪ risks of the research on organ allocation systems and policies
    ▪ provisions for safety monitoring

  • Reimbursement to the OPO for research-related costs

- Large-scale multicenter trials that involve transplantation after donor or donor organ interventions should be reviewed at the national or regional level. This type of approval could then be relied upon at a local OPO level. This would create significant efficiencies and ensure a more consistent level of review.

DONOR HOSPITAL APPROVAL: IS INDIVIDUAL DONOR HOSPITAL IRB REVIEW AND APPROVAL REQUIRED TO PERFORM DECEASED DONOR RESEARCH?

The requirement of IRB review and approval is triggered by the conduct of research on living human subjects. Therefore, IRB review and approval is not required for research that is limited to deceased donors or donated organs and tissues because, as noted above, there is no living human subject. The IRBs are generally not familiar with reviewing research involving the donation of organs and tissue from decedents given that their regulatory mandate is to assess the risk benefit ratio to potential human subjects of proposed research. Further, the human subject informed consent forms IRBs routinely review and approve cannot be used in the deceased donation context as their content is largely irrelevant. As discussed, there are no physical risks or benefits to a deceased donor comparable to the risks and benefits IRBs evaluate in the living human subject context.

It is nonetheless important for transparency and public trust that research on deceased donors and donor organs and tissues is properly reviewed and approved. This could occur at a local OPO, regional or national level. Because donor research interventions may physically occur at the donor hospital, it is important that the donor hospital is aware of the planned research and has confidence that it has been properly vetted. Moreover, some hospitals may have policies that govern research on the newly deceased or other discarded tissue and for which IRB review of some sort (for example, administrative review by the Chair or other designee) is required by policy even if not required by law. Hospitals are

appropriately concerned about research occurring on their premises. This is an important issue for the donation and transplantation community to properly address to successfully remove existing barriers to conducting wide-scale clinical research trials involving donor or donor organ interventions.

Proposed Approach to Donor Hospital Review/Approval

- Donor hospital IRB review is not required for interventional research that is limited to deceased donors or donor organs. However, donor hospitals should be informed in advance of planned clinical research protocols that involve interventions on the deceased donor or on the donor organ that will take place on-site at the donor hospital.
- This communication could be either to the Hospital IRB or appropriate clinical leadership and should include a summary description of the research, the review, and approval process it went through (local, regional, or national level) as well as confirmation that donor authorization for research will be obtained.

RECIPIENT CONSIDERATIONS

Additional complexities arise when a transplant recipient will receive an organ through a deceased donor research protocol. Is the recipient of such organs always a human subject in those circumstances, whether or not specimens, outcomes or other data are collected for research purposes? This depends on whether receiving an organ that has been part of a research protocol confers "human subject" status on the recipient absent other interaction or intervention with the recipient for research purposes. Does a transplantation endpoint require transplant center IRB review? And if so, does that automatically bring the deceased donor portion of the research under the IRB's purview? How can the timing and other logistics inherent to the organ allocation process allow for appropriate IRB oversight and informed consent from recipients, if required? How can the potential for coercion of the recipient to participate in the research be minimized given that their organ offer may be conditioned on agreeing to participate in the study? If the applicable regulations do not require IRB review on the recipient side, what ethical and safety review would nonetheless be appropriate? Should the degree of monitoring and oversight be tiered based on risk and, if so, how should the risks of deceased donor research be categorized? Do nontargeted organs in a deceased donor intervention protocol raise the same questions and concerns in multiorgan recoveries? A considered response to these questions is beyond the scope of this article but will be integral to establishing a comprehensive approach to multi-center trials where transplantation of impacted organs is anticipated.

CONCLUSIONS

There are a number of regulatory barriers both perceived and real that have hampered widespread clinical research in the field of donation and transplantation. Clarification of existing legal requirements within the United States and their application to the conduct of research on deceased donors

TABLE 1.

Requirements or recommendations for deceased donor research oversight and permission

	Type of oversight or permission required/recommended				
Type of Research	IRB Approval	OPO or Donor Review Board Approval	Research Informed Consent	UAGA Authorization (For Gift to be Used for Research Purpose)	HIPAA Authorization (For the Use of PHI)
Human subjects research (outside of organ donation context)	Required (unless regulatory exemption applies)	Not applicable	Required (unless waived)	Not applicable	Required if PHI will be used (unless waived or regulatory exception applies)
Deceased Donor Management Interventional Research	Not required or recommended	Recommended	Donor Not required or recommended	Donor Required Recipient Not required or recommended	Donor Required if PHI will be used (research authorization exception likely applies)
Deceased Donor Ex Vivo Organ Interventional Research	Not required or recommended	Recommended	Donor Not required or recommended	Donor Required Recipient Not required or recommended	Donor Required if PHI will be used (research authorization exception likely applies)
Transplantation of Research Organ in Recipient (intervention or data/specimen collection for research after transplantation)	Required	Recommended	Donor Not required or recommended Recipient Required	Donor Required for research and transplantation purposes Recipient Not required or recommended	Recipient Required if PHI will be used (research authorization exception likely applies)

and donor organs and tissues resolves some of the ambiguity surrounding deceased donor authorization for research, HIPAA requirements and the role of IRB oversight. (Table 1) The successful conduct of clinical research in the field of donation and transplantation requires an understanding of these regulatory nuances as well as identification of important ethical principles to consider. Facilitation of these concepts within an established framework will ultimately provide support for innovative research designed to increase the availability of organs for transplantation. Further work identifying the optimal infrastructure for centralized overview of clinical research in the field should be given priority.

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8. Only 14 states specifically permit research use of gifted organs and tissues when authorized through a general intent registry. See CA—West's Ann. Cal.Health & Safety Code §7150.50; CT—C.G.S.A. §19a-289j; IL—755 ILCS 50/5-12; IN—IC 29-2-16.1-10; ME—22M.R.S.A. § 2951; MA—M. G.L.A. 113A § 11; MI—M.C.L.A. 333.10111; NV—N.R.S. 451.571; NH—N.H. Rev. State. § 291-A:11; OK- 63 Okl.St.Ann. § 2200.11; RI—Gen.Laws 1956, § 23–18.6.1-11; VT—18V.S.A. § 5250 k; VA—VA Code Ann. § 32.1-291.11; WV—W. Va. Code, § 16-19-11. Four state UAGAs are silent on the issue. See DE 16 Del.C. § 2712; FL—West's F.S.A. 765.514(2); NY McKinney's Public Health Law 4302; PA 20 Pa.C.S.A. 8612. The remaining 34 states limit the use to transplantation or therapy consistent with the 2006 model UAGA.
9. 45 CFR Parts 160, 162, and 164.
10. 45 CFR 164.512(h).
11. 45 CFR 164.514(e).