Published in final edited form as:
Crit Care Med. 2011 February ; 39(2): 280–283. doi:10.1097/CCM.0b013e3181feeb04.

Informed Consent in Research to Improve the Number and Quality of Deceased-Donor Organs

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Abstract

Improving the management of potential organ donors in the ICU could meet an important public health goal by increasing the number and quality of transplantable organs. However, randomized clinical trials (RCTs) are needed to quantify the extent to which specific interventions might enhance organ recovery and outcomes among transplant recipients. Among several barriers to conducting such studies are the absence of guidelines for obtaining informed consent for such studies, and the fact that deceased organ donors are not covered by extant federal regulations governing oversight of research with human subjects. This paper explores the underexamined ethical issues that arise in the context of donor management studies, and provides ethical guidelines and suggested regulatory oversight mechanisms to enable such studies to be conducted ethically. We conclude that both the respect that is traditionally accorded to the prior wishes of the dead and the possibility of post-mortem harm support a role for surrogate consent of donors in such RCTs. Furthermore, although recipients will often be considered human subjects under federal regulations, several ethical arguments support waiving requirements for recipient consent in donor management RCTs. Finally, we suggest that new regulatory mechanisms, perhaps linked to existing regional and national organ donation and transplantation infrastructures, must be established to protect patients in donor management studies while limiting unnecessary barriers to the conduct of this important research.

Keywords

informed consent; organ donation; transplantation; research ethics

The persistent gap between the supply of and demand for transplantable organs has engendered growing interest in maximizing the quantity and quality of organs recovered

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Dr. Rey was employed by the Summer Fellowship Center for Bioethics at the University of Pennsylvania. All other authors have no potential conflicts of interest to disclose.

from deceased donors. In addition to initiatives aimed at increasing organ donation consent rates,(1) recent efforts have focused on improving the clinical management of consented donors to maximize organ viability. Early observational studies have suggested the utility of donor management strategies in increasing the recovery of transplantable organs.(2-8) However, randomized clinical trials (RCTs) are needed to quantify the extent to which specific interventions might enhance organ recovery and recipient outcomes.

Such RCTs of donor management interventions raise unique ethical and regulatory challenges.(9) Although guidelines have been proposed for interventional research on the dying(10,11) and non-interventional research on the recently dead,(12,13) the requirements for informed consent from potential donors, recipients, or both remain uncertain in the specific context of deceased donor management research. In this essay, we explore when, how, and from whom consent should be sought for research on brain-dead potential donors after neurological determination of death (DNDD), also known as brain-dead donors. We furnish our ethical arguments with lessons learned in the Beta-agonists for Oxygenation in Lung Donors (BOLD) study (NCT00310401), a placebo-controlled trial led by two of us (L.B.W. and M.A.M.) testing the effect of nebulized albuterol on oxygenation, donor lung utilization and transplant outcomes. Although we use US research regulations to guide our discussion, the underlying principles are consonant with those articulated in the international Declaration of Helsinki.(14)

Consent of the Potential Donor

Because potential DNDD have been declared dead, they are not considered human subjects under existing federal regulations.(15) Thus, it is uncertain whether consent is – or ought to be – required from donors under the existing regulatory framework. Indeed, this lack of clarity may explain why consent practices have varied. Among donor management RCTs published to date, three groups obtained surrogate consent prior to enrolling the decedent(16-18) and two others either did not obtain separate research consent or did not report a consent process.(19,20) The lack of uniform standards also created confusion in the BOLD study. A reviewer of the original grant application expressed concern that the protocol specified no plans for donor consent; non-consented donor enrollment proceeded after independent ethicists and IRB directors determined that consent was not required. The organ procurement organization (OPO) expressed similar concerns, however, and after several months of enrollment the protocol was modified to require donor consent.

The Function of Consent from the Dead

Informed consent is intended to promote individuals' autonomy and dignity and to protect them from exposure to potential risks or harms without warning.(21,22) It might, therefore, seem counterintuitive to speak of consent for the deceased as it is unclear that dead bodies possess such interests.(23) However, in a pluralistic society, not all will agree that death is equivalent to non-existence; separating the person from the body may not accord with many conceptualizations of personhood.(24) Indeed, society regularly displays respect for the autonomy of the deceased. We require consent for organ donation and enable decedents to determine (through wills) what will become of their bodies and estates. There may be reasons, then, to respect the interests of the person that existed ante-mortem and to extend respect for these interests post-mortem.(25,26) Nevertheless, the autonomy granted to the deceased is often of a diminished variety: bequests can be challenged and altered in the courts, and surrogates are often empowered to make choices regarding donation, even for decedents who had indicated such preferences pre-mortem.(27) Thus, both normative arguments and prevailing social standards provide bases for according some respect to the autonomy of the dead.

A second challenge to an informed consent requirement is that there is little potential for harm after death, and thus little need for the protections of informed consent. Such reasoning has been used to argue that consent is unnecessary prior to practicing procedures on or procuring transplantable organs from the recently dead.(28,29) A contrasting view is that postmortem harm is possible in the form of damage to reputation or loss of privacy.(26) The sheer extent of the debate regarding posthumous harm precludes an unambiguous declaration that the potential for harm ceases at death.(23,25,26,28) A perhaps more broadly acceptable and complementary argument is that if living persons face uncertainty that their wishes will be followed after death, distress and harm may result pre-mortem. Thus, both respect for the autonomy of the dead as well as the possibility of harm suggest that informed consent from DNDD is warranted.

The Role of Surrogate Consent

Because few patients will have indicated pre-mortem their preferences for donor management research participation, a requirement for informed consent will often amount to a requirement for surrogate consent. This is consistent with the broad decisional authority given to surrogates to execute the presumed wishes of the deceased.(24) If the decedent's preferences are known, corresponding consent standards for organ donation should be followed: family assent would be encouraged but not required for decedents who had indicated preferences for research participation, and surrogates would not be authorized to consent if the decedent had clearly refused.(30)

The Form of Donor Consent for Research

Donor consent might (a) assume that consent to donate organs includes consent for donor management research, (b) entail a separate, general research consent to cover all research on the dead, or (c) require a specific consent for donor management research. Some might view consent to organ donation as encompassing consent for participation in donor management research because, unlike other forms of research on the dead, such studies intend to promote successful donation itself. Others may believe that the need for research consent is unnecessary in the common cases in which the intervention being tested entails few specific risks and is routinely used in clinical care (e.g., albuterol in the BOLD study). However, because donor management studies, even of interventions in common clinical use, aim to produce generalizable knowledge rather than to secure organs for individuals, some form of research consent is required.(31)

The normative goals of obtaining research consent for donor management research might be satisfied by including it within the general research consent form suggested by the Uniform Anatomical Gift Act (UAGA).(30) For example, it might be incorporated into the generic process by which OPOs disclose risks and obtain permission for a broad and unspecified range of basic research on tissues from the deceased. However, because many individuals view research and organ donation as mutually exclusive,(32) desires to donate organs might hinder enrollment in research unless it is clearly presented as having the goal of enhancing donation opportunities. As such, separate and specific consent for donor management research may promote autonomous choice. Thus, the relative merits of either a specific consent for such research or its clear inclusion as one component within a more general research consent should be considered by investigators and regulatory agencies in the contexts of each particular study.

Consent of the Potential Recipient

Standards are similarly lacking regarding consent from the recipients of organs recovered from donors enrolled in research studies. Despite the concerns of some reviewers, the BOLD

study has not required recipient consent, in part due to a lack of precedent for this process. Indeed, among published donor management RCTs, we could identify only two that explicitly addressed recipient consent. In one, prospective recipient consent was obtained.(20) In the second, consent was deemed unnecessary.(16) The open question of whether to require recipient consent in donor management studies rests first on whether recipients are considered research subjects, and if so, whether compelling reasons exist to waive general requirements for such subjects' consent.

Recipients as Research Subjects

In order to be considered a human subject, investigators must obtain either identifiable private information or data through an interaction with the participant.(15) Although it might be argued that direct intervention occurs only in donors, recipients are also affected by manipulations of donor care. For example, in the typical two-armed RCT, recipients may obtain organs subjected to the donor interventions or organs from control donor. In this way, they are no less “human research subjects” than are recipients of blood products, bioprosthetic devices, or pharmaceuticals that have been randomly assigned to one or another preparative intervention. Analogously, in a recent study comparing transfusion of leukoreduced and non-leukoreduced red blood cell units, transfusion recipients were considered human research subjects, and an emergency exception to informed consent was granted.(33)

Nevertheless, if no data were collected on recipients they still might not be considered human research subjects under current regulations. For example, if outcomes of such studies were limited to metrics such as the number of organs recovered or results of recovered organ biopsies, then recipients would not be research participants because there is no recipient data collected. Recipient consent would be unnecessary. However, in more definitive studies designed to observe both donor- and recipient-related outcomes (e.g., graft function or patient survival), recipients would be classified necessarily as research subjects. Further, from a normative standpoint, for the recipient, there is little difference between the two scenarios; in both cases, recipients are exposed to similar risks and could receive similar organs. Thus requirements for research consent should apply equally to all recipients of organs regardless of investigators' decisions to collect recipient data.

Is Recipient Consent Necessary?

Even when recipients are human research subjects, requirements for recipient consent might still be waived. From a regulatory perspective, there are two exceptions to the requirement for prospective consent – the emergency research consent waiver and the minimal risk research waiver. The emergency waiver was designed for research on potential life-saving interventions in emergent situations where there is no time to obtain consent.(34) Donor management studies may qualify under this exception in part. Given that the specific study in which a recipient will participate will not be known until an becomes organ available, there will rarely be time to obtain truly informed recipient consent regarding a specific organ prior to its placement.(35) There would, however, be time to obtain recipient consent for the collection of longer-term outcomes data following transplant. Alternatively, if risks are minimal, then consent requirements may be waived if an IRB determines that (a) waiving consent does not infringe on the rights of participants, (b) the research could not practicably be conducted without a waiver, and (c) when possible, subjects are informed about the ongoing or completed study.(15)

Because interventions on donors, such as albuterol use in the BOLD study, will rarely pose unique risks to recipients, such research will often meet regulatory criteria for minimal risk.(15,36) Indeed, many donors would have received albuterol within days of donation as part

of routine ICU care. If potentially higher-risk interventions were studied, such as the administration of human growth factors, then consent processes similar to those advocated for potential recipients of nonstandard organs may be warranted.(35) In such circumstances, ethical standards of disclosure of foreseeable risks would be required whether such risks arose in research or in clinical settings.

Beyond these regulatory concerns, requiring recipient consent raises ethical concerns. Because an entire donor service area is likely to be engaged in ongoing research studies, refusal of participation would effectively preclude patients' access to life-saving organs. For example, in the BOLD study, all donor hospitals affiliated with the California Transplant Donor Network were asked to participate in the study. If recipient consent had been sought, patients listed for lung transplantation in this region could not have declined research participation and yet remained eligible for a timely transplantation. This undue influence cannot be reconciled with the intent of consent to promote autonomy.

In the rare cases in which recipients may be identified before the donor intervention under study is implemented, it would be possible to seek the recipient's consent prior to enrolling the identified donor in the study. However, the moral bases for granting recipients authority over management of donors is questionable, and in any event would introduce biases into the research, thereby undermining the study's scientific validity and ethics.(37)

Recipients might consent prior to the collection of outcome data, as has been proposed in emergency research and as was conducted in the aforementioned transfusion study.(33,38) However, the protections afforded by such consent would be limited to assurances of data privacy, which recipients are accorded anyway through standard collection of their de-identified data by the Organ Procurement and Transplantation Network (OPTN). In order to inform patients, and to meet the final criterion for a waiver of informed consent, patients could both be informed at the time of listing that donor management studies may be ongoing in their region, and, if they wish notified following transplantation of the specific study of which they were a part.

Regulatory mechanisms

In summary, donor management RCTs may serve an important public health goal by increasing the number and quality of deceased-donor organs. We have argued that in most such studies, there will be a legitimate ethical basis for requiring donor consent and for waiving this requirement for recipients. However, to date, regulatory mechanisms are unavailable to accommodate, let alone facilitate, these ethical arguments. The lack of uniform standards attributable to the exclusion of the deceased under the Common Rule creates the potential for unacceptable variation in practice standards for approving or rejecting donor management studies if adjudicated at the hospital level. Furthermore, individual IRBs may reject such responsibilities in light of the view that donors are deceased and hence not federally protected. Finally, requiring review by each institution's IRB is inefficient in light of the multiple hospitals that will often be required both to serve potential recipients and to generate sufficient donors for constructive research.

Instead, effective oversight mechanisms should be established through agreement among the partners in the organ transplant process, including transplant centers, investigators, community members, OPOs, Regional Review Boards, and OPTN. To maximize the efficiency of review, consistency of oversight, and involvement of local communities, new regulatory structures should be established, not within the existing IRB system, but at the levels of OPOs, Regional Review Boards, and the OPTN itself. Studies would be evaluated for appropriate patient protections at levels of this hierarchy that are appropriate to the scope of the research. Thus, trials within a region managed by a single OPO could be regulated

locally, whereas higher levels of regulation could be sought when research activities cross regional lines or when uncertainties arise at lower levels of review. Such a system would protect research participants from risks without unnecessarily curtailing this critical line of investigation.

Acknowledgments

Mr. Rey was supported by a summer internship from the University of Pennsylvania Center for Bioethics. Drs. Matthay and Ware were supported by NIH grants HL088263, HL087115 and HL081619. Drs. McGuire and Halpern were supported by Greenwall Foundation Faculty Scholar Awards in Bioethics.

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