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Review Article

Examining consent for interventional research in potential deceased organ donors: a narrative review

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Summary

In the last decade, research in transplant medicine has focused on developing interventions in the management of the deceased organ donor to improve the quality and quantity of transplantable organs. Despite the promise of interventional donor research, there remain debates about the ethics of this research, specifically regarding gaining research consent. Here, we examine the concerns and ambiguities around consent for interventional donor research, which incorporate questions about who should consent for interventional donor research and what people are being asked to consent for. We highlight the US and UK policy responses to these concerns and argue that, whereas guidance in this area has done much to clarify these ambiguities, there is little consideration of the nature, practicalities and context around consent in this area, particularly regarding organ donors and their families. We review wider studies of consent in critical care research and social science studies of consent in medical research, to gain a broader view of consent in this area as a relational and contextual process. We contend a lack of consideration has been given to: what it might mean to consent to interventional donor research; how families, patients and health professionals might experience providing and seeking this consent; who is best placed to have these discussions; and the socio-institutional contexts affecting these processes. Further, empirical research is required to establish an ethical and sensitive model for consent in interventional donor research, ensuring the principles enshrined in research ethics are met and public trust in organ donation is maintained.

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Introduction

Since early experiments with renal transplantation in the 1950s, transplant medicine has focused on improving outcomes for organ recipients, in terms of their survival and quality of life. Advances in this area have included developments in immunosuppression, surgical technique and critical care therapy [1]. In recent years, research in transplant medicine has focused on interventions in the management of the deceased organ donor as a means of improving the quality of transplantable organs [2]. This

interventional research, usually carried out in critical care settings, ranged from simple changes to donor management, such as lung protective mechanical ventilation, to administering hormone or cardiovascular treatment measures, such as vasopressin, in order to improve organ usage, graft survival, and, ultimately, produce better outcomes for organ recipients [3–5]. Although advances in this field hold the promise of improving both the quality and quantity of organs for transplant, the processes involved in undertaking

interventional donor research have recently come under scrutiny, particularly regarding the ethics and practicalities involved in gaining consent for these procedures [6]. This scrutiny is only likely to increase, given that the range and complexity of potential future interventions is growing. For example, pre-clinical laboratory research raises the prospect of immunomodulatory and genetic therapies. Furthermore, in controlled donation after circulatory death (DCD), which now accounts for 40% of deceased donation in the UK, interventions may require research which needs to be carried out while the donor is still alive [7].

In this paper, we review the ambiguities in consent for interventional research in deceased organ donors and the policy context to these concerns, including the UK recommendations for gaining consent in donor research. We limit our exploration to deceased organ donation programs, namely donation after brain death (DBD) and DCD. By reviewing literature from studies in critical care, alongside insights provided by the social sciences on consent for medical research, we critically examine the current understanding of consent in the context of interventional donor research, with a focus on the implications for deceased organ donors and their families. In so doing, we highlight shortcomings in this area and argue the need for further insight into the nature and context of consent in this unique area of research.

Ambiguities around consent in interventional donor research

Whereas there is consensus about the need to advance the area of interventional donor research, progress is understood to be hampered by the ethical and legal ambiguities it engenders. These particularly relate to clarifying the issue of consent for this type of research [6, 8].

These matters were brought into sharp focus in 2015 with the publication of a randomised controlled trial into the effects of therapeutic hypothermia in DBD donors in the USA [9]. The study reported that authorisation (consent) for the interventional research was gained on the part of the deceased, either via documentation by the donor on a state registry before their death or authorisation via a surrogate decision-maker (such as next of kin). However, the Institutional Review Board ruled that recipient consent was not required due to their view that the intervention was low risk, in relation to its administration and effect on the donor organs. Following publication of the study, the US consumer group, Public Citizen, challenged the ethical status of the research, particularly with regard to the fact that consent was not taken from recipients who received kidneys from the trial. They called for an investigation into the trial and for

sanctioning of the institutions who failed to protect the human subjects in the research [10].

The study by Niemann et al. and the challenge by a public group regarding the ethics of this type of research only represents the tip of the iceberg in highlighting the ethical ambiguities in relation to interventional donor research. Previous studies in this vein, conducted in contexts such as the US, UK, Germany and Spain have taken different, sometimes conflicting, approaches to consent. Whereas some studies report seeking and documenting specific consent for participation for the research from substitute decision-makers, such as a relative, of the donor [11–16], and/or recipient [16–18], others did not consent, or did not report to consent, anyone who might have been affected by the research [19, 20].

Concerns over the matter of who should consent for interventional donor research have been highlighted in various stakeholder commentaries, mostly in the US, where clinical practice and legal and ethical governance structures are different from the UK. These commentaries emphasise the uniqueness of this type of research, which *“straddles boundaries rarely encountered in traditional clinical trials”* referring to the fact that, whereas the intervention happens in the deceased donor, the study outcomes are usually measured in relation to transplant recipients [6].

Interventional donor research involves multiple stakeholders in relation to consent: both the donor and recipient, but also the family of the deceased [21, 22]. In the case of the latter, commentators have drawn attention to the way in which families may be faced with two difficult related consent decisions – those of donation and of research – at a time of great emotional distress. As such, some commentators have classed them as potentially ‘vulnerable populations’, arguing that careful consideration also needs to be given to who is best placed to seek consent from this group [23, 24]. In relation to recipients of the research organs, questions of what exactly they are consenting to and when to consent have been raised. For example, does consent relate to accepting a research organ or to participate in the research in terms of following up outcomes, or both? [1, 6, 8].

These commentaries have drawn attention to the ambiguities around consent in relation to clarifying *who* the research subjects are; what, exactly, patients are being asked to consent to (in the case of recipients); and how consent is best, and most ethically, taken. Ultimately, these issues are tied up with preserving the dignity and rights of both donors and recipients, as well as fears over the potential for this type of research, if done badly, to interfere

in public trust in the organ donation and transplantation process.

The policy context

In response to these debates, a limited number of guidelines have been developed which attempt to clarify the legal and ethical issues around interventional donor research. For example, in the US context, the National Academies of Science, Engineering and Medicine published a 2017 consensus report on the matter [25]. This outlines the ethical, legal and regulatory issues relevant to donor intervention research in the US and makes recommendations in response to these issues. The report highlights the need for research participants to be respected by a 'robust process' of informed consent and recommends that:

- Specific research consent should be incorporated into consent registers for organ donation. If this specific consent for research does not exist, then in potential donors who lack capacity (which is almost invariably the case), a surrogate decision-maker should take their wishes and values into account when authorising for the research on their behalf
- Potential organ recipients require a two-stage process for taking consent:
 - 1 Consent to receive a research organ when first placed on the transplant waiting list
 - 2 Further consent should be sought when the research organ is offered to the recipient.

The focus of their recommendations therefore revolves around the ideal of acquiring generic donor consent at the time of registering a decision to be an organ donor after death, and the need to consent transplant recipients if organ donor intervention research had occurred.

In the UK context, the legal and ethical decision-making in terms of consent in the context of donor research performed after death rests clearly with relatives, as outlined in the Human Tissue Act of 2004 [26]. However, the accompanying guidance to the HTA indicates that consent for research, even for interventions before the removal of organs, can be gained generically during the family discussion at the time of consent for organ donation [27]. This 'generic consent' includes a general provision authorising research use if an organ/tissues retrieved for the purposes of transplantation are not able to be transplanted. However, generic consent does not necessarily cover interventions within the body of the donor before organ retrieval, which would be regulated instead by the Mental

Capacity Act (2005) if the patient is alive and the Health Research Authority. Consent therefore becomes problematic in the UK in the context of interventional donor research.

Recognising this issue, the now disbanded independent UK Donation Ethics Committee, developed a summary of the 'practical issues' impeding the development of transplantation research and its guidance on how to proceed [21]. It highlighted that obtaining donor (or surrogate) consent for research was part of good practice but acknowledged that this "*risks placing donor families under additional stress at a difficult time*" (p.863). They went on to recommend that donor consent forms should be altered to include a general consent to research being undertaken and for more detailed discussions to be had with families in the case of interventional donor research. In the case of recipients, they advised a similar two-stage process to the one outlined in the USA: consent at the time of wait-listing and specific consent at the time of the allocation of the research organ.

More recently, NHS Blood and Transplant's (NHSBT) Research, Innovation and Novel Technologies Advisory Group have developed a classification of study methodologies which help determine the requirement for specific, rather than generic, consent for donor research, even if not strictly required by the HTA Code of Practice [28]. Recognising that the wishes of the donor and their family are paramount when it comes to adequate consent under the guiding principles of the HTA, NHSBT guidance requires that specific consent is obtained from the family for interventional research in potential donors. To add to the myriad of potentially applicable professional and legal advice, the Organ Donation (Deemed Consent) Act 2019 was recently passed in England [29], and an updated accompanying code of practice is expected shortly. The Act is similar to legislation implemented in Wales since 2015 [30]. Scotland is in the process of changing the applicable legislation to an 'Opt Out' system as well but will have specifically different legislation covering intervention in the potential organ donor [31]. Research is currently excluded from deemed legislations in all UK jurisdictions but that may not be enough to prevent confusion.

Despite all the recommendations and guidelines, from both the US and UK contexts, confusion persists around the very nature, practicalities and context of consent itself, in this unique form of research. Our argument is that current guidelines only lead to further questions about consent for interventional donor research. These include: how do donor families (and recipients) understand, experience and make decisions about donor research; what does it mean, from

the perspective of health professionals, to seek consent for such research; and who is best suited to take consent in such situations? To consider the complexities of consent in this vein, we review the literature on consent in critical care research as well as social science studies of consent for medical research.

Contextualising consent in interventional donor research

There has been little interventional donor research internationally, and virtually none in the UK. Much of the evidence that underpins practice in this area has been extrapolated from expert consensus, and published from non-randomised, unblinded cohort studies often undertaken in single centres, or within localised donation and transplant programs. Those interventional studies that have been done have usually taken place in a critical care setting, involving deceased patients (following determination of death using neurological criteria, 'brain death') who were having continued organ support while awaiting organ retrieval [25]. The last decade has seen the rapid development of donation following the re-introduction of DCD, described earlier. Research within a DCD context may involve consideration of interventions whilst the patient is alive, with potentially wide-ranging adverse effects ranging from physical harms to the donor, through the loss of the ability to donate, to related psychosocial harms and family experience at the time of patient death. Insight into research and guidance on consent in critical care settings can help us begin to unravel the complexities that may be involved in practically undertaking consent for interventional donor research, and how this form of consent might be experienced by different agents in the process (donor families, health professional, specialist nurses in organ donation).

The critical care setting is a unique and complex care environment, in which prospective research participants are most often unable to make their own decisions regarding treatment or research since their lungs are ventilated, they are unconscious [32] and, in the case of most donor research, deceased, meaning that research consent is often given by a substitute decision-maker such as a relative. Current research guidance for incapacitated patients stresses that potential harms and benefits to the patient should be explained to substitute decision-makers, but formal consent is then sought retrospectively from the patient on recovery, which is clearly impossible in the context of donation [33, 34]. Other interventions undertaken within end of life care (e.g. palliative care research) may be done using best-interests decision-

making in incapacitated patients, but the benefits are overwhelmingly centred on the patient in such circumstances [35]. Research ethics panels have traditionally been unwilling to countenance invasive and risky research on incapacitated patients done explicitly for the benefit of others with little, or zero, potential benefit to the patient. Whilst the potential for successful organ donation is widely accepted as a 'good' in patients who have consented to organ donation after their death, there is no mention of research interventions before or after death within the organ donor register, so patient opinion is unknown. At present, then decision-making for interventional donor research would clearly lie with substitute decision-makers.

Researchers have shown that gaining research consent from substitute decision-makers in a critical care environment is a complicated and problematic process, which may not reflect the needs of patients, their family, staff or the study itself [36]. There is also indirect evidence that substitute decision-makers are often overwhelmed by the consent process, especially at times of stress [37]. Crucially, critical care researchers have highlighted the importance of considering who approaches substitute decision-makers about consent for research on their relative. For example, studies have found that decisions to provide consent by substitute decision-makers are influenced by the level of trust placed in the healthcare professionals caring for their relative; the perceived experience, skills and personality of the member of staff approaching them about research; and how information about the study is explained and discussed [36, 37]. Others have highlighted the potential for the approach for consent to disrupt existing relations between critical care staff and families if not done sensitively [32]. In addition, resources and timing also play a role. Critical care researchers have found that greater time given to the consent conversation can be a predictor of substitute decision-makers providing consent and of better-reported experiences of the consent process [36, 38, 39]. As such, the importance given to the role of those seeking and discussing consent, and the time and resources they are given to do this, is crucial in the context of consenting for research in the critical care setting.

Taking these insights one step further, scholars working at the intersections of medical sociology, anthropology, and science and technology studies have studied the processes and practices underpinning 'informed consent' in medical research, arguing for the need to understand the contexts shaping consent. These scholars have consistently drawn attention to the tensions between the procedural ideal of informed consent (i.e. that people make a rational, qualified

decision based on the information they are provided with) and its everyday reality (i.e. how consent is actually done in clinical settings and how people make decisions around consent) [40, 41]. The largely qualitative research in this area has shown that potential participants often do not understand, use or even look at the written information provided to them when making decisions about consent [40, 42–44]. Instead, decisions about participating in medical research are linked to broader social and moral reasoning [42]; personal concerns and experiences [40, 44, 45]; perceptions about medical research; and trust in the institutions conducting the work [43, 46].

Such issues are likely to be present, if not more prominent, in the context of families being asked to consent to interventional donation research on their relative's behalf so soon after being asked to consent for organ donation. Substitute decision-makers may struggle to understand the focus and structure of decision-making for incompetent patients, and their decisions are likely to encompass wider considerations than the wishes of the deceased, even if these are known. In the case of potential recipients of research organs, the desire to have a transplant may overwhelm all other information provided to them about potential risks of such organs.

Like the critical care findings discussed above, social science research has also evidenced the important role played by those seeking and taking consent for medical research. Studies have found that the person taking consent is key to decision-making, including in their ability to 'translate' information about the research to patients/families [43]. Similarly, the practices of those taking consent are shaped by the demands and perceived characteristics of the people they seek to consent [47, 48]. In this way, consent should be considered as a highly relational, rather than individual, act which is affected by the interactions and meanings created between those taking and those providing consent.

These insights are crucial, in particular, for understanding potential issues around consent in the context of substitute decision-makers being approached about interventional donor research. In the UK context, Specialist Nurses in Organ Donation (SNODs) currently approach relatives for organ donation consent (family agreement if the patient is already a registered donor), following which they ask about research in general or for the use of retrieved but subsequently not transplanted organs for research. Only if there is a study requiring specific consent would the specialist nurse explain to the substitute decision-maker the research methodology, envisaged benefits and risks. The expertise and training of SNODs is

directed toward gaining consent for organ donation and generic research, but not for specific interventional research methodologies.

This leads to the question of how and by whom consent should be sought in the context of interventional donor research and what consequences this may have on the donation process as a whole. The length of the donation process can be a reason why families decline or withdraw their agreement to donate [49]; If SNODs take additional research consent, this could detract from their management of the donation itself. This could have potential implications for the duration of the donation process, family consent and an increased potential for additional distress on the part of the family.

Conclusion

What is clear from this examination is that the ethical and practical 'problem' of consent for interventional research in deceased organ donors is far from resolved. Commentators, policies and guidance have, thus far, largely focused on the following ambiguities in terms of donation research: who should provide consent for this type of research (donors, who are the research subjects, and their substitute decision-makers; recipients of the research organs); what is actually being consented for (in the case of recipients); and how this consent should be procedurally carried out. Whilst the production of guidance is obviously important, our argument is that these have taken the notion of consent itself for granted, in that a lack of consideration has been given to the very nature of what it might mean to consent to this type of research (interventions in the body of the donor before and after death which has an effect on the donated organ/s); how families, patients and health professionals might experience providing and seeking this kind of consent; who is best placed to have these discussions; and the social and institutional contexts which will affect these experiences and processes.

Insights into research on consent in critical care settings and broader social science studies on consent for medical research shows that consent needs to be considered as a highly relational process, which is shaped and underpinned by socio-institutional contexts, such as resourcing, issues of trust and wider understanding of research. In the context of consent for interventional donor research, understanding consent in this way, as a situated, relational process (rather than the traditional model of informed consent as one which is about information and choice) is vital if developments are to be made in interventional donor research.

If we fail to fully explore and grasp the issue of consent for interventional donor research, the implications may be

serious. These could range from prolongation of the research process to the extreme of loss of public trust in medical research generally and organ donation specifically, with potential consequences for donor rates. The UK's history of such loss of trust, following the Alder Hey organ retention scandal in particular, makes this a possibility that needs to be taken seriously. We argue that it is therefore vital that empirical research is done to look at the processes, practices and experiences of consent in this form of research. Doing so could lead to an effective, ethical and sensitive model for consent in interventional donor research, greater transparency and acceptability in the consent process, and, ultimately, ensuring that the principles enshrined in research ethics are met and public trust in organ donation is maintained.

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