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Cover image caption

Portrait illustrations of pioneer philosophers through the years. From left to right, starting at the top: John Locke, John Rawls, Baruch Spinoza, Janet Radcliffe Richards, Abdallah Daar, Jean-Jacques Rousseau, David Price†, Michele Goodwin, Alexander Capron, Immanuel Kant, Martin Wilkinson, Govert Den Hartogh, Arthur Caplan, Thomas Gutmann, Aristoteles, Tom Beauchamp, Heather Draper, Robert Veatch†, James Childress.

Ethical and legal aspects of organ donation and transplantation

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It has long been recognized that organ donation and transplantation do not involve clinical aspects only. There are various ethical and legal considerations that emerge in modern donation and transplantation. This special issue is for all members of the multi-disciplinary team that care for organ donors, donor families and transplant patients, and who want to increase their knowledge beyond the clinical practice.

Featuring 16 publications, this issue covers ethical, legal, psychosocial, and cultural aspects of deceased -and living organ donation and transplantation from countries across the globe. It provides an abundant source of knowledge and guidance for donation and transplant clinicians, ethicists, lawyers, philosophers, psychologists and other professionals working in the field of donation and transplantation. Topics covering living organ donation include long-term experiences of unspecified kidney donation, anonymity in paired donation, organ trade, transplantation of elderly people and donor autonomy. Topics covering deceased donation include cultural, legal, and ethical challenges of brain death and organ transplantation, directed donation after euthanasia, countries' experiences with changing to an opt-out system, radiological screening methods and inequitable access of patients to transplantation who have impaired decision-making capacity.

Together, these publications represent the latest research developments, challenges and innovations in contemporary donation and transplant ethics. We are convinced that they provide a valuable and helpful resource for donation and transplant clinicians and researchers globally.

ISSN 1432-2277
ISBN 978-2-8325-4858-5
DOI 10.3389/978-2-8325-4858-5

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EDITORIAL
published: 09 April 2024
doi: 10.3389/ti.2024.13011

Ethical and Legal Aspects of Organ Donation and Transplantation

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Keywords: transplant ethics, law, culture, psychology, bio-artificial organs

Editorial on the Special Issue

Ethical and Legal Aspects of Organ Donation and Transplantation

In organ transplantation, increasing emphasis is given to ethical and legal aspects. The persisting global organ shortage, in combination with fast-moving medical, technological, geopolitical and socio-economic changes, has given rise to an array of ethical and legal challenges for professionals working in the field of organ transplantation [1, 2]. This Special Issue provides a contemporary overview of ethical and legal considerations, both in deceased–and living organ donation and transplantation, reported by transplant professionals from across the globe. The publications do not only provide descriptions of current practices and considerations, but also offer inspiration and insight into how ethical, legal and cultural challenges can be overcome to further improve organ donation and transplantation rates around the world.

The first section of this issue focuses on ethical and legal challenges in deceased organ donation and transplantation, ranging from survey studies on opt-in -and opt-out systems Mihály et al. and radiological screening methods Chotkan et al. to difficulties in comparing deceased organ donation rates, even between countries that have similar cultures and organ donation systems Milross et.al. Many countries have changed their laws from an opt-in to a presumed consent system, among which the United Kingdom and Netherlands. Jansen et al. reflect on the experiences in these countries during these major changes, thereby offering valuable knowledge and guidance for professionals and policymakers who are considering changing national organ procurement laws. Rooted within discussions of organ procurement systems also lie cultural and religious considerations, which are highlighted in Atreya et al. contribution from Nepal. The authors offer solutions to how, among others, donation after brain death can be boosted in a country that faces considerable religious and cultural opposition to this form of donation.

The next publication focuses on directed donation after euthanasia Van Dijk et al. It is currently not possible to opt for directed donation following euthanasia. With more patients requesting deceased donation after euthanasia, Van Dijk et al. ask under which ethical considerations directed donation after euthanasia is ethically permissible. The authors offer a set of criteria under which it would be appropriate to proceed with directed donation following euthanasia. Another topic of debate is the question whether adults with impaired decision-making capacity should be allowed to be transplanted. In their literature review, Thom et al., on behalf of the ELPAT Working Group on Ethical and Legal Issues, describe how these adults face inequitable access to transplantation. They

Editorial

OPEN ACCESS

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Received: *20 March 2024*
Accepted: *22 March 2024*
Published: *09 April 2024*

Citation:
Ambagtsheer F, Annema C, Forsythe J, Jansen N and Paredes-Zapata D (2024) Ethical and Legal Aspects of Organ Donation and Transplantation. Transpl Int 37:13011. doi: 10.3389/ti.2024.13011

offer ethical and legal arguments, followed by recommendations, in support for allowing people with impaired decision-making capacity to be transplanted.

The second part of the Special Issue covers ethical and legal considerations in living organ donation and transplantation. It kicks off with a systematic review of reasons for and against anonymity in kidney paired donation by Marcus et al. This is followed by a unique interview study by Pronk et al. amongst unspecified donors in Netherlands who look back on their donation experiences. Next, Courtney et al. address, in their ELPAT paper, the issue that older patients are significantly less likely to receive a living donor transplant. The authors highlight the advantages of living donor transplantation in older patients, as well as systemic barriers, ethical, legal and social issues to explain the low representation of older individuals in living donor transplantation. Shifting from older donors to younger donors, Choi et al. evaluated the knowledge of and attitudes toward liver and kidney transplantation from minor donors in South Korea. They further assessed if receiving structured information on the outcomes of living organ transplantations and donations may change attitudes towards liver and kidney transplantation from minors. Several states in the United States, Canada, Belgium, Luxembourg, Norway, Sweden, the United Kingdom, Indonesia and South Korea allow donations of minors under exceptional circumstances Choi et al. Mamode et al. article explores issues raised by cases involving motivated living kidney donors whose willingness to take risk differs from that of the healthcare team. The authors explore the issues raised by these cases and consider the principles which might help to guide decision-making.

Following the rise of transplant tourism from Japan to China and the Declaration of Istanbul's promulgation that transplant professionals have a duty to help prevent organ trade, several hospitals in Japan have announced that they will not provide follow-up care to patients suspected of participating in organ trafficking. Takimoto examines whether the refusal of follow-up care for transplant tourists is ethically acceptable, using two prevailing rationales—deterrent effect and conscientious objection. Although there have been calls for removing disincentives and allowing incentives for deceased–and living organ donation, there is limited information about their social acceptability. Ambagtsheer et al. present the results of a systematic literature review on public opinions towards removal of financial disincentives and the introduction of incentives for deceased and living organ donation in Europe. Next, they describe the results of a randomized survey experiment conducted on this issue in the United States. They propose this experiment's framework as a blueprint for European research on this topic.

The final section of this Special Issue presents a cutting-edge topic in organ transplantation, namely the development of bio-artificial organs. To address the lack of ethical guidance for the safe and responsible design and conduct of early-phase clinical trials of bio-artificial organs, De Jongh et al. conducted a systematic review to examine the literature on early-phase clinical trials in these adjacent fields. They also present a thematic analysis of relevant ethical points to consider for early-phase clinical trials of transplantable bio-artificial organs. In this issue's final study, Aguilera et al. present the results of an international survey among liver transplant providers regarding disparity and female leadership. The survey suggests that liver transplant providers may experience discrimination based on gender or race, lack of mentorship or support for discriminatory actions and very low rates of female representation in living transplant leadership positions, the lowest being in liver transplant surgery. The authors further identify higher rates of overall discrimination, discrimination in job promotion as well as compensation differences reported by female living transplant providers compared to male respondents. Several calls for action are proposed.

It is our hope that the combination of new empirical insights and ethical and legal guidelines presented in this issue offer a valuable framework for transplant professionals globally, be it to improve quality of patient care, to reduce inequity of access to transplantation or to reduce organ scarcity.

AUTHOR CONTRIBUTIONS

FA wrote the editorial. CA, JF, NJ, and DP-Z provided input to drafts. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 12 September 2023
doi: 10.3389/ti.2023.11498

Approaching the Families of Potential Deceased Organ Donors: An Overview of Regulations and Practices in Council of Europe Member States

Sándor Mihály[1], Anikó Smudla[2], Beatriz Dominguez-Gil[3], Alicia Pérez[3], Francesco Procaccio[4], Emanuele Cozzi[5], Marta López Fraga[6], Danica Avsec[7], Axel Rahmel[8], John Forsythe[9], Franz Immer[10], Janis Jushinskis[11] and Alex Manara[12]*

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The primary aim of this study was to describe regulations and practices concerning the family approach to discuss donation, specifically after the neurological determination of death, one of the most challenging steps in the donation pathway. A secondary objective was to assess the impact of legislation on consent rates for organ donation. The Council of Europe surveyed 39 member states about national regulations, practices, and consent rates; 34 replied. Opt-out legislation is present in 19, opt-in in 9 and a mixed system in six countries. An opt-out register is kept by 24 countries and an opt-in register by 18 countries, some keeping both. The mean consent rate was 81.2% of all family approaches. Most countries regulate how death using neurological criteria is confirmed (85.3%), while regulation of other aspects of the deceased donation pathway varies: the timing of informing the family about brain death (47.1%) and organ donation (58.8%), the profile of professional who discusses both topics with the family (52.9% and 64.7%, respectively) and the withdrawal of treatment after brain death (47.1%). We also noted a mismatch between what regulations state and what is done in practice in most countries. We suggest possible reasons for this disparity.

Keywords: deceased organ donation, family approach, family communication, consent for organ donation, Council of Europe

OPEN ACCESS

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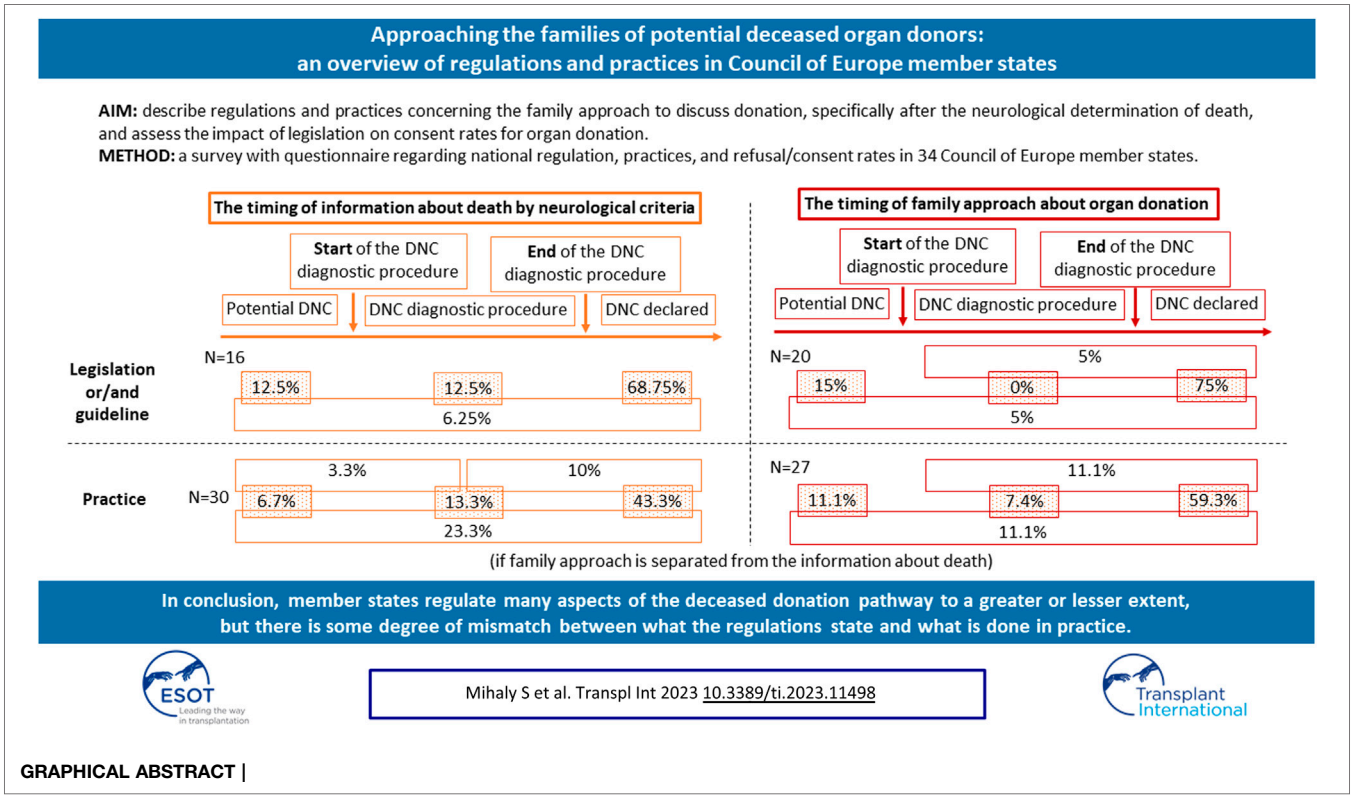
Received: *20 April 2023*
Accepted: *30 August 2023*
Published: *12 September 2023*

Citation:
Mihály S, Smudla A, Dominguez-Gil B, Pérez A, Procaccio F, Cozzi E, López Fraga M, Avsec D, Rahmel A, Forsythe J, Immer F, Jushinskis J and Manara A (2023) Approaching the Families of Potential Deceased Organ Donors: An Overview of Regulations and Practices in Council of Europe Member States. Transpl Int 36:11498. doi: 10.3389/ti.2023.11498

Abbreviations: CD-P-TO, European Committee on Organ Transplantation of the Council of Europe; DBD, donation after brain death (neurological determination of death); DCD, donation after the circulatory determination of death; DNC, to determine death using neurological criteria; HCP, healthcare professional; ICU, intensive care unit; PMP, per million population; SD, standard deviation.



GRAPHICAL ABSTRACT |

INTRODUCTION

Organ transplantation is often the only treatment option for patients with end-stage organ failure but is limited by the availability of organs [1]. To maximize the availability of organs, all potential organ donors must be identified, referred, and managed along pathways that ensure most potential donors become actual donors. The ultimate objective is for all nations to achieve self-sufficiency in transplantation, as recommended by the Madrid Resolution [2].

Families declining organ donation is an important reason for the loss of donation potential, the rates of which vary among countries but remain a matter of concern in Europe. Consent to organ donation is influenced by many factors, particularly a known donation decision made by the deceased during life and whether a trained individual is involved in the family conversation [3]. The impact of legislation is less clear. In 2017, 19 Council of Europe countries that had implemented opt-out legislation achieved 27.4 deceased donors per million population (pmp), more than twice that achieved in the 11 countries with opt-in legislation (12.1 pmp). Interestingly, the average family decline rate in states with opt-in legislation (15.8 pmp in 6 countries) was double that in states with opt-out systems (7.3 pmp in 13 countries). The family decline rate in opt-in countries exceeded the deceased donor rate (15.8 vs. 12.1 pmp). In opt-out countries the decline rate was a quarter that of deceased donors (7.3 pmp vs. 27.4 pmp). The number of families declining donation as a proportion of all family donation conversations (decline rate) was 20.4% in 13 opt-out countries, compared with 47.8% in 6 opt-in countries [4]. However, the decline rate may be calculated differently, and legislation is not necessarily the most important influencing factor. Public support for donation and transplantation, trust in the individual jurisdiction's system, spiritual or cultural beliefs and practices for approaching families to discuss donation may have a greater impact [5].

A decline to organ donation can represent an individual's decision expressed during life by registering an opt-out decision, but often results from a decision made on the potential donor's behalf by their family [6]. Consent to organ donation is also influenced by factors associated with the family approach: when, how, and by whom the family is informed about donation opportunities [7]. The timing and temporal separation ("decoupling") of discussions regarding brain death or a decision to withdraw life-sustaining treatments from discussions seeking family support for organ donation can also influence consent [3, 8, 9]. Some countries have regulations (legislation or guidance) on how professionals should approach families to discuss deceased donation [10–16]. However, to the best of our knowledge, no granular information is available on the regulatory frameworks and current practices concerning the family approach in individual member states.

The main objective of this study is to describe current regulations and practices covering the family approach to discuss donation, specifically for DBD (donation after brain

TABLE 1 | Legislation on consent in the Council of Europe member states.

	Country	Organ and tissue donation consent models	Family veto in opt-out systems	Family veto in opt-in systems	Opt-out registry	Opt-in registry
1	Andorra	Presumed consent (opt-out)	No	Yes	No	No
2	Austria	Presumed consent (opt-out)	No	—	Yes	No
3	Belarus	Presumed consent (opt-out)	No	—	Yes	No
4	Belgium	Presumed consent (opt-out)	No	—	Yes	Yes
5	Bulgaria	Presumed consent (opt-out)	No	—	Yes	No
6	Croatia	Presumed consent (opt-out)	No	—	No	No
7	Cyprus	Other	—	Yes	Yes	Yes
8	Czech Republic	Presumed consent (opt-out)	Yes	—	Yes	No
9	Denmark	Informed/explicit consent (opt-in)	—	Yes	Yes	Yes
10	Estonia	Presumed consent (opt-out)	No	Yes	Yes	Yes
11	Finland	Presumed consent (opt-out)	No	—	No	No
12	France	Presumed consent (opt-out)	No	—	Yes	No
13	Georgia	Informed/explicit consent (opt-in)	—	No	No	Yes
14	Germany	Informed/explicit consent (opt-in)	—	No	No	No
15	Greece	Informed/explicit consent (opt-in)	—	Yes	Yes	Yes
16	Hungary	Presumed consent (opt-out)	Yes	—	Yes	No
17	Ireland	Informed/explicit consent (opt-in)	—	No	No	No
18	Israel	Informed/explicit consent (opt-in)	—	No	No	Yes
19	Italy	Other	No	Yes	Yes	Yes
20	Latvia	Presumed consent (opt-out)	No	—	Yes	Yes
21	Lithuania	Informed/explicit consent (opt-in)	—	Yes	No	Yes
22	Moldova	Other	No	Yes	Yes	Yes
23	Netherlands	Presumed consent (opt-out)	No	No	Yes	Yes
24	Norway	Presumed consent (opt-out)	No	Yes	No	No
25	Poland	Presumed consent (opt-out)	No	—	Yes	No
26	Portugal	Presumed consent (opt-out)	Yes	—	Yes	No
27	Romania	Informed/explicit consent (opt-in)	—	No	No	Yes
28	Serbia	Presumed consent (opt-out)	No	—	Yes	No
29	Slovak Republic	Presumed consent (opt-out)	No	—	Yes	No
30	Slovenia	Other	No	Yes	Yes	Yes
31	Spain	Presumed consent (opt-out)	No	Yes	Yes	Yes
32	Sweden	Other	No	—	Yes	Yes
33	Switzerland	Informed/explicit consent (opt-in)	—	Yes	Yes	Yes
34	United Kingdom	Other	No	No	Yes	Yes

death/neurological determination of death). A secondary objective is to assess and describe the impact of legislation on consent rates for organ donation. This may be useful for individual countries reviewing their current regulatory framework and its practical implementation.

MATERIALS AND METHODS

The European Committee on Organ Transplantation of the Council of Europe (CD-P-TO) had accepted a project proposal, then established an *ad hoc* working group who held a consensus meeting to design a questionnaire that was endorsed by the Committee. The questionnaire consisted of 33 questions eliciting 56 responses on the following areas: the regulations and practices regarding discussing a diagnosis of brain death with families, the approach for organ donation, and the family decline/consent rate, questions regarding donation after the circulatory determination of death (DCD), and questions on the possibility and regulation of organ donation from non-citizen/non-resident deceased persons. The last two items are not included in this study due to low response rate and an intention to publish separately. The questionnaire was sent to representatives of 39 Council of Europe countries during the second half of 2021 (see **Supplementary Material**), who completed it using information and validated data obtained from their official national sources. All the data and information were reviewed by the authors who requested further clarification from the respondents during the validation. Other donation metrics for 2016 to 2020 were derived from the *Newsletter Transplant* [4, 17–20].

Data were analyzed with the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois) including descriptive statistics and tests of significant differences. Continuous variables were analyzed with independent samples *t*-test for variables with two categories. Fisher's exact test was used for statistical differences between two categorical variables. The significance level was set to 5% ($p \leq 0.05$).

Definitions (possible, potential, actual, utilized organ donor) used in this paper have been adopted by the authors from the Critical Pathway [1].

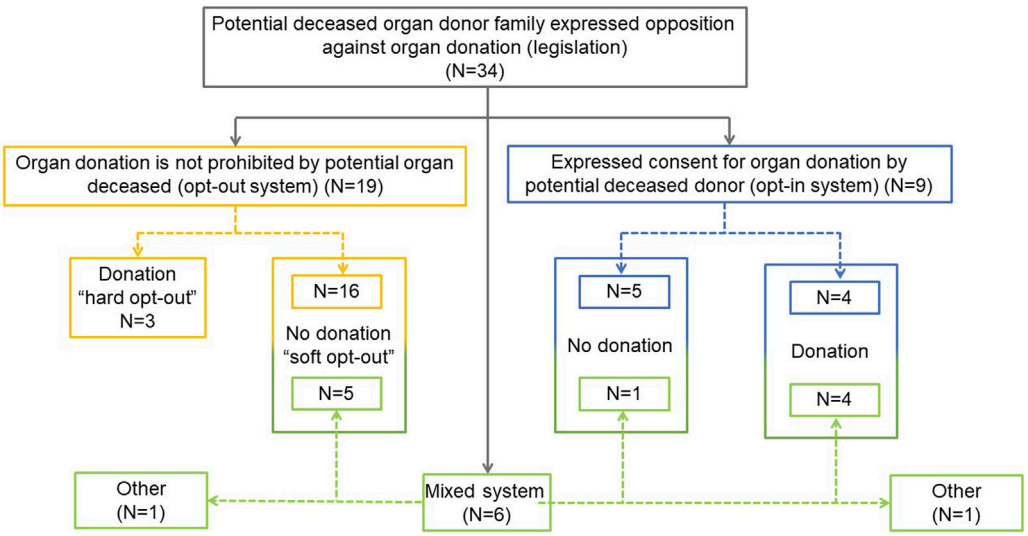


FIGURE 1 | National legislation applicable to the family approach and consent for organ donation.

RESULTS

The response rate was 87% (34 of 39 member states who received the questionnaire).

National Regulations Regarding Brain Death and Consent for Organ Donation

A summary of national regulatory frameworks is shown in **Table 1**.

Opt-out (presumed consent) legislation is present in 19 countries (56%), opt-in legislation in 9 (26%) and a mixed legal system (countries without a defined opt-out or opt-in model) in the remaining 6 (18%). Twenty-one countries (16 opt-out and 5 mixed) operate a system where donation will not proceed if the family objects, even if there is no written objection from the donor. Three countries operate a "hard opt-out" system: donation will proceed despite family opposition, unless there is written evidence that the deceased chose not to be an organ donor. In 6 (5 opt-in and 1 mixed) countries families can override an opt-in decision and donation will not proceed. Finally, in 11 countries (3 "hard opt-out," 4 opt-in and 4 mixed system countries) organ donation will proceed despite family opposition when there is written evidence of the deceased's decision to donate (**Figure 1**).

An opt-out register is available in 24 countries (71%): 15 opt-out, 3 opt-in and 6 mixed system countries. Four countries with opt-out legislation have no opt-out register. An opt-in register is available in 18 countries (53%), including 5 opt-out and all 6 mixed system countries. Among the 16 countries with no opt-in register, 2 require informed/explicit consent (**Table 1**).

The determination of death using neurological criteria (DNC) is regulated by legislation in 25 (73.5%) countries and by guidelines only in 5 countries (14.7%). Four countries have both.

The time at which the family is informed about a brain death diagnosis is regulated in 16 countries (47.1%): 6 by legislation, another 6 by guidelines, and by a combination of both in 4 countries. In 3 (2 + 1) of these countries, the family may be informed that the patient's condition may progress to brain death before DNC is confirmed. However, in 11 of 16 countries the family can only be informed about DNC after the diagnosis is confirmed. In 3 (2 + 1) countries, the family may be informed that the clinical condition is compatible with DNC before the diagnosis is confirmed (**Figure 2**).

In 20 countries (58.8%) the timing of the family approach to discuss donation is regulated: by legislation in 6 countries and by guidelines in 9; 5 countries have both. Organ donation can be discussed when DNC is a likely outcome but has not yet occurred (3 + 1 countries; n = 4; 20%), when the patient has a clinical condition consistent with DNC, but before the diagnosis is confirmed (1 + 1 countries; n = 2; 10%), or only after DNC has been officially declared (15 + 1+1 countries; n = 17; 85%) (**Figure 2**).

The healthcare professional (HCP) who should inform the family about DNC is regulated in 18 countries (52.9%): by legislation in 9 (26.5%), by a guideline in 6 (17.7%) and by a combination of both in 3 (8.8%). The HCP should be a medical doctor (n = 17; 94.4%) or a donor coordinator (who can be a medical doctor) (n = 6; 33.3%). Both types of professionals are permitted in 5 countries (27.8%) (**Figure 3**).

The HCP who discusses organ donation with the family is regulated in 22 countries (64.7%): by law in 12, by a guideline in 6, and by a combination in 4 countries. A medical doctor is required to do this task in 18 countries (81.8%), a nurse in 5 (22.7%) and the donor coordinator in 14 (63.6%). All 3 HCPs can approach families to discuss organ donation in 2 countries (9.1%), medical doctors and nurses in 3 countries (13.3%) and medical doctors and donor coordinators in a further 8 countries (36.4%) (**Figure 3**).

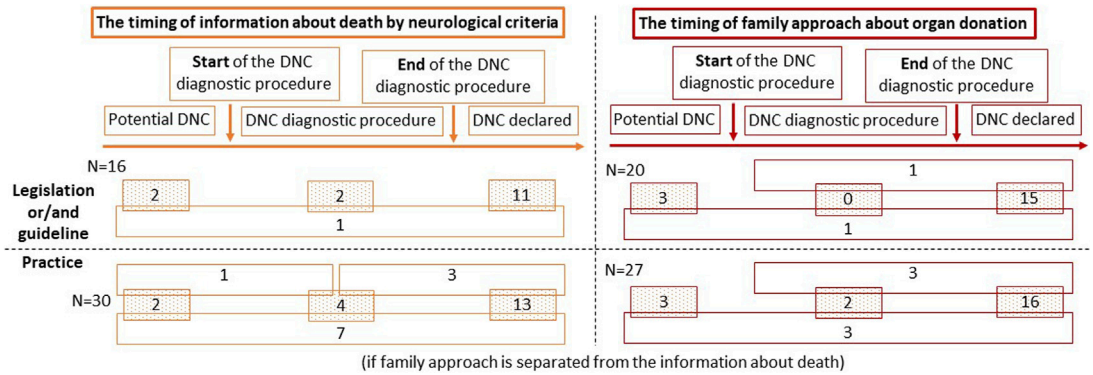


FIGURE 2 | The timing of information given to the family about death by neurological criteria and the timing of family approach to address the possibility of organ donation. Abbreviations: DNC, death by neurological criteria.

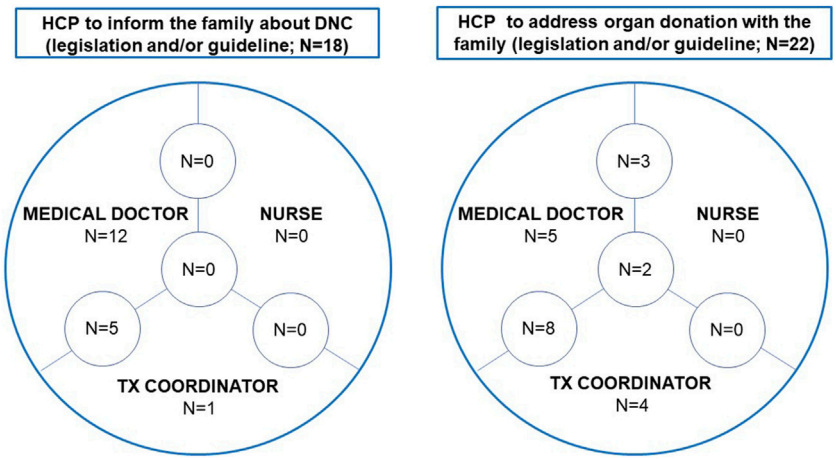


FIGURE 3 | The healthcare professional to inform the family about death by neurological criteria and to address organ donation with the family. Abbreviations: DNC, death by neurological criteria; HCP, healthcare professional.

The information that should be provided to the family is detailed in the regulatory framework of 17 countries (50%): guidelines in 13 countries, legislation in 2 and both in 2 countries.

Finally, the withdrawal of mechanical ventilation after confirming DNC is regulated in 16 countries (47.1%) when organ donation cannot proceed: by legislation in 12 and by guidelines in 4. It is also regulated in 18 countries (52.9%) when a family declines the offer of organ donation after a diagnosis of DNC: by legislation in 13 countries and by guidelines in 5.

Practices Regarding the Family Approach for Potential Organ Donation

There was no donation activity over the survey period in 2 participating countries; therefore, practices were surveyed in the other 32 countries.

Although in two countries HCPs (one country with legislation and one country without legislation or guideline) may deliver information on organ donation in one step, a gradual approach is used in most countries (56.3%), as many families need time to process and accept the death of their loved one before making a decision about organ donation. Decoupling the conversation about a brain death diagnosis from the approach for organ donation is used in 25% of the countries.

In most countries (13 + 3+7 countries; n = 23; 71.9%) the family is usually informed about DNC when the diagnosis has been officially declared. Less commonly (4 + 1+3 + 7 countries; n = 15; 46.9%) the family is informed that the patient's clinical condition is consistent with DNC before the diagnosis has been confirmed. In 10 countries (1 + 2+7 countries; 31.3%) DNC is communicated to the relatives at an early stage, when it is a likely outcome but has not yet occurred (**Figure 2**). In countries where the time to inform families about DNC is not regulated, the family is more commonly informed when the patient has a clinical

TABLE 2 | National legislation and guidelines regarding informing the family about diagnosing death using neurological criteria and what happens in practice.

Legislation and guidelines			What happens in practice		
			HCP may inform the family about DNC when DNC is expected in the short term	HCP may inform the family about DNC when DNC is suspected but not yet confirmed	HCP informs the family about DNC only after DNC has been confirmed
			Yes N (%)	Yes N (%)	Yes N (%)
Does the legislation/guideline specify the HCP responsible for informing on DNC?	Yes	16	5 (31.3)	6 (37.5)	9 (56.3)
	No	16	5 (31.3)	9 (56.3)	14 (87.5)
If yes, specify the type of regulation	Legislation	6	0 (0)	1 (16.9)	5 (83.3)
	Guideline	6	2 (33.3)	2 (33.3)	4 (66.7)
	Legislation + Guideline	4	1 (21)	0 (0)	3 (75)
According to the legislation/guidelines:					
The HCP can inform the family about DNC when it has not yet occurred but is expected to do so in the short term	Yes	3	3 (100)	1 (33.3)	0 (0)
	No	13	2 (15.4)	5 (38.5)	9 (69.2)
The HCP can inform the family about DNC when the diagnosis is suspected but has not yet been confirmed	Yes	3	1 (33.3)	1 (33.3)	1 (33.3)
	No	13	4 (30.8)	5 (38.5)	8 (61.5)
The HCP can only inform the family after DNC has been confirmed	Yes	12	3 (21)	4 (33.3)	8 (66.7)
	No	4	2 (50)	2 (50)	1 (25)

Abbreviations: DNC, death using neurological criteria; HCP, healthcare professional.

TABLE 3 | National legislation and guidelines regarding the timing of the family approach for organ donation and what happens in practice.

Legislation and guidelines			What happens in practice		
			HCP may inform the family about organ donation when DNC is expected in the short term	HCP may inform the family about organ donation when DNC is suspected but not yet confirmed	HCP may inform the family about organ donation after DNC has been confirmed
			Yes N (%)	Yes N (%)	Yes N (%)
Does the legislation/guidelines specify when the HCP must/should approach the family to discuss organ donation?	Yes	19	4 (21.1)	5 (26.3)	11 (57.9)
	No	11	2 (18.2)	3 (27.3)	11 (100)
If yes, specify the type of regulation	Legislation	5	1 (20)	1 (20)	4 (80)
	Guideline	9	3 (33.3)	2 (22.2)	4 (44.4)
	Legislation + Guideline	5	0 (0)	2 (33.3)	3 (66.7)
According to the legislation/guidelines:					
The HCP must/should approach the family to discuss organ donation when DNC has not yet occurred but is expected to do so in the short term	Yes	4	3 (75)	2 (50)	1 (25)
	No	15	1 (6.7)	3 (20)	10 (66.7)
The HCP must/should approach the family to discuss organ donation when the diagnosis of DNC is suspected but has not yet been confirmed	Yes	2	1 (50)	1 (50)	0 (0)
	No	17	3 (17.7)	4 (23.5)	11 (64.7)
The HCP must/should approach the family to discuss organ donation only when the diagnosis of DNC has been confirmed	Yes	16	2 (12.5)	3 (18.8)	10 (62.5)
	No	3	2 (66.7)	2 (66.7)	1 (33.3)

Two countries (one with legislation and one without legislation and/or guidelines) did not comment on the practice regarding informing the family about organ donation.
Abbreviations: DNC, death using neurological criteria; HCP, healthcare professional.

condition consistent with DNC (56.3% vs. 37.5%) or when DNC has been officially declared (87.5% vs. 56.3%) when compared to countries with legislation and/or guidelines. In those countries where there is legislation to inform the family about DNC after it has been confirmed, in practice this is done on 83.3% of occasions. By contrast, only two-thirds of countries that use

guidelines will follow them in practice. In these countries, the possibility of DNC is discussed with the family at an early stage, when it is a likely outcome but has not yet occurred. Although these early discussions are not permitted by legislation and/or guidelines, they may still occur in 3 of 16 (18.8%) countries (**Table 2**).

In 22 of 32 countries (16 + 3+3 countries; 68.8%), the option of organ donation is only discussed with family after DNC has been confirmed, the family has been informed of the diagnosis and given time to accept that their relative has died. A less frequent practice is to discuss organ donation with the family earlier when the patient has a clinical condition consistent with DNC, but before the diagnosis (2+3+3 countries; 25%) or when progression to DNC is likely (3+ 3 countries; 18.8%) (**Figure 2**). Relatives are approached for organ donation after the confirmation of DNC in 100% of countries without legislation and/or guidelines on the timing of the family approach, and in 57.9% of countries with any type of regulation. However, the implemented practice is different; families are approached after confirmation of DNC in 80% of the countries with legislation and in 44.4% of those with guidelines. Only 50% of countries follow this practice even if it is regulated by both legislation and guidelines. In 15 countries, discussion about the possibility of organ donation is prohibited before DNC has been confirmed. Despite the legislation and/or guidelines, in practice this happens in 3 countries (**Table 3**).

The majority (28 countries) prefer decoupling the conversation informing relatives that DNC has been confirmed from the conversation exploring the option of organ donation. The conversations are usually separated in time and may be led by a different HCP. For example, a medical doctor informs and discusses the confirmation of DNC with the family and the same doctor, or a donor coordinator, explores the potential for organ donation with them. In practice, the conversation about the confirmation of DNC is led by a medical doctor in 28 countries and by the donor coordinator in the other 8 countries. In two countries not regulating this process, this conversation can be led by a nurse. In practice donor coordinators lead the conversation regarding the confirmation of DNC in only 3 of 6 countries where this practice is permitted.

Nurses and donor coordinators are, however, more commonly involved in the organ donation conversation with the family. The family is approached by a medical doctor (alone on 15.6% of occasions, with a donor coordinator in 31.3%, and with a nurse in 9.4%), by a donor coordinator alone in 25%, and by all in 15.6% (one country did not answered this question). In eight countries, donor coordinators are not allowed to participate in the family approach to discuss organ donation; despite this, they are involved in the family approach in 2 of these countries.

Information on Family Decline/Consent Rate for Organ Donation

Our study results and data from the *Newsletter Transplant* [4, 17–20] shows that the annual number of family interviews pmp in the DBD setting between 2016 and 2020 varied among countries (mean 25.0–27.9). In Council of Europe member states there are on average 1.8 times more family approaches for donation than there are actual DBD donors (range 0.97–6.8 times more family approaches).

The mean proportion of the number of family declines to the number of family approaches was 18.8% (SD: 12.8%; $n = 13$). Two countries reported no family declines during the 5 years investigated. The mean family decline rate in comparison with the DBD rate was 30.5% (SD: 22.2%).

In view of the limited responses, the annual data for 2012–2017 from the *Newsletter Transplant* publications of the Council of Europe were also analyzed. In the examined 6 years period, 20 countries reported data for an average of 4.6 years. The rate of family declines was 26.7% as a proportion of the number of conversations (SD: 9.8%).

DISCUSSION

The World Health Organization's Guiding Principles on human cell, tissue and organ transplantation establish that "Organs may be removed from the bodies of deceased persons for the purpose of transplantation if: a) any consent required by law is obtained, and b) there is no reason to believe that the deceased person objected to such removal" [2, 22].

Accordingly, donation and transplantation systems worldwide must develop strategies to exclude any known objection to donation by the potential donor. Jurisdictions should also introduce legislation and/or guidance to regulate the consenting process. Consent legislation is rooted in one of four principles: altruism (opt-in and opt-out), incentivizing (financial and non-financial), mandating (the law obliges all adults to register their donation decision), and confiscating (organs considered a public resource). Systems primarily based on altruism are the most common. In opt-in systems, organs can be recovered from a deceased individual if the person or their legally recognized representative expressly consents to it. In opt-out systems, organs may be recovered from a deceased individual, unless they had previously expressed their opposition to donation [23].

Opt-out consent systems are more widespread in Europe and recently more European countries have introduced opt-out legislation. Netherlands and England implemented opt-out legislation in 2020 [24], Scotland in 2021, Northern Ireland plans to implement opt-out legislation in 2023 and Switzerland in2024. Despite this, the evidence that opt-out systems increase consent or donation rates is not scientifically robust and remains inconclusive [21, 25]. An individual's donation decision should always be established as best as possible and the individual's autonomy and right to self-determination should be respected. However, in practice families may overrule this principle because some countries' legislation allows them to do so. Family overrides raise ethical questions in both opt-in and opt-out systems. Some consider that overriding an active decision to opt-in made by an individual during their lifetime breaches that individual's autonomy. Others may also question the ethics of allowing a family override in opt-out countries, since arguably an individual is more likely to record a strong objection to donation than they are to record a willingness to donate. Overrides also undermine the philosophy of utilitarianism.

Therefore, in many European countries, there is a mismatch between the legislation and the way consent to organ donation is ascertained in practice. The implementation of practices that are not necessarily aligned to the legislation and guidance may occur because HCPs choose to incorporate deeply rooted societal values, etiquettes, and traditions in the way they approach and deal with grieving, bereaved families. Another issue perpetuating this mismatch is that when an individual has not registered a decision to be an organ donor or informed their family of this decision, the default position in practice is to assume that the individual did not wish to be an organ donor. This assumption influences the consent rate in both consent models, significantly reducing the donor pool. These issues are important when training HCPs on how best to approach the family for organ donation, particularly when the potential donor's decision is unknown.

Some countries with either opt-in or opt-out legislation operate both opt-in and opt-out registers. Other countries do not maintain either type of register, irrespective of whether they have implemented opt-in or opt-out legislation. It is unclear whether registers increase a country's consent rate or improve other donation metrics. Their impact is also difficult to assess when families are allowed to override an individual's registered organ donation decision. Opt-in registers are, however, helpful in that the consent rate is significantly increased when the family and HCPs know that the individual had registered a decision to donate their organs, compared to when their decision is unknown [3].

The process of diagnosing DNC is regulated in all member states, with most preferring to use legislation, possibly in the belief that it is stronger and safer than guidance. The timing of delivering information about brain death and organ donation to the family, and who delivers it, is regulated in half of the countries, indicating that these areas of practice are considered important enough to justify regulation and reduce variations in practice. Since the determination of death must not be influenced by any consideration of donation, more than half the responding counties have introduced regulations to allow the withdrawal of mechanical ventilation and organ support after a diagnosis of DNC has been made in situations where organ donation cannot proceed. These regulations help increase the public's acceptance and understanding that DNC is death, and that all organ support will be stopped. Post-mortem organ donation simply influences the timing of withdrawal of ventilation.

The timing of discussing brain death and the possibility of organ donation with the family is regulated in most countries, and usually involves separate conversations. In practice both conversations take place at an earlier stage than would be allowed by regulation. In countries that do not regulate the timing of these conversations, information about organ donation is usually provided only after the confirmation of brain death.

This practice of only approaching the family after the confirmation of death is, however, only relevant to the practice of DBD. It is not possible in controlled DCD or in the setting of Intensive Care to Facilitate Organ Donation (ICOD). ICOD is the initiation or continuation of intensive care measures with the intention of maintaining donation potential in patients with a devastating brain injury where death is anticipated, and active treatment is deemed futile [26, 27]. The incorporation of organ donation into their end-of-life plan can only be achieved following a discussion with the family before the patient dies, informing them of the purpose of initiating or continuing intensive care and establishing whether this is consistent with the patient's values and preferences. Different processes are required for these ethically, professionally, and legally challenging pathways, and regulatory frameworks are essential for such pathways to succeed [28].

Member states of the Council of Europe vary as to who should discuss brain death or organ donation with families, and there is a mismatch between the regulations and actual practice. While there is little evidence to support which HCP is best placed to discuss brain death with families, it is reasonable to expect that this is best done by HCPs with knowledge and expertise of brain death and training on how to communicate. Similarly, it is reasonable to expect that those with knowledge and expertise of organ donation and training in discussing organ donation are best placed for this task. There is significant evidence that when trained donor coordinators lead this conversation, the consent rate is significantly higher than when other HCPs do this [3].

Given our secondary objective of assessing and describing the impact of legislation on organ donation consent rates, the results of our "snapshot" should be interpreted with caution before drawing any conclusions. For example, there is wide variability in the relationship between the number of family approaches weighted by population and the number of deceased donors: one country had 7 times more conversations about donation pmp than organ donors pmp. It is easy to conclude that this is due to the timing of the approach to the family or who leads that approach. It is also possible to conclude that this is a result of other regulations or practices in that country. Such conclusions are, however, unjustified as they are narrow in focus and do not consider the wider picture of the different values and traditions held by the country's population and HCPs.

Data on the number of family declines to organ donation were provided by only 13 of the 34 respondents (38%), so it is impossible to draw any conclusions on the effect of a country's legislation and its practices on the consent rate for organ donation. It is essential that all countries in the Council of Europe take responsibility for collecting, recording, and sharing data on the number of family approaches for organ donation and whether such conversations result in a family consenting to or declining organ donation.

The quality of the organ donation process may be improved by our recommendations (**Figure 4**). More granular data on all aspects of the process of approaching a family for donation will be required if we are to identify and understand the modifiable factors that may influence the outcome of such conversations at a local, national, and international level. It is also important to identify why families who initially decline organ donation later consent to donation, and why some families who initially consent to donation withdraw that consent. Any assessment of whether one consent system is superior to another should consider not only donation metrics, but also other relevant outcomes from the donor family perspective.

In conclusion, the public and HCPs should be made aware of the regulations governing deceased donation in their country and how

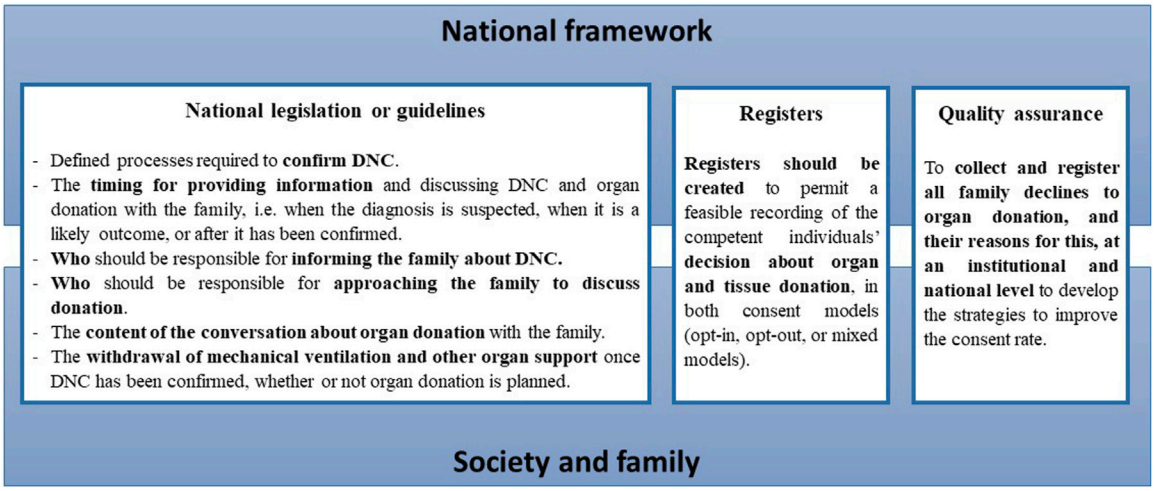


FIGURE 4 | The recommendation to member states of the Council of Europe to improve the quality of the organ donation process. A robust national framework is built to address all the relevant legal, professional, ethical and practical issues associated with deceased organ donation pathways and transplantation. The public is provided updated information on the national legislation about deceased organ donation procedures and donation metrics. This should be responsibility of the relevant national organ donation authority and the government.

they are interpreted and implemented in practice. This is particularly true for the consent model established in their jurisdiction. This will allow individuals to consider their donation decision, record it and make their families aware of that decision. Our study shows that many Council of Europe member states regulate many aspects of the deceased donation pathway. Some states use legislation, guidelines, or both to regulate each step of the pathway; other states do not regulate some steps at all. The regulations vary among individual states, but in most states, there is some degree of mismatch between what the regulations state and what is actually done in practice. The reasons for this mismatch need to be better understood. In some situations, it is possible that HCPs are unaware of the regulations. However, it is also possible that the regulations do not align with routine practice. Finally, it is likely that organizations and individuals interpret and implement regulations in a fashion that they believe respects the long-standing traditions and etiquettes of families and of that country, all of which tend to be deeply rooted when dealing with death, bereavement, and grief.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving humans were approved by European Committee on Organ Transplantation (CD-P-TO). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

SM, BD-G, EC, ML, DA, AR, JF, FI, and JJ contributed to conception and design of the study. SM organized the data collection. SM and AS performed the statistical analysis. SM, AS, BD-G, AP, FP, DA, AR, FI, JJ, and AM wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the following for their invaluable data collection contribution: David Pérez Surribas (Andorra), Martina Brix-Zuleger (Austria), Siarhei Liashchuk (Belarus), Luc Colenbie (Belgium), Evelina Tsvetkova (Bulgaria), Martina Anusic Juricic (Croatia), Chrystalla Despoti (Cyprus), Milos Adamec (Czech Republic), Helle Haubro Andersen (Denmark), Virge Pall (Estonia), Heikki Mäkisalo (Finland), Meriam Lamraoui (France), Gia Tomadze (Georgia), Georgia Menoudakou (Greece), Jean O'Reilly (Ireland), Tamar Ashkenazi (Israel), Letizia Lombardini (Italy), Mindaugas Masedunskas (Lithuania), Tatiana Timbalari (Moldova), Morten

Hagness (Norway), Jarosław Czerwiński (Poland), Catarina Bolotinha (Portugal), Victor Zota (Romania), Vladimir Resanovic (Serbia), Ivana Dedinska (Slovakia), Helena Almén (Sweden), Beyeler Franziska (Switzerland), Nichon Jansen (Netherlands), Liz Middlehurst (United Kingdom).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11498/full#supplementary-material

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ORIGINAL RESEARCH
published: 04 July 2022
doi: 10.3389/ti.2022.10466

Changing to an Opt Out System for Organ Donation—Reflections From England and Netherlands

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Recently England and Netherlands have changed their consent system from Opt In to Opt Out. The reflections shared in this paper give insight and may be helpful for other nation considering likewise. Strong support in England for the change in legislation led to Opt Out being introduced without requiring a vote in parliament in 2019. In Netherlands the bill passed by the smallest possible majority in 2018. Both countries implemented a public campaign to raise awareness. In England registration on the Donor Register is voluntary. Registration was required in Netherlands for all residents 18 years and older. For those not already on the register, letters were sent by the Dutch Government to ask individuals to register. If people did not respond they would be legally registered as having "no objection." After implementation of Opt Out in England 42.3% is registered Opt In, 3.6% Opt Out, and 54.1% has no registration. In contrast in Netherlands the whole population is registered with 45% Opt In, 31% Opt Out and 24% "No Objection." It is too soon to draw conclusions about the impact on the consent rate and number of resulting organ donors. However, the first signs are positive.

Keywords: organ donation, Opt Out, Opt In, Donor Register, consent rate, consent system

INTRODUCTION

Recently England and Netherlands changed their consent system for deceased organ and tissue donation from Opt In to Opt Out. The aim of this article is to give insight into the process of changing the law, implementation and initial impact.

OPEN ACCESS

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Received: *25 February 2022*
Accepted: *25 May 2022*
Published: *04 July 2022*

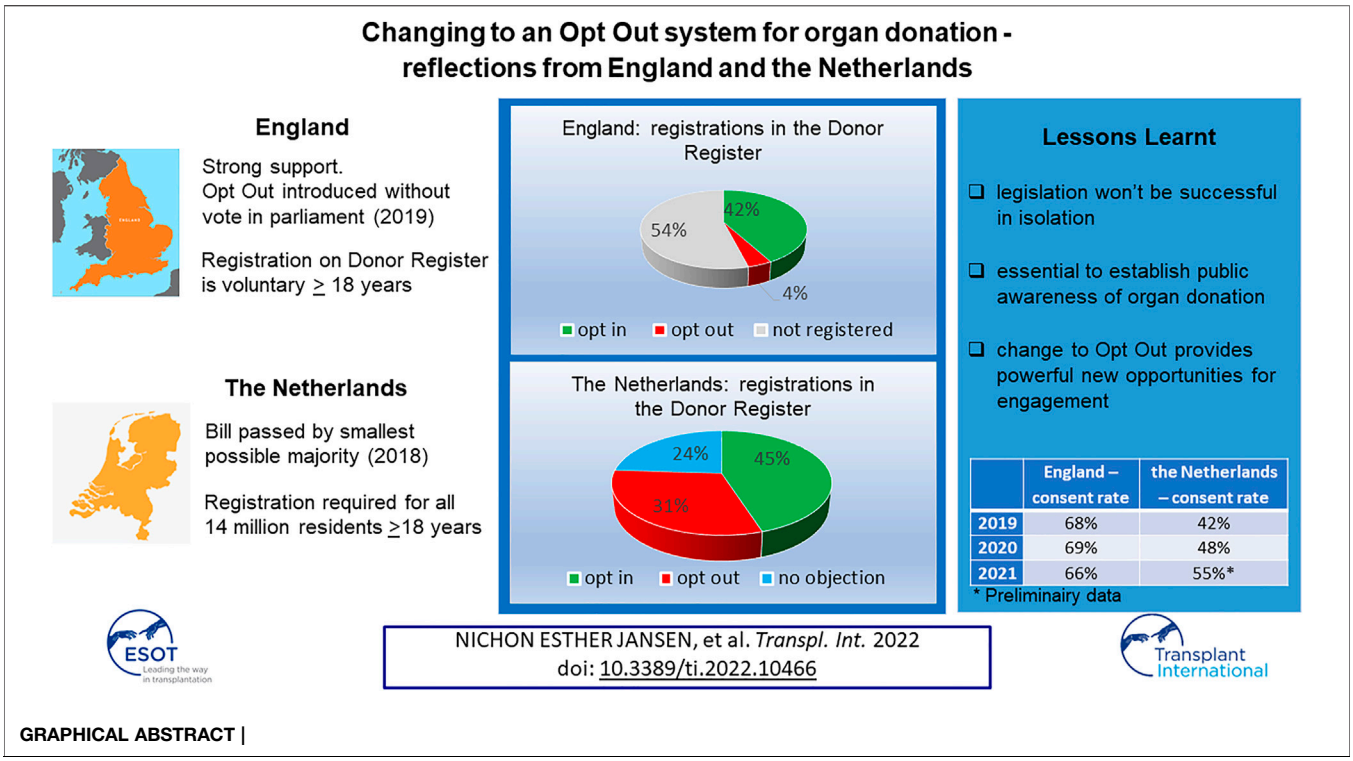
Citation:
Jansen NE, Williment C, Haase-Kromwijk BJJM and Gardiner D (2022) Changing to an Opt Out System for Organ Donation—Reflections From England and Netherlands. Transpl Int 35:10466. doi: 10.3389/ti.2022.10466

THE DONATION LANDSCAPE PRIOR TO OPT OUT

England

The modern era of organ donation in the United Kingdom (UK) commenced in 2008 with the implementation of recommendations from the Organ Donation Taskforce.[1] Key initiatives included the creation of National Health Service Blood and Transplant (NHSBT) as a single donation organisation for the UK, resolving ethical and legal barriers to donation, and the introduction of champion roles in hospitals for donation such as the clinical lead for organ donation (normally an intensive care doctor) and a lay chair of an organ donation committee; both roles to be supported by the embedding of specialist nurses for organ donation into intensive care units. This change led to a

[1]https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/4245/organsfortransplantstheorgandonortaskforce1streport.pdf.



GRAPHICAL ABSTRACT |

50% increase in deceased donations by 2013 but consent rates remained stubbornly static (1). A second national strategy in 2013 "Taking Organ Transplant to 2020" called for a revolution in consent (2). This would be achieved through marketing and media campaigns, specialist nurse training and specialisation in the family approach for consent and emphasising that the family discussion about organ donation should be a collaborative and combined effort between hospital staff and the specialist nurse for organ donation. Consent rose accordingly but not to the levels peer nations were achieving. To increase consent, societal change was required.

Wales passed Opt Out (Deemed Consent) legislation in 2013, with implementation in 2015 (3). Previously, individuals could make their donation decision known by opting in (registering) on the National Health Service Organ Donor Register (NHS ODR), or by verbally expressing to family and friends they would be willing to be a donor after death. Where no known decision in life had been made, the law gave the decision regarding organ donation to the family. Following the introduction of Opt Out in Wales, the NHS ODR was changed to allow individuals to register an Opt Out decision. Since the NHS ODR is applicable across the UK, this allowed anyone in the UK to register a decision not to donate. Applicable only in Wales, if no organ donation decision was known, the individual would be considered to have no objection to becoming a donor.

Support in England for organ donation led the government to seek to amend the consent legislation to Opt Out in 2019.

Netherlands

In 1997 the Organ Donation Act was passed, based on an Opt In consent system for organ and tissue donation. All people aged 18 years and older received a letter from the government, asking them to register their donation preferences. The preferences allowed in the Donor Register were; "Yes, I want to be a donor," "No, I do not want to be a donor," "Decision by next of kin," or "Decision by a specific person." Ten years after implementation of the law 5.2 million (40%) of the 13 million Dutch residents, from 18 years and older, had registered their donation preferences. Despite this, there were still not enough donors to meet the number of patients on the waiting list.

In 2007, a TV show revealed in a dramatic way the need for more organ donations. In a live national broadcast, "Dutch Donor Show," a terminal ill woman was asked to choose between three candidates and donate her kidney to that person. At the moment she announced her chosen recipient, the presenter intervened, explaining that this offer was not for real. It was a fake scenario. The potential donor was an actress but the kidney recipients on the show were genuine and on the waiting list, all fully aware of the nature of the show. Not even the Dutch Transplant Foundation or the government had been made aware of the truth. The aim of the broadcast was a wakeup call for politicians and Dutch society to do something about the shortage of organ donors for patients on the waiting list for a transplant.

Following the show, a coordination group "Organ Donation" was formed in 2007, consisting of several stakeholder organisations and led by an independent chairman. Within 1 year a Master Plan Organ Donation (4) was established based on 4 pillars: 1) changing the Opt In consent system into an Opt Out system; 2) facilitating organ donation in hospitals in a more efficient way; 3) education of the public to positively support organ donation; 4) taking away financial barriers for

living organ donation. The overall aim was to increase the number of organ transplants by 25%: 15% by changing to Opt Out and 10% through improvements in donor hospitals and public information. In 2014 the Master Plan Organ Donation was evaluated, the increase in numbers of transplants was 11%.[2]

Three out of the four pillars were actively being addressed. For a more efficient way to facilitate organ donation, hospitals were divided into seven donation regions. Donation intensivists were introduced in larger hospitals together with a donation coordinator, to support and promote donation policy in a cluster of hospitals. National teams were introduced to facilitate organ retrieval in donor hospitals. Several campaigns were launched to educate the public in organ donation. The living donor program had achieved considerable success since 2008 (306–520 transplants in 6 years, 70%) by removing financial barriers and through the implementation of organisational and promotional activities (5). The only pillar that had not been addressed was changing to an Opt Out system.

PARLIAMENTARY PROCESS TO INTRODUCE OPT OUT

England

There had been many failed attempts to introduce Opt Out legislation to England over the last 30 years but was achieved on 20th May 2020. In October 2017 the Prime Minister stated her intention to shift "the balance of presumption in favour of organ donation" and "introduce an opt out system for donation."

Fortuitously a parliamentarian from the opposition party had successfully had his name drawn from a legislation ballot (a system which allows a few "Private Members Bills" to be considered by parliament from a randomly chosen subset of legislation suggestions), for a new Opt Out Bill. This led to an unusual alignment of opposing political parties, working together on a new policy. Due to this cross party support, the Bill progressed through Parliament and never had to be put to a vote.

England's Opt Out legislation built on the positive experience in Wales and Parliament was further reassured by the response to a public consultation on the draft Bill, which asked how Opt Out should be introduced. The Government usually expects between 200 and 500 responses; over 17,000 responses were received. The responses were supportive and gave a strong steer for the issues needing to be addressed.

The main issues raised by the public were: the need for autonomy and individual choice; the role of the family; the need to respect faith and beliefs through the donation process. The government worked closely with NHSBT to identify ways to ensure that these issues were addressed. Ministerial commitments also secured additional resources such as increased recurrent funding.

The final inspiration came from two young people—Max Johnson and Keira Ball. When the Bill was introduced, Max Johnson, a 9 year old boy, was in desperate need of a heart transplant. The UK media—particularly the Mirror newspaper—campaigned for the introduction of Opt Out legislation. Max's life was saved through the gift of donation by Keira Ball, also aged nine, who tragically lost her life in a road traffic collision. The Opt Out legislation is known as Max and Keira's Law, in their honour.

FIGURE 1 | Marketing NHS new law organ donation.

Netherlands

On the 1st of July 2020 the Opt Out system for organ donation was implemented in Netherlands. Changing the organ donation law from an Opt In consent system into an Opt Out system had not been easy. It took more than 12 years of political discussion to reach the milestone of a majority.

In 2012 a member of the House of Representatives prepared a Bill to change the consent system into an "Active Donor Registration." On the 16th of September 2016 the Bill was passed by the smallest possible majority in the House of Representatives, 75 members voted in favour of the Bill and 74 members against. On the 16th of February 2018 the vote in the Senate again ended in a close call, 38 senators voted in favour of the Bill and 36 members against. The Bill could only pass after a required amendment to develop a "Quality Standard Donation," which describes the role of the doctor and the family in the

[2]https://zoek.officielebekendmakingen.nl/kst-28140-85.html.

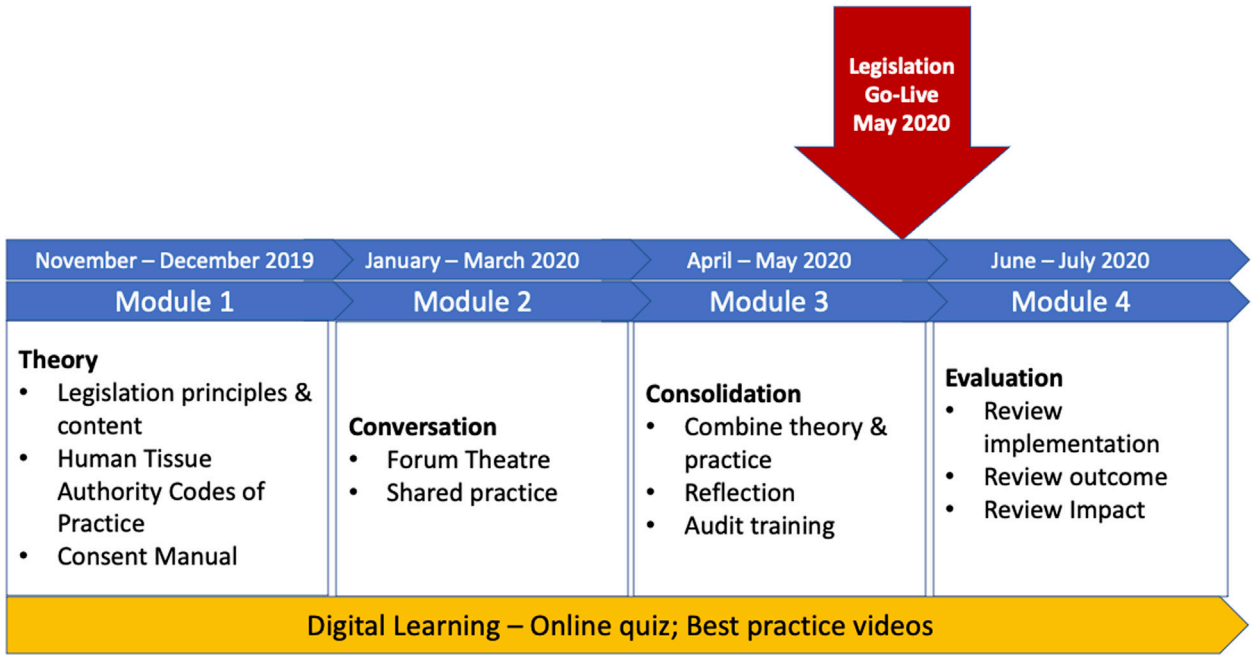


FIGURE 2 | Training programmes new donor law for Specialist Nurses for Organ Donation.

donation conversation, based on the different outcomes of the Donor Register.

The Active Donor Registration means that Dutch residents without a registration in the Donor Register, 7 million, will be asked by letter to register their donation preferences (same options as in the Opt In system). If they do not respond to a first and second letter, they will receive a third and final letter with the confirmation that they will be registered as having "No Objection" to organ and tissue donation. Under the new legislation "No Objection" would legally be considered the same as a registration of "Yes, I want to be an organ donor." Registrations can be changed 24 h a day *via* the Internet. It could therefore be argued that while the change in law was to introduce Opt Out, it has similarities to a model of mandated choice for organ and tissue donation (6).

IMPLEMENTATION

England

The learning from Wales made it clear that there needed to be at least a year of marketing activity, so the public understood the change in legislation and what action they should take. The "Pass It On" campaign was developed to include advertising on TV, radio and social media, as well as posters and billboards. The marketing gave clear messaging as shown in **Figure 1**.

In the first 9 months, the advertising was kept low-level, but this ramped up significantly in the final 3 months prior to the go-live date. The onset of the COVID-19 Pandemic required the removal of the "Pass it on" slogan, but the general message remained consistent.

There was also engagement with different communities, to raise awareness of the change in law and dispel myths. Significant concern was expressed by some regarding the role of the family, the loss of autonomy and the impact on adherence to faith/belief requirements following death. Following close working with community and faith groups to discuss their concerns and identify approaches to provide reassurance, the NHS ODR was amended to enable people to record that they wanted their faith/beliefs to be taken into consideration.[3] Community champions were provided with materials to raise awareness including a guide to the journey through intensive care and organ donation.

Work was also underway to ensure the clinical donation community were aware of the change in law and its potential impact. Codes of practice were developed by the Human Tissue Authority, to interpret the legislation and provide best practice guidance (7).

In the UK the main healthcare professional who makes the family approach to discuss organ donation is the Specialist Nurse for Organ Donation. The government provided funding for recruiting 27 additional nurses and training programmes were established for all Specialist Nurses. This included four modules, as shown in **Figure 2**. As the pandemic evolved these moved to virtual training.

The digital infrastructure was also changed to support the legislation. The NHS ODR already included the ability to opt out, as well as opt in, as a result of the Welsh legislation in 2015. The NHS ODR became integrated with the new NHS app, meaning

[3]https://www.nhsbt.nhs.uk/news/faith-and-beliefs-declaration/.

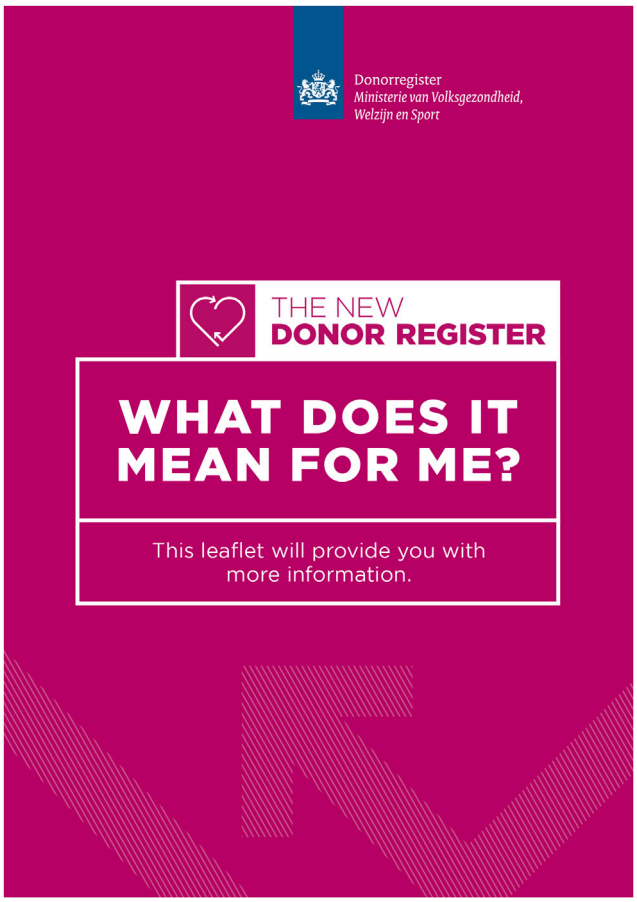


FIGURE 3 | Front cover of a leaflet sent by the Ministry of VWS explaining the new organ donation law.

that for the first time people could see and directly amend their own record. Online consent forms and associated paperwork were amended to enable records and databases to capture where a deemed consent scenario applied and the outcome.

The cost of implementation to NHS Blood and Transplant was £7.8 million for operational activity including funding the programme, changes to digital infrastructure and new staff appointments and training. Marketing allocation was £11.7 million with £7 million being spent in the last year before implementation. This was England's largest single organ donation marketing budget. Other costs to develop and implement the legislation change incurred, e.g., government, local organ donation committees.

Netherlands

The law "Active Donor Registration," Opt Out system, was implemented on the 1st of July 2020, which was during the COVID-19 pandemic, just after the first wave. Due to this pandemic the Minister of Health, Welfare and Sports (VWS) decided to postpone the implementation process, including media campaigns, until the 1st of September 2020. The process of sending letters to 7 million residents without a registration, lasted until the end of July 2021. At that date the donation preferences of the whole population from the age of 18 years onwards, 14 million in total, were registered in the Donor Register.

To prepare the Dutch population for the change of law the Ministry of Health, Welfare and Sports (VWS) was responsible for the public campaigns (e.g., see **Figure 3**) and the Dutch Transplant Foundation for educating medical professionals.

The Ministry of VWS released a significant amount of money to implement the new law. In total nearly €40 million; €24 million for sending the letters using the existing structure of the tax authority and €15 million for media campaigns. It was a major communication challenge, as the law impacted on everyone in Netherlands. The aim was to achieve a minimal level of knowledge about the new law for all different types of residents, for example; people with mentally impairment, people with low literacy, inmates, people with a migration background, homeless people, elderly people in nursing homes, blind and visually impaired, deaf and hearing impaired.

The mass media campaigns were divided into two phases. The first phase started in 2019 and aimed to inform the public about the new donation law and motivate and activate Dutch residents, without a registration, to actively register their donation preferences. In this phase registration was voluntary. The second phase started in 2020 by sending people letters to register their donation preferences. If they did not respond they would be legally registered as having "No Objection" to donation, which could be changed at any time. Since registration in this phase was required, the information in the campaign was explicitly neutral, not giving a direction to any resident. In addition to the mass media campaigns there were initiatives to reach out to target groups, for example faith groups, elderly in nursing homes, illiterate people, etc. (see **Table 1**). Meetings were organised in a small scale setting to get in close contact with people who may not be reached by mass media.

The Dutch Transplant Foundation was responsible for preparing medical professionals for the new donation law, including how to request for donation in accordance with the Quality Standard Donation. Training programmes were developed, not only for intensivists who approach families for organ donation, but also for physicians who are involved in tissue donation. Furthermore, the website of the Dutch Transplant foundation provides an interactive decision tree for the correct steps to approach families based on the donor registration. There is also a "Frequently Asked Questions" section on the website to help doctors.

IMPACT ON ENGAGEMENT

England

Whilst the change in law was considered a positive move to increase organ donation, it is the conversation, debate and education it prompted that will lead to the biggest benefits. The campaign encouraged people to consider organ donation, register a decision and speak to their family. The data would suggest that people followed this approach, as the numbers on the NHS ODR continue to rise and after over 17 months since the

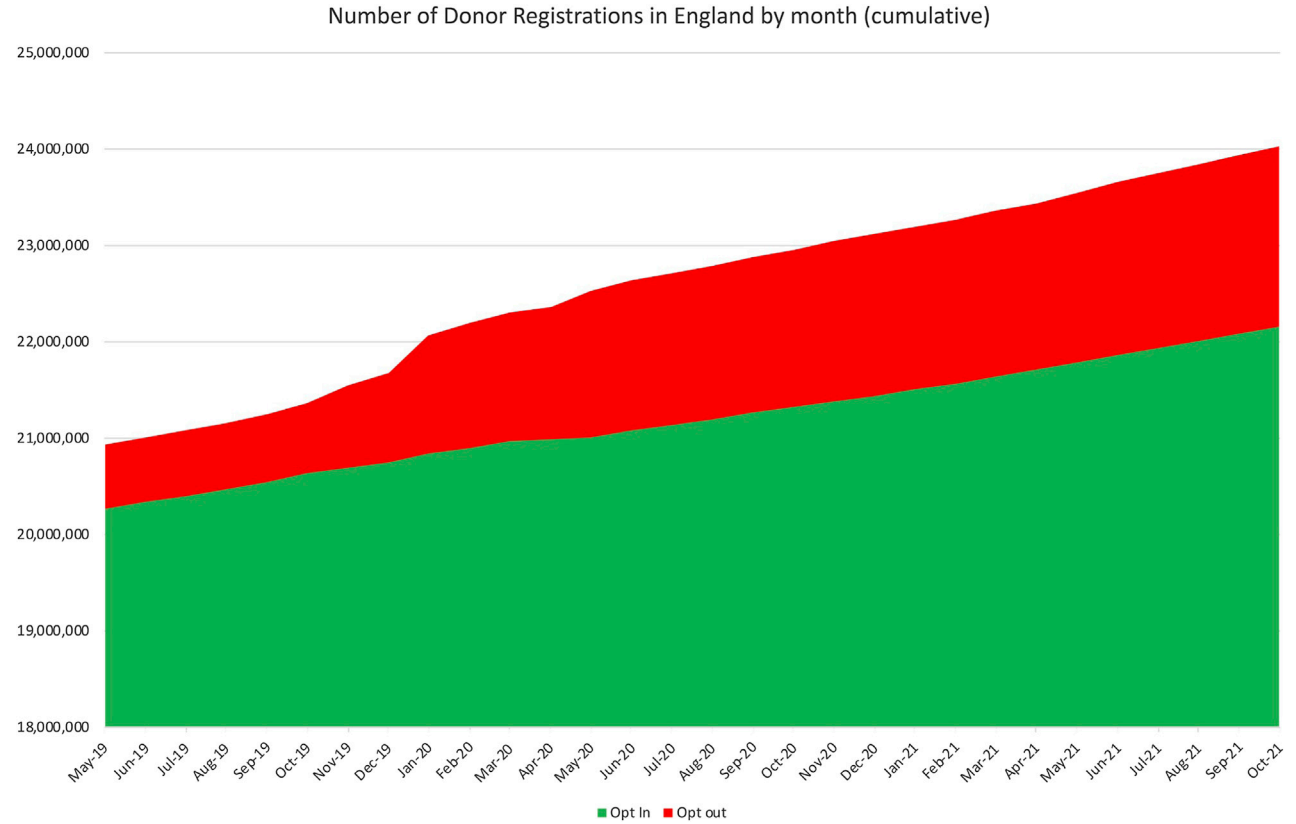


FIGURE 4 | Number of Donor Registrations in England by month; May 2019–October 2021 NB. It is legally possible to appoint a representative to make a decision on your behalf, this requires in the UK a written application, and only 139 people (roughly equivalent to the yellow in **Figure 5**) from England have done so. Population of England aged 18 or over: 52,383,965.

original campaign, public awareness of the law change is sustained at around 70%.

Further materials are also demonstrating the initial discussions held with stakeholders are having a longer term impact and supporting peer education. For example, in September 2021 the Office of the Chief Rabbi launched new education materials to raise awareness of organ donation and the impact of the change in law.[4] Education is also being taken forward in schools, with the law prompting the introduction of blood, organ and tissue donation into the mandatory curriculum for secondary school children. Patient support groups and donor families had been lobbying for this change for nearly 2 decades without previous success. NHSBT supported this by providing teaching resources.[5]

Netherlands

It was important that the public were aware of the impact of the new law and that they were required to be on the Donor Register. If they had not responded to the letters they would be registered as having "No Objection." In practice, although consent for donation is given by the donor, families need to know each other's donation preferences as donation will only take place after informing the next of kin. All media campaigns launched by the Ministry of VWS about the Opt Out system were aimed at encouraging people to talk about organ and tissue donation and register their preferences. The effects of the campaigns were monitored, before and during the implementation of the Active Donor Registration. The outcome of all campaigns is that 85% of the population has knowledge about the new law.[6]

To tackle the challenge of informing all residents in Netherlands, several "targeted" actions started. Special Donor Dialogue teams were trained, to raise awareness of the new law with community leaders of diverse populations. Unfamiliarity with the subject of organ and tissue donation and language barriers, such as low literacy, can play a role in the number of registrations in the Donor Register.[7] The Donor Dialogue team organised meetings in several neighbourhoods in the four largest cities in Netherlands, to discuss donation and how this relates to the culture and religion of the participants.

[4]https://chiefrabbi.org/all-media/changes-to-english-law-on-organ-donation-faqs/.
[5]https://www.nhsbt.nhs.uk/how-you-can-help/get-involved/download-digital-materials/donation-teaching-resources/.
[6]https://www.rijksoverheid.nl/documenten/kamerstukken/2021/07/07/kamerbrief-over-afronding-implementatie-nieuwe-donorwet.
[7]https://inclusia.nl/projecten-2/50-jaar-migratie/.

TABLE 1 | Summary of implementation measures in England and Netherlands.

	England	Netherlands
Media/Marketing campaigns	TV commercials Radio commercials Online and social media campaigns Billboards	TV commercials Radio commercials Online and social media campaigns Billboards Door-to-door newspapers/flyers
Targeted actions	**Before the law** Focus groups informed implementation e.g., Paediatric, Socio-economic, Faith and beliefs **During implementation** Faith and beliefs engagement Community engagement Ethicists e.g., British Medical Association ethics committee, Nuffield Council of Bioethics Organ Donation Regional Collaboratives Intensive Care Society State of the Art 2019 drama production "Choose your own organ donation approach"	People with low literacy: www.hoewerktorgaandonatie.nl People with learning difficulties: www.vgn.nl/nieuws/update-16-3-faq-nieuwe-donorwet-voor-zorgorganisaties People with a migration background: www.donorregister.nl/voorlichtingsmateriaal/arabic Deaf and hearing impaired: www.donorregister.nl/voorlichtingsmateriaal/nederlandse-gebarentaal Homeless people: Information packages were sent to social care counselors and social relief institutions People in nursing homes: Tailor-made information campaign aimed at intermediaries (informal carers, carers, family) Blind and visually impaired people: Audio file was distributed to interest groups of blind people Inmates: Information packages were distributed to prisons Information meetings in the 4 largest cities with community leaders of diverse populations—Donor dialogue teams: www.inclusia.nl/projecten-2/50-jaar-migratie/
School education	Published teaching materials and organ donation became a mandatory part of secondary school curriculum	Guest lectures Online education package www.donorwise.nl
Call centre	Call centre handled calls from the public regarding change in the law and requests to record a decision on the NHS Organ Donor Register 20,000 calls between May 2019–December 2020 to a dedicated line In addition to 46,000 calls received via our standard NHS Organ Donor Line (on any topic)	Call centre handled calls from the public regarding change in the law and registration in the National Organ Donor Register 46,000 calls between July 2020 until May 2022 In addition 40,000 calls received on any topic about donation
Training medical professionals	Face to Face (pre-COVID), then virtual online training Video examples can be seen at: https://www.odt.nhs.uk/deceased-donation/best-practice-guidance/consent-and-authorisation/	Online training Practical training in the hospitals www.transplantatiestichting.nl/medisch-professionals/donatiegesprek

For many years, with funding from the Ministry of VWS, the Dutch Transplant Foundation has run "Donorwise," an education package for primary and secondary schools, and a yearly campaign to encourage those turning 18 to register their donation preferences. Following the law change the yearly campaign now "requires" those turning 18 to register a donation decision.

IMPACT ON NUMBER OF REGISTRATIONS IN THE DONOR REGISTER BEFORE AND AFTER THE CHANGE OF LAW

England

Since Wales implemented Opt Out in 2015, anyone in the UK has been able to register an opt-out on the NHS ODR. As of 20 September 2021, 3.3% of the English population (3.6% of the population 18 years or over) had registered an opt-out decision on the NHS ODR, compared to 6.2% in Wales (Opt-in: England: 39.2%; Wales 42.7%). The largest spike in opt-out registrations occurred in January 2021, 5 months before the law was implemented, when 295,000 individuals registered an opt-out decision. This was associated with fake news circulating on social media. The next highest month for opt-out registration was 144,000 corresponding to May 2021, when the law was implemented. In the 5 months since the law was implemented there have been no peaks in opt-out registrations and an average of 23,000 people register an opt-out each month compared to 73,000 opt-in (**Figure 4**).

Netherlands

When the process of sending registration letters to 7 million non-registered residents was completed, by the end of July 2021, the impact on the number of registrations compared to the beginning of 2020 was as follows.[8] The registration "Yes, I want to be a donor" increased by nearly one million (from 3.8 million to 4,8 million), the number of registration "No, I don't want to be a donor" increase even more (from 2.3 million to 4.3 million), the "Decision by next of kin"/"Decision by a specific person" showed an increase from 0.8 million to 1.5 million. The number of people who did not respond to the letters, asking to

[8]https://www.cbs.nl/nl-nl/nieuws/2021/40/3-7-miljoen-meer-actieve-registraties-in-donorregister-sinds-2020.

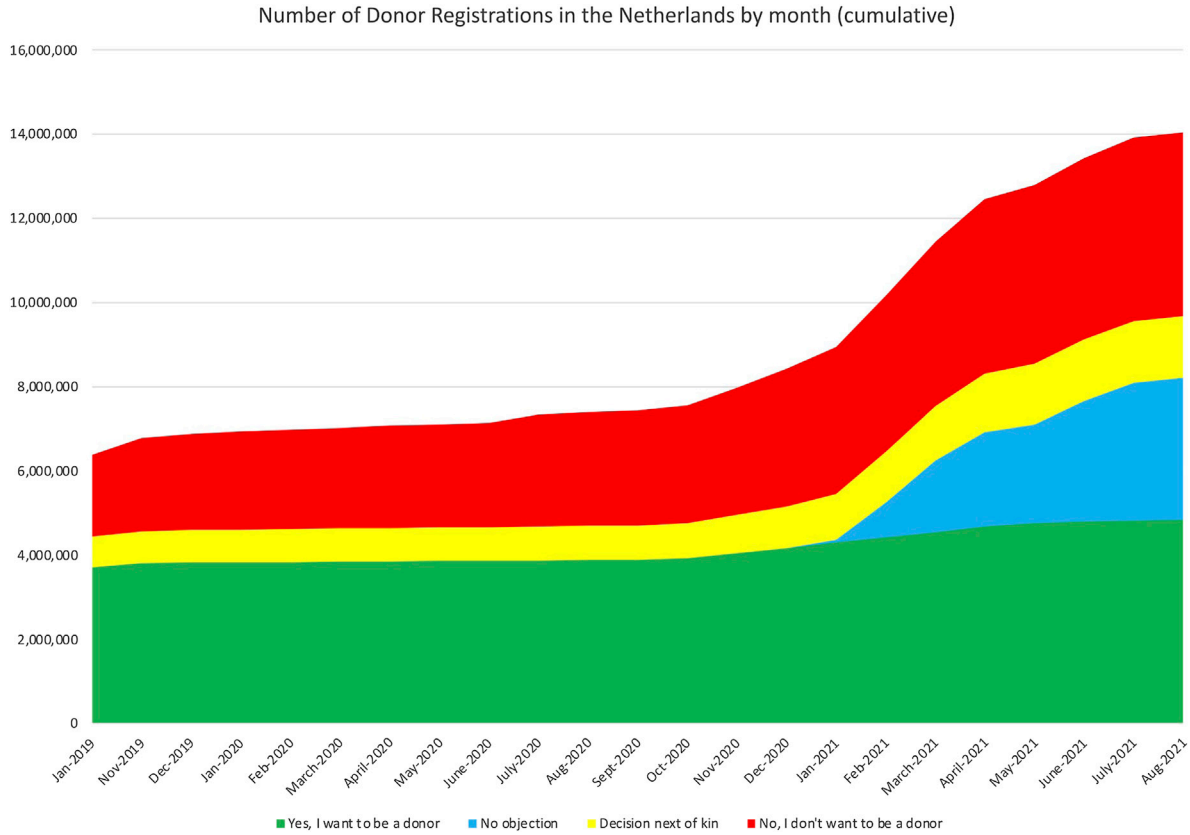


FIGURE 5 | Number of Donor Registrations in Netherlands by month; January 2020–Augustus 2021.

TABLE 2 | Comparison of England and Netherlands—donation consent system.

	England	Netherlands
Former consent system	Opt In. Consent from family if no Opt In registration	Opt In. Consent from family if no Opt In registration
Parliamentary process	Private Members Bill with no formal objections raised as it progressed through Parliament. No vote required	The Bill was passed with the smallest possible majority in the House of Representatives (1 person) and Senate (2 people)
Aim of changing the consent system	To better reflect the public support for organ donation and increase the consent rate	To know the donation preferences of the Dutch population. And for families to know the preferences of the donor when approached for donation
Messaging from the Government	Positive messaging highlighting: the law is changing; a call to action to make your organ donation decision and inform your family; promoting the benefits of organ donation for patients and donors	Neutral messaging highlighting: register your preference and inform your family; implications explained if individuals, who were not registered already, did not respond to the mailout letters
Registrations in the Donor Register	Voluntary registration Of the Population of England aged 18 or over 42% opt in, 4% opt out, 54% not registered, N/A no objection	Required registration Of the Population of Netherlands aged 18 or over 45% opt in, 31% opt out, N/A not registered, 24% no objection
Consent in practice	Families must be consulted Donation not enforced in the face of family objection	Families must be consulted Family arguments opposing donation respected

N/A, not applicable.

register their donation preferences, was 3.3 million. They are registered with "No Objection" to donation. Overall, the number of active registrations increased by 3.7 million, from 6.9 million in January 2020 to 10.6 million in August 2021. This means that 75% of the population registered their donation preferences. Adding the 3.3 million "No Objection" registrations means that all 14 million

TABLE 3 | Comparison of England and Netherlands—annual consent rate.

Calendar Year	England		Netherlands	
	Implemented 20th May 2020		Implemented 1st July 2020	
	Annual consent rate (%)	Monthly range (min %, max %)	Annual consent rate (%)	Monthly range (min %, max %)
2019	68	(64, 74)	42	Not available
2020	69	(65, 74)	48	Not available
2021	66	(58, 72)	55[a]	(43, 63)

[a]*Preliminary data.*

people from 18 years of age and above are registered in the Donor Register (**Figure 5**). This demonstrates that the communication was effective and that people were considering donation and recording their decision. This achieved a key aim of the new donor law to know the donor preferences of the whole population of 18 years of age onwards. This record provides clarity to the potential donor family when approached for organ donation.

An overall comparison of the Donation Consent System between England and Netherlands is shown in **Table 2**.

IMPACT ON CONSENT RATES AND DONOR NUMBERS

England

The experience from the introduction of Opt Out in Wales in 2015 was that change to consent rates did not happen immediately (8). However, in a study comparing Wales to England, after 3 years (2015–2018) the chance of consent in Wales was double that seen in England and donor numbers had risen more rapidly (Wales: 18.0 to 28.9 donors pmp; England: 20.0 to 24.3 donors pmp) (9). Interestingly, compared to Donation after Brain Death, the change in consent rates for Donation after Circulatory Death did not reach statistical significance.

By September 2020 England had its highest consent rate on record (70.3%) but since then there has been a steady decline in consent, see **Table 3**. Judging any change is extremely difficult owing to the COVID-19 pandemic and its impact on intensive care and society (10). Similarly, although donor numbers have risen in England this most likely reflects donation numbers recovering from the large drop in 2020 caused by the pandemic (11).

Netherlands

The first registrations of "No Objection" to donation only commenced in January 2021. It is too soon to draw definitive conclusions about the impact of the new donation law on the consent rate and organ donor numbers. Although we see positive signs, see **Table 3**.

Also the impact of COVID-19, especially the first wave, had a dramatic effect on the number of organ donors and number of transplantation. The total amount of all organ transplants decreased with 67% (12).

More time is needed to adjust to the new donation law, not only for the public but also for the doctors. The effect of the new law will be monitored closely in the coming years. Like the experience in England, unpicking the legislation change with the impact of the COVID-19 pandemic is extremely challenging.

Another benefit observed in Netherlands following the new donation law was the effect on the number of tissue donors. Tissue donors increased by 26% (from 1923 tissue donors in 2020–2427 in 2021) with consent rising from 20% in 2020 to 43% in 2021. What we saw in the former years is that "no registration" in the Donor Register was a very difficult situation for the donor family to respond to. We see now that consent registration based on a registered "no objection" gives a positive direction for the donor family, knowing the preferences of their loved one to donate. This results in a higher consent for tissue donation.

LESSONS AND RECOMMENDATIONS

From our experiences in England and Netherlands we would share the following lessons from introducing Opt Out:

(1) Legislation won't be successful in isolation - before the law changes it is essential to have an effective operational infrastructure for organ donation and an established public awareness of organ donation.
(2) Acceptance of the law will be easier if there is already widespread political and societal support for introducing Opt Out.
(3) Implementation of a required registration in the Donor Register for the whole population of 18 years onwards, as in Netherlands, poses different challenges in disseminating the message/campaigns.
(4) Implementing legislative change into practice requires a comprehensive plan covering: training of healthcare professionals, codes of clinical practice, digital infrastructure (e.g., Organ Donor Register changes), public awareness campaigns and engagement with stakeholders from all areas of society.
(5) The legislation can act as an enabler for wider change and engagement. For example by increasing donation funding for staff and public campaigns, changing school curriculum to make donation education mandatory, greater involvement of faith and community groups.
(6) There is a responsibility to monitor and evaluate the impact of Opt Out and share findings with the world wide donation community.

CONCLUSION

It's still too early to tell what the final impact of the introduction of Opt Out into England and Netherlands will be. We hope the reflections shared in this paper give insight into changing the consent system and help for any other nation considering likewise.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

NJ: Designing the article and drafting the manuscript; CW: Designing the article and drafting the manuscript; BH-K: Critically reviewing the draft and making improvements; DG: Designing the article and drafting the manuscript. All authors contributed substantially to the design of the article and its content.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

We would like thank Susanna Madden, Principal Statistician, Statistics & Clinical Research NHS Blood and Transplant. We would like to thank Anja Tangermann, senior policy advisor organ and tissue donation at Netherlands Ministry of Health, Welfare and Sports, for her input for this manuscript.

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ESOT | Transplant International

REVIEW
published: 28 November 2023
doi: 10.3389/ti.2023.11882

Brain Death and Organ Transplantation in Nepal: Navigating Cultural, Legal, and Ethical Landscapes

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Organ transplantation after brain death is challenging in Nepal due to cultural beliefs, legal frameworks, and ethical considerations. The Human Body Organ Transplantation (Regulation and Prohibition) Act (HBOTA) has not met with substantial success after its amendment. This review critically appraises the current state of brain death and organ transplantation in Nepal. It explores challenges, evaluates progress, and provides recommendations. Literature review of databases was conducted to find articles on brain death, organ donation, and transplantation in Nepal. Analysis of cultural, legal, ethical, and practical factors influencing implementation. Key challenges include limited awareness, religious beliefs, infrastructure gaps, and family consent barriers. HBOTA amendments in 2016 enabled brain death donations, however, donation rates remain low. Strategies are needed to improve public education, resources, personnel training, and collaboration. Cultural sensitivity and stakeholder engagement are crucial. A multifaceted approach addressing cultural, legal, ethical and practical dimensions is essential to improve organ donation rates in Nepal. Despite progress, substantial challenges persist requiring evidence-based strategies focused on awareness, capacity building, policy improvements, and culturally appropriate community engagement.

Keywords: organ transplantation, brain death, Nepal, cultural barriers, ethical considerations

OPEN ACCESS

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Received: *02 August 2023*
Accepted: *10 November 2023*
Published: *28 November 2023*

Citation:
Atreya A, Bastola P, Bhandari S, Nepal S and Bhandari PS (2023) Brain Death and Organ Transplantation in Nepal: Navigating Cultural, Legal, and Ethical Landscapes. Transpl Int 36:11882. doi: 10.3389/ti.2023.11882

INTRODUCTION

Organ transplantation after brain death diagnosis remains challenging in Nepal due to cultural beliefs, legal frameworks, and ethical considerations. The Human Body Organ Transplantation (Regulation and Prohibition) Act (HBOTA), enacted in 1998 and amended in 2016, aimed to facilitate organ donation and transplantation, but has not achieved expected success [1].

This review focuses specifically on the current landscape of brain death determination and organ transplantation in Nepal. It assesses the multifaceted cultural, legal, infrastructural, and ethical factors that influence the implementation of deceased organ donation programs. The review critically evaluates HBOTA legislation and amendments in terms of their impact on enabling or hindering organ donation rates. It highlights persistent barriers to transplantation in Nepal, including limited

public awareness, inadequate health infrastructure, lack of trained personnel, and religious/cultural opposition.

By synthesizing evidence on these challenges, the review offers targeted strategies and recommendations to improve donation rates within Nepal's sociocultural context. It emphasizes the need for collaborative efforts engaging key stakeholders—government, legal, healthcare, religious, public. The review intends to inform healthcare policies and practices to establish an ethical, effective, and context-appropriate organ transplantation system in Nepal.

This review provides evidence-based recommendations centered on addressing the specific cultural, legal, and ethical barriers to organ donation that are unique to the Nepali context. By providing a comprehensive analysis focused on Nepal's complex transplant landscape, this review seeks to catalyze improvements that will save more Nepali lives through organ donation.

DECLARATION OF BRAIN DEATH IN NEPAL

In Nepal, the first organ transplant from a brain dead donor occurred on 8 May 2018. Over the course of approximately 6 years, only 13 people have managed to receive organs from brain dead donors. Despite the introduction of a strong act on brain death in Nepal, expected success has not been achieved due to inadequate implementation measures [1].

According to the Human Body Organ Transplantation (Regulation and Prohibition) Act (HBOTA), the physician shall declare brain death according to Section 12(b) if there is a certainty of brain death in a patient during a health examination, and then the coordination unit should be informed immediately after declaring brain death. After the family approval, a postmortem examination should be performed, and a report should be prepared before proceeding to harvest organs [2]. According to HBOTA Section 12(f), the physician who examines the patient should be a) an MBBS doctor with a minimum of 5 years of experience in the field, b) registered with the Nepal Medical Council as a specialist physician, and c) a citizen of Nepal. According to Section 12(i) of the HBOTA, the doctor-declaring a person brain dead must be someone other than the surgeon performing organ transplantation [3].

In the health institution where the declaration of brain death is made, the following prerequisites must be fulfilled [2]:

a. At least one anesthesiologist or intensivist and a consultant specialist physician.
b. At least two ventilators.
c. An intensive care unit (ICU) with at least two monitors.
d. An operation theater with an anesthesia machine, monitor, ventilator, and electro-surgical unit (diathermy).
e. Facilities for arterial blood gas and computed tomography (CT) scan in the health institution or another local hospital.

Thousands of people are killed in road accidents in Nepal each year, and the number of fatalities has been increasing over the last decade [4]. Many of these unfortunate victims have the potential to become brain-dead organ donors [5]. In a country of about 30 million people, only about 2,100 have agreed to donate organs after brain death. In terms of the disease, this number is considered negligible [6]. Beating heart organ donors are literally nonexistent in Nepal as the beating heart hinders the acceptance by the general population that the person is clinically dead. Those families who reject the brain death of a person with a beating heart insist on keeping them on a ventilator in the belief that they have extended the life of the person. This situation results in the unfortunate misuse of ventilators for futile treatments, which impedes critically ill patients in desperate need of the necessary care and treatment they require [3].

Overall, the HBOTA guidelines need more detailed and flexible clinical, ancillary testing and implementation criteria for successful uptake of brain death diagnosis in Nepal. Based on a comparison of Nepali HBOTA guidelines with international practices on brain death diagnosis [7, 8], here are some key limitations and recommendations:

Limitations of Nepali HBOTA Guidelines for Brain Death Diagnosis

a. Strict prerequisite of having an intensivist and multiple specialist may not be feasible in many centers, limiting brain death diagnosis.
b. Mandating Nepali citizenship for diagnosing physicians can restrict expertise.
c. No clear minimum observation period stated before testing brain death.
d. No specific guidance on the clinical examination, apnea testing protocols or ancillary tests for brain death diagnosis.
e. No provisions for diagnosis in children or specific circumstances such as trauma, cardiac arrest, etc.
f. Only CT scans are needed for imaging, whereas magnetic resonance imaging (MRI), angiography, and nuclear scans may be needed.
g. Does not address documentation, qualifications, education or legal aspects in detail.

Recommendations for Improvement

a. Consider minimum observation periods before testing according to international guidelines.
b. Provide detailed guidance on the stepwise clinical examination, apnea testing protocols and ancillary testing criteria.
c. Include special considerations for diagnosis in children and specific clinical circumstances.
d. Allow for wider neuroimaging modalities like angiography, MRI, nuclear scans if needed.
e. Standardize the documentation and qualification requirements for diagnosing physicians.
f. Develop education programs and simulation training in brain death diagnosis.
g. Address legal provisions on time of death, dispute resolution, continued organ support, etc.
h. Relax strict specialty and citizenship requirements to increase the availability of qualified physicians, especially from foreign countries willing to work or volunteer in Nepal.

CHALLENGES AND BARRIERS FOR ORGAN DONATION

Multiple obstacles impede the donation of deceased organs in Nepal despite the legal recognition of brain death.

Although major religions endorse organ donation, deeply rooted cultural beliefs in Nepal pose barriers to the acceptance of brain death and deceased donation. For example, in many Nepali communities, bodies are traditionally cremated rapidly after death, reflecting the belief that the soul transitions quickly upon death [3]. Organ donation conflicts with this death ritual. There is also a reluctance to remove organs after brain death since the heart is still beating. Families insist on mechanical life support believing that it extends life, not accepting brain death [9]. Limited public awareness and established cultural beliefs hinder acceptance of brain death. Many Nepalis believe death only occurs after the heart stops beating, resisting organ donation if the heart is still functioning after brain death [3]. Misconceptions that donated organs may be improperly used or family care will be withdrawn also breed distrust. Targeted awareness campaigns are needed, especially in rural communities.

The issue of acquiring organs from deceased individuals becomes a challenge first, in cases involving deceased patients and their families. Second, the family's consent is crucial for organ donation to proceed. Without explicit consent from the deceased's family, it would be impossible to proceed with the removal of organs, even if the deceased had previously expressed their consent to be an organ donor. Respecting the wishes and emotions of the family is paramount in such circumstances [10].

A huge gap exists between the demand and supply of organs due to a lack of awareness and a shortage of potential donors. Even when an individual is pronounced brain dead, various obstacles hinder organ donation, including limited awareness, lack of trust and acceptance in the healthcare system, inadequate training of healthcare professionals [5], and incorrect perceptions of brain death.

Inadequate healthcare infrastructure poses barriers to thoroughly assessing and declaring brain death. Diagnostic facilities to conclusively determine brain death are concentrated in major cities [3]. Smaller centers lack ventilators, imaging technology, and specialized medical personnel required by HBOTA to declare brain death. Expanding the capacity of provincial hospitals is essential.

The shortage of trained medical staff also limits the donation processes of deceased. Doctors must receive specialized training to coordinate organ procurement and transplantation according to Nepal's legal requirements [2], but such training opportunities are limited. More programs are needed to develop this specialized expertise across the country.

DISPARITIES IN ACCESS TO TRANSPLANTATION IN NEPAL

There are several disparities in access to transplantation in Nepal, including gender, socioeconomic, and geographic disparities. Here are some examples:

Gender Disparities

Nepal exhibits one of the most extreme gender biases in organ transplantation globally. Among 178 kidney transplants performed at Nepal's two main transplant centers from 2008 to 2015, 84% of recipients were male while 75% of living donors were female [11]. The majority of organs (65%) were transferred from women to men, while only 6% were transferred from men to women. Mother-to-son donation was the most common (30%), followed by wife-to-husband donation (27%) [11].

This stark disparity stems from deeply gendered social and economic roles in Nepal. Women often feel compelled to donate kidneys to their husbands or sons due to fears of becoming destitute widows or failing their domestic duties [11, 12]. As wives are expected to manage household affairs, women also wish to avoid burdening extended families [11]. Sons represent critical breadwinners and mothers' parental obligations persist into their children's adulthood. In contrast, men rarely donate kidneys to female relatives as their livelihoods are not dependent on their wives' survival [11].

While women assert some agency in choosing to donate, their decisions occur within a patriarchal context that limits autonomy. Legal restrictions on living donation to unrelated individuals exacerbates gender bias by severely limiting women's donor options [11, 12]. Caste and socioeconomic factors further intersect to shape gendered motivations and perceptions around organ transplantation [11].

Targeted efforts to promote gender equity and men's donation to women are needed to address this imbalance. Increased public outreach and financial subsidies have been instituted but restrictive legislation continues to constrain women's access to transplantation in Nepal [11, 12]. Systemic changes transforming women's societal status and independence are critical to creating an ethical and equitable organ transplantation system.

Socio-Economic Disparities

Nepal exhibits extreme socio-economic disparities in access to organ transplantation. Due to high costs, transplantation is disproportionately accessed by wealthy socio-economic groups.

A study on 161 kidney transplant patients observed that higher socioeconomic status was associated with better quality of life for transplant recipients [13]. It provides some indication of socioeconomic disparities in access to kidney transplantation in Nepal [13]. Given the high costs and limited availability of transplantation services in Nepal, it is likely more affluent patients are better able to access these treatments [13]. The positive association between socioeconomic status and quality of life outcomes suggests wealthier patients may experience improved wellbeing and recovery after receiving scarce transplantation resources [13]. Although further research is needed, these results imply there may be significant socioeconomic barriers limiting access to organ transplantation for lower income Nepalese patients with end-stage renal disease. Tackling such disparities will be key to ensuring more equitable provision of transplantation services and improving outcomes for economically disadvantaged patients in need of vital organ transplants.

Caste and Education Based Disparities

Caste also impacts access to transplantation in Nepal. Recipients are disproportionately upper-caste Brahmin and Chhetri groups, likely reflecting greater household incomes. Costs pose major barriers to lower-caste and marginalized indigenous groups accessing transplantation through legitimate channels.

Educational status similarly impacts access to transplantation. Illiteracy rates are higher among lower castes and classes in Nepal. Lack of transplant awareness and inability to navigate complex medical systems impedes illiterate and uneducated patients from obtaining transplants.

Geographic Disparities

Access to transplantation services is limited in rural areas of Nepal [3]. This is due to the lack of infrastructure and trained human resources in these areas, which makes it difficult to provide transplantation services. The lack of awareness of organ donation in rural areas is another factor that contributes to geographic disparities in access to transplantation [3]. Geographic barriers significantly limit access outside Nepal's major cities. Few facilities offer organ transplant services in rural areas, and transportation of organs across long distances is logistically difficult [3]. Geographic region further determines access. More than 80% of Nepal's kidney transplants take place in the capital city of Kathmandu. Fewer centers and nephrologists in rural areas constrain access to transplantation and workup for rural patients. The cost of travel and accommodation to reach the city's transplant center is prohibitive for poor Nepalis.

PUBLIC AWARENESS AND EDUCATION

The prevalence of chronic diseases and end-stage organ damage has been rising. Advancements in medical technologies continue to enhance our ability to diagnose these conditions, intensifying the demand for organ transplantation. Organ transplantation provides the most effective treatment for end-stage organ failure, offering patients an opportunity for healthier living [3]. Comprehensive public awareness campaigns are pivotal to increasing organ donation in society. No major religion explicitly prohibits organ donation, so religious leaders have an important role in advocating its merits among their communities [5]. Educating and informing families about brain death is crucial to overcoming reluctance towards donating organs [14].

In Nepal, successful promotion of organ transplantation requires multifaceted awareness strategies to dispel myths, correct misconceptions, and challenge traditional beliefs impeding organ donation. These include targeted campaigns [3], school education programs [15], community engagement initiatives [15], public-private sector collaboration [16], and culturally appropriate education [17]. Collectively, these efforts boost public awareness, address misconceptions, and promote a supportive environment for organ transplantation in Nepal. This comprehensive approach can help narrow the gap between organ supply and demand, saving more lives.

LEGAL AND ETHICAL CONSIDERATIONS

The 1998 HBOTA law severely restricted organ sales for transplantation, curbing unethical practices. However, it also unintentionally limited organ donations preventing patients with organ failure from receiving transplants even when willing donors were existed. To address this, the HBOTA was amended in 2016, expanding possibilities for organ donation among close relatives [2]. This amendment introduced pair-exchange programs, enabling transplants from clinically deceased donors to recipients in need. The 2016 HBOTA amendment significantly expanded the scope of organ donation and enabled life-saving transplantations (**Figure 1**) [2].

The revised HBOTA (Section 1a) provides a clear definition of brain death as irreversible loss of brain stem functions. It stipulates that brain death can be confirmed [Section 12(b)1] if a doctor performs two separate examinations 6 hours apart and finds:

a) Irreversible brain damage
b) Absence of brainstem reflexes
c) Absence of spontaneous respiration

Written consent must be obtained from patient's family before examination [Section 12(b)2]. If unavailable, examination can occur with district administration office oversight [Section 12(b)3].

In situations where the examination is performed by the concerned head of the office, Section 12(b)4 stipulates that other senior doctors from the same institution must also be present. This provision ensures that the examination process is conducted with appropriate oversight and expertise.

According to Section 12(e) of HBOTA, doctors must inform families of examination details and diagnosis. In cases where the family members are unavailable or if the patient is unclaimed, the doctor is required to submit information regarding the diagnosis of brain death to both the concerned district administration office and the Ministry of Health. According to Section 12(i) of HBOTA, the doctor determining brain death cannot be the transplant surgeon, ensuring accountability.

As per Section 17 of HBOTA, it is explicitly prohibited to extract organs from the body of a deceased person and transplant them into another body in a way that interferes with the postmortem findings. This restriction applies specifically to cases where the person's death is a result of murder, suicide, or occurs under doubtful circumstances.

PROGRESS AFTER APPROVAL FOR BRAIN DEATH DONATION IN NEPAL

The amendment of the HBOTA act in December 2016 approved organ donation from brain dead donors, marking a significant step in Nepal's history of organ donation and transplantation [2]. Following this, a single organ transplant center situated in the country's capital successfully initiated procurement of kidneys from brain dead donors and transplanted them in two patients on 11 May 2017 [15]. Moreover, the same team achieved successful kidney transplants from two additional brain-dead donors,

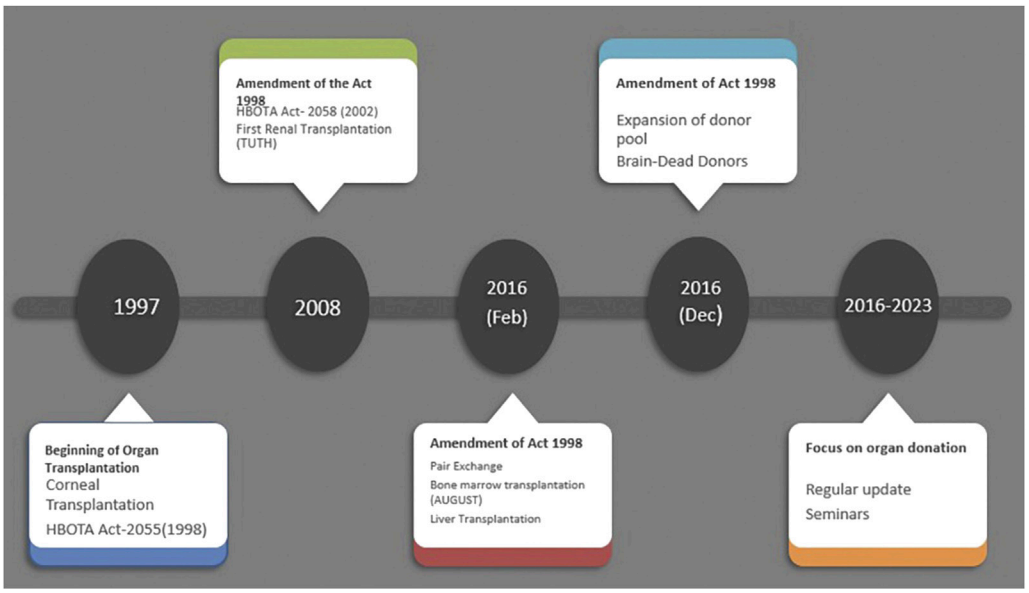

FIGURE 1 | Legislature related to human organ transplantation in Nepal and its amendments.

benefiting four recipients. These noteworthy accomplishments contributed to the growth of brain-dead donation and transplantation. However, hospitals equipped with state-of-the-art technology have not been able to perform single brain-dead donation and organ transplantation. The infrastructure and human resources at the human organ transplant hospital provided a strong foundation for the execution of its first kidney transplant from a brain-dead donor, with the availability of skilled doctors and staff performing kidney transplants in a large number since 2012. Nevertheless, other centers regularly performing kidney transplantation with adequate resources for the same have not gained a considerable pace in initiating kidney transplantation from brain dead individuals. The absence of such initiation lies in multiple barriers and challenges faced by the institutions primarily in training, as the HBOTA act emphasizes the need for skilled human resources with a minimum of 6 months of training in the field of organ procurement and transplantation center [2]. One of the biggest hurdles lies in generating funding to train a good number of human resources and other skilled personnel.

It has been repeatedly emphasized the growing need for organs for the ever-rising number of organ failures (kidney, liver, heart, lungs), who are denied the potential resource of organs from brain dead donors available in our country are being overlooked.

IMPROVING INFRASTRUCTURE AND RESOURCES

Organ transplantation is based on regional or national allocation programs for the efficient coordination, fair distribution of organs, logistical, and laboratory support. The immediate allocation of organs to donor identification is essential due to limited storage time. Proper transport and storage facilities are vital to maintain organ viability and ensure optimal conditions for successful transplantation. These facilities are essential for a well-functioning organ transplant system [18]. Hence, it has become essential to improve the infrastructure, allocate resources and facilities for the prompt diagnosis and effective management of organ donation from deceased patients. Currently, only one center has successfully performed kidney transplantation from brain dead donors.

The HBOTA act of Nepal has elaborated on the requirements of any hospital in Nepal that seeks permission for the donation and transplantation of deceased organs [2]. More specifically, the Act ensures the availability of equipment required for transplantation of kidney and liver by the anesthesiologists and surgeons in the operative room and the postoperative room, e.g., facilities for monitoring, dialysis, mechanical ventilator, and color Doppler [2]. The human resources requirements include qualified anesthesiologist, surgeon, nephrologist, gastroenterologist, radiologist, cardiologist, cardiothoracic surgeon, and pathologist. However, the act addresses organ donation, transplantation infrastructure, and human resource requirements for kidney and liver [2].

The current state of tertiary care center hospitals in Nepal, both at the governmental and some private levels, have met the required infrastructure; however, the skilled human resources to perform deceased organ donation and transplantation of organs other than kidneys remain undertrained. Proper planning of infrastructure usage and trained human resources capable of working from the level of notification of declared deceased donors to successful transplantation of organs need rigorous planning and implementation.

Studies have highlighted the unavailability of proper infrastructures as an important barrier to the execution of brain-dead organ donation and transplantation in developing countries [19].

COLLABORATION AND NETWORKING

It is essential to develop a well-developed networking and collaborative effort at two main levels. First, an efficient system of informing organ procurement organizations (OPO's), often referred to as the OPO's, upon arrival of patients in the emergency department, or in the intensive care unit who are potential donors of organs. Second, further communication of the OPO's to the Organ Procurement Transplantation Network (OPTN) [20].

In the context of Nepal, the establishment of HBOTA Act 2073 has legalized organ procurement and transplantation from brain dead donors, however, the establishment of a well-developed network of organizations working for its implementation is lacking. Hence, the need to develop organizational bodies that can strengthen networking with other organizations working at the state level to smoothen the organ donation and transplantation process has become essential. Functioning of such bodies in our neighboring country India, that collaborates with the national government to develop and implement standardized procedures, oversee transplant operations, ensure the maintenance of a centralized database for organs and transplants, promote organ donation, and educate staff members involved in organ donation, has been able to achieve better results in organ transplantation [21].

One of the recent plans of the Nepali government is to implement organ donation and transplantation in the seven provinces of Nepal through improved collaboration and networking with the National Transplant Center [22]. Working models developed in countries with higher success in organ donation and transplantation, with well-established networking within the hospital Intensive care units regularly audited for reformation and improvisation of the services, can be studied by developing countries like Nepal [20]. However, sociocultural and financial constraints may limit its implementation.

Countries in their early stages of implementation of brain death acts, governments' support is essential for the achievement of various tasks, such as providing training for transplant coordinators, establishing nationwide networks for organ transplants, implementing fair systems for organ allocation, and promoting the voluntary declaration of intent to donate through organ donation cards, driver's licenses, and insurance documents [23].

At the level of hospitals, studies have suggested poor coordination among the transplant team within the hospital as one of the barriers to successful implementation of brain death organ donation process [19]. Therefore, it becomes essential to develop trained human resources who can effectively perform organ procurement and transplantation. One of the needs highlighted in the recent international-level meetings carried out in Nepal emphasized the proposal for establishing a reputable institution dedicated to training specialists in the field of transplantation.

OVERCOMING CULTURAL AND RELIGIOUS BARRIERS

The cultural practices of people in Nepal are heavily influenced by their existing religious beliefs. Respect and the sacred belief of individuals toward the human body, more specifically when in a state of illness, has strongly limited the acceptance of organ donation by the public. It is imperative and holy to accept bodies in an intact state after the death of individuals, which is supported by different religious beliefs [23]. It is important to make the public aware that organs from potential donors are not removed from patients for organ transplantation. The concept of 'dead donor rule' plays a vital role in preserving the rights of intended donor patients who are not denied optimal care to save their lives. Therefore, the rule emphasizes that donors are first declared dead before the organ procurement process is initiated [20]. The cultural belief of the public has limited their acceptance of organ donation after the death of their closest ones as factors like essential care being denied, along with other beliefs of organs being abused, misused, and misappropriated [7, 19]. Hence, organ donation from brain dead patients must be made culturally, ethically, and legally acceptable, by maintaining public trust at each step, emphasizing counseling with the patients near ones by the doctors taking care of their near ones in the intensive care unit.

To overcome the cultural and religious barriers in initiating and implementing brain death organ donation, educating and informing the public can be implemented through educational initiatives aimed at improving public awareness and fostering a positive mindset towards organ donation through well-designed public campaigns [23]. The influence of religious leaders, eminent figures, and media influences holds a powerful ability to raise awareness among the public [7, 24]. In Nepal, the approval of organ donation after brain death has been declared by the current Prime Minister of Nepal to inspire acceptance of it by the public [25]. However, the importance of unplanned media coverage of transplant-related stories should not be overlooked. By showcasing patients' appeals for organs and sharing stories of successful transplants, media coverage can generate public support and enhance trust in the transplantation process [23].

The need to identify the awareness and willingness to donate organs among the public through research at state levels will provide a strong base to plan activities to raise awareness among the public and raise acceptance of the brain death organ donation process [26]. The lack of government funding for such research has slowed down the process of identifying factors hindering the acceptance of public to brain death organ donation.

EVIDENCE-BASED STRATEGIES TO INCREASE DECEASED ORGAN DONATION IN NEPAL

Public Education and Awareness

- Culturally-targeted education campaigns are needed, especially in rural communities, to correct misconceptions about brain death and promote organ donation acceptance. Formative research identifying knowledge gaps and cultural barriers can inform campaign design.
- Collaborations with religious leaders and strategic media engagement offer opportunities to gain wider public support for organ donation across diverse communities.
- School health programs and community outreach providing brain death and organ donation education represent potential strategies based on success in other countries.

- Controlled studies are warranted to identify optimal public education approaches and quantify impacts on organ donation rates.

Healthcare Infrastructure and Training

- Expanding diagnostic facilities and building specialized medical expertise in provincial hospitals are essential to increase capacity for brain death determination and organ procurement across Nepal.
- Standardized training programs focused on the complex process of deceased donation are needed to develop skilled coordination teams and transplant personnel aligned with international guidelines.
- Healthcare collaborations can facilitate knowledge transfer and share best practices in deceased donation processes.

Legal/Policy Reform and Organ Allocation

- Refining Nepal's brain death legislation to integrate clinical diagnostic criteria from established international guidelines.
- Government-led initiatives to develop organ sharing networks across all provinces to help address geographic disparities.
- Establishing transparent organ allocation policies and oversight mechanisms to countering public distrust and perceptions of organ misuse.
- Further research into gender, socioeconomic, and cultural norms influencing organ access to provide a guide for legislative reforms.

CONCLUSIONS

This article critically reviews various factors that determine brain death and organ transplantation in Nepal. Strategies to account challenges and barriers, such as limited awareness, religious beliefs, and family consent issues are needed. Collaboration, networking, and skilled human resources are crucial to advance organ transplant practices.

Promoting culturally sensitive approaches to guide cultural and ethical consideration, engaging religious leaders and the media are essential for public acceptance of organ donation after brain death. Recommendations for public awareness campaigns, infrastructure developments, and increased collaboration among healthcare centers offer possible strategies to improve transplantation rates in Nepal.

A multifaceted approach that addresses cultural, legal, and ethical dimensions is needed to develop a sustainable and effective organ donation system in the country. Successful implementation of such measures will improve healthcare, and demonstrate Nepal's commitment to saving lives through organ donation, and support global efforts to reduce the burden of organ failure worldwide.

AUTHOR CONTRIBUTIONS

AA conceived the study and was involved in its conception, design, review, and drafting of the initial manuscript. PB, SB, and SN conducted the literature review and drafted the manuscript in sections. PSB provided critical revisions. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ESOT | Transplant International

POINT OF VIEW
published: 30 May 2023
doi: 10.3389/ti.2023.11259

Directed Organ Donation After Euthanasia

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Organ donation after euthanasia is performed in Belgium, the Netherlands, Canada and Spain. Directed deceased organ donation is currently possible under strict conditions in a limited number of countries, while it is currently not possible to opt for directed donation following euthanasia. While organ donation after euthanasia is a deceased donation procedure, directed organ donation after euthanasia could be seen as a deceased donation procedure with a living donation consent process. Therefore, directed organ donation after euthanasia is feasible on medical and ethical grounds. Strict safeguards should be in place, including the requirement of a pre-existing familial or personal relationship with the proposed recipient, without any evidence of coercion or financial gain.

Keywords: recipient selection, end of life, deceased donation, euthanasia, directed donation

INTRODUCTION

The majority of deceased organ donations occurs in patients who were comatose and could not provide first person consent. Physicians rely on surrogate decisions and/or their donor registration. Most countries do not allow "directed deceased donation," wherein it is possible to choose a specific recipient. Organs from a deceased donor are allocated to those who most urgently need it on the transplant waiting list. This differs from living donors who can donate their organ to specified recipients, most often a relative.

Organ donation after euthanasia is being performed in Belgium and the Netherlands for several years [1]. Research based on Belgian euthanasia data demonstrated that 10% of patients who undergo euthanasia might be medically eligible for organ donation [2]. The majority of euthanasia patients however suffer from malignancy, which makes them unsuitable for organ donation [2,3]. Canada legalized euthanasia (which is referred to as "medical assistance in dying" (MAID)) in 2016, and after multiple patient-initiated requests, implemented organ donation after euthanasia in accordance with national guidelines [4,5]. In 2021, this combined procedure also became possible in Spain.

Euthanasia requires the administration of intravenous drugs by a physician, in contrast with (physician) assisted suicide, where a patient can take a lethal medicine themselves [6]. Euthanasia and assisted suicide are currently subject of debate in a growing number of countries.

Patients who choose euthanasia are conscious and competent, which makes them capable of making a well informed decision about organ donation after euthanasia, but which could also allow them to choose a specific recipient for their organ(s). Directed donation after euthanasia is generally not possible, either because a country does not allow euthanasia, or because directed deceased donation is not allowed [7]. According to Cronin and Price, directed and conditional donations

Point of View

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***Received:** 05 April 2023*
***Accepted:** 11 May 2023*
***Published:** 30 May 2023*

Citation:
van Dijk N, Shaw D, Shemie S, Wiebe K, van Mook W and Bollen J (2023) Directed Organ Donation After Euthanasia. Transpl Int 36:11259. doi: 10.3389/ti.2023.11259

provide immediate and evident challenges to the traditional construct of altruistic donation and impartial (equitable) allocation [8].

This article addresses the observation that an increasing number of countries allow euthanasia, and how organ donation organizations can respond to patient requests for directed donation after euthanasia. The ethical aspects of autonomy, vulnerability, distribution of resources and avoiding organ trade are discussed more in detail, since these seem to be the most significant threshold for allowing directed organ donation after euthanasia. Next, we propose a set of criteria under which it would be appropriate to proceed with directed donation following euthanasia.

Can Directed Organ Donation After Euthanasia be Legal?

Uniform to all euthanasia laws, which vary by jurisdiction, a patient can undergo euthanasia only if they are suffering from a grievous and irremediable condition, if they have intolerable suffering that cannot be alleviated under conditions acceptable to the patient, if they are mentally competent, and if the request has also been evaluated and deemed eligible by a second independent physician.

The Organ Donation Acts in Belgium and the Netherlands state that in a deceased donation procedure, neither the donor nor his relatives are allowed to choose a recipient. Allocation is legally performed through Eurotransplant, an organization that allocates donated organs for eight European countries, depending on urgency and compatibility. In Canada, policy and practice regarding patient initiated requests for deceased directed donation varies per province/territory [9].

The current Canadian policy on donation after euthanasia states that directed donation should not be offered or encouraged [4]. If a patient insists on directed donation, the request should be carefully considered on a case-by-case basis. This has occurred at least once, although the directed donation was not possible as the recipient did not have a compatible blood type [10,11]. Directed organ donation after euthanasia is thus very likely to happen in Canada, as the current legislation does not prohibit it.

Belgium and the Netherlands allow living kidney donors to choose a specific recipient, but directed donation after euthanasia is not allowed because it is legally a deceased donation. We feel that directed organ donation after euthanasia is actually a deceased donation procedure with a living donation consent process.

In the United States, India and the United Kingdom, directed deceased donation (without euthanasia) is allowed under strict conditions [12–14]. As an example, the UK policy requires that the request for the allocation of an organ to a specific recipient should be to a relative or friend of long standing, while no other patients are in urgent clinical need of the organ, that the specific recipient is on the transplant waiting list or could be considered to be placed on the waiting list, and that in life, the deceased had indicated a decision to donate to a specific recipient in need of an organ, or, in the absence of that indication, that the family of the deceased expresses such a decision. However, the consent for directed organ donation is not allowed to be conditional, so if not all requirements for directed donation can be met, organ donation should proceed to other recipients.

What are the Medical Considerations?

From a medical point of view, a deceased directed donation procedure could result in better compatibility between the donor and the recipient, due to better human leukocyte antigen matching, assuming the donor and recipient are commonly relatives [15]. Chances of a successful transplantation would therefore be higher compared to an unrelated donation after allocation by the transplant organization, based on the transplant waiting list. Research demonstrates that lungs, kidneys and livers transplanted following organ donation after euthanasia function adequately [16–18]. Recently, the Netherlands started heart donation following euthanasia as well, which will also have a significant impact on the transplant waiting lists—even though this is not the primary goal [19].

Would it be Ethical to Allow Directed Organ Donation After Euthanasia?

There are several ethical aspects that need to be addressed in the context of this combined procedure.

Vulnerability and Autonomy

As stated by Case et al., "patients wishing to donate organs as part of the euthanasia process are a population that might be considered vulnerable and in need of protection given perceived threats to their autonomy" [10]. The possibility of directed donation after euthanasia gives patients the opportunity to help close family or friends after death by providing an organ for transplantation. In this sense, euthanasia enables patients to benefit other patients, in line with the principle of beneficence. However, this potential benefit does complicate the consent process for both euthanasia and donation, as there is a potential risk that the possibility of donating to a relative or friend might compromise or contaminate the consent process for euthanasia. The principle of respect for autonomy requires that any decision to engage in euthanasia (with or without organ donation, whether directed or not) is voluntary, and free from any potentially coercive influences. For example, a patient who is terminally ill might either choose to die sooner through euthanasia as waiting for a natural death might deny their relative the organ. In addition, the donor's commitment, once made, may influence the ability to change their mind about continuing euthanasia, because of a desire not to "let down" the intended recipient.

However, these concerns should be addressed carefully. It is recommended that the patients request organ donation after euthanasia themselves, and, the medical team must attempt to establish that such factors do not play a role in the decision to choose euthanasia, acknowledging that this may be challenging. Furthermore, it is always made clear to patients that they can change their mind about euthanasia or donation at any point. This is also important in view of the principle of non-maleficence. While voluntary consent to euthanasia and directed donation are

not in principle incompatible, the safeguards mentioned here are reliant upon full honesty from the patient, and it may be difficult in practice to ensure that the decisions being made are fully autonomous. Even if the patient is fully honest, it might be hard for the patient themselves to be entirely sure whether the wish to donate influences the decision to seek euthanasia. Even though the consent procedures for euthanasia and donation are separate, in the patient's mind they may be very closely linked in a way that could make full voluntariness challenging.

Generally, both procedures should be kept as separate as possible, and it should also be investigated whether any reciprocal obligation would arise with the recipient or his relatives. The recipient of the organ, or members of their social network might also feel more social pressure and obligation to the donor's family—which is a negative consequence of the donor not being anonymous, as is the case in directed living donation as well.

At the same time, one could argue that, the principle of autonomy means that one should be able to decide to choose euthanasia in order to donate an organ to a relative. However, given that one can only pursue euthanasia if one is suffering hopelessly and unbearably, one is already in a vulnerable position, and society will expect physicians to protect these patients. If one would allow euthanasia because of a wish to donate, even if all other due diligence requirements are fulfilled, this might currently have a negative impact on the public view on organ donation in general—which should certainly be avoided.

Organ donation after euthanasia based on psychiatric suffering is already possible in Belgium and the Netherlands. In the Netherlands, about one in four cases of organ donation after euthanasia was the result of psychiatric suffering, and 115 (1.3%) of Dutch euthanasia cases in 2022 was due to psychiatric suffering [20]. Euthanasia because of mental illness is not possible in Canada until March 17, 2024.

Avoiding Organ Trade

There is also a risk of commercial trading in organs [21,22]. The patient who is about to donate his organs after euthanasia might have found a request on social media from a patient who is willing to pay for an organ. The treating physician and the consulted independent physician (as required by the euthanasia procedure), and perhaps the organ donation coordinator, should investigate the wish of the patient to donate to a specific person who is not a family member or pre-existing friend. However, the same criticism applies to cases of directed living donation and this is not a categorical objection to directed donation after euthanasia.

Resources

Deceased directed donation could be seen as involving unfair distribution of scarce resources, since the transplant waiting lists are bypassed, and someone on that list might be in higher need of an organ than the patient who actually receives it. However, this is not any different from living donation directed to a specific individual, and someone lower on the list could receive an organ more quickly as it will remove someone from the transplant list. It is possible that directed donation after euthanasia would exacerbate existing socio-economic inequalities by benefitting both donors and recipients with large social networks, greater social media skills and better socioeconomic positions: donors are more likely to be able to identify someone in need, and those in need with large networks are more likely to be able to find a donor [23]. Again, the same issues of justice also affect directed living donation, where they are not seen as fundamental reasons to prevent the practice.

The same applies to the context of directed donations to a specific group or class, without specifying a particular individual. For example, if a member of an equity deserving group (e.g., indigenous person) undergoes euthanasia, they may wish the organ to be donated back to their community without having a specific individual in mind. One can envision many populations who are disadvantaged by structural inequities in the system that may wish to repair this inequity through directed donation to a class. Although very understandable, this seems to go against the principle of justice which is an important aspect of organ donation policies.

Scientific literature has discussed the effectiveness of directed donations in achieving specific goals, such as reducing poverty or improving health outcomes in specific populations [24,25].

In terms of the principle of beneficence, facilitating the patient's last wish through allowing them to donate their organs after euthanasia benefits both the patient and the recipients. There does not seem to be a relevant difference whether an organ is donated through standard allocation or through directed organ donation after euthanasia, except inasmuch as helping a known recipient may benefit the patient more than helping a stranger. If one would refuse directed organ donation after euthanasia, there is a risk that the potential donor will not choose organ donation at all, consequently also affecting other patients that would receive an organ.

DISCUSSION

Directed organ donation after euthanasia may be legally, medically and ethically acceptable. It is an increasingly timely issue to be addressed as more and more jurisdictions enact legislation permitting euthanasia.

If directed organ donation after euthanasia is not possible, two theoretical alternatives exist for a patient who will undergo euthanasia and wishes to donate to a specific recipient. The patient could request a directed living donation a few days before undergoing euthanasia. The majority of patients who undergo organ donation after euthanasia suffer from a neurodegenerative disease which poses a high risk for anesthesia and surgery [2]. A living donation procedure could thus potentially cause death or influence the patient's quality of life in his last days. A patient who is already suffering unbearably is likely not interested in spending his last days in the hospital to undergo surgery before undergoing euthanasia.

The second theoretical alternative would be "organ donation euthanasia": anesthetizing the patient and donating his organs [26]. However, such hypothetical "death by donation" procedure

is legally considered a living donation procedure, a procedure during which the donor is legally not allowed to be harmed, and which is therefore illegal. To circumvent this issue, a patient who fulfills all criteria for euthanasia might be anesthetized to donate one kidney, as a living directed donation procedure, immediately followed by administration of the euthanasia drugs by his own physician. This would then result in death, which would make it possible to procure all other organs (non-directed) following the no touch period, still respecting the dead donor rule. However, this is currently still a hypothetical situation that would be in contrast with the requirement that a patient reaffirms their euthanasia request immediately before the euthanasia drugs are administered. In the Netherlands this was also deemed to be an issue in procedures where a patient is sedated at home before being transported to the hospital where euthanasia and organ donation are performed. However, euthanasia review committees have judged that the euthanasia due diligence requirements were still fulfilled in these cases [27].

Opponents of euthanasia worry about coercion, which was also one of the main criticisms in the discussion during the referendum on the End of Life Choice Act in New Zealand. If directed organ donation after euthanasia would be available, and if a terminally ill patient's relative would be in need of an organ, this was considered to potentially lead to an enormous pressure on the patient to choose this combined procedure. While it would also be unjust not to allow this patient to donate to his relative, safeguards are essential to investigate the social situation and to avoid any coercion. The patient should always be able to refrain from organ donation after euthanasia or from euthanasia itself.

Given all of the above arguments and based on what we can learn from areas that currently allow for directed deceased donation, directed organ donation after euthanasia could be permitted under certain circumstances, subject to rigorous safeguards.

These should include:

- the request for directed organ donation after euthanasia is a voluntary request made by the conscious donor who is about to undergo this combined procedure
- the request should be donor initiated without any evidence of coercion or financial gain
- the donor should have a pre-existing familial or personal relationship with the proposed recipient, to avoid potential commercial trading and distrust from the public
- the intended recipient is on the waiting list or meets the listing criteria, and the donor organ is medically compatible for the intended recipient
- the donor should be able to refrain from either procedure until the very last minute.

In the requirements that are applied in the UK (where euthanasia is not allowed), as mentioned above, there is the requirement of unconditionality in case there are other patients in urgent clinical need of the organ. However, this seems in essence unenforceable, and it opposes the patient's autonomy while the latter principle is at the center of the organ donation after euthanasia procedure. If the donor would be informed about another patient in more clinical need, they might decide to postpone dying to still be able to perform a directed donation.

In Canada, introducing directed organ donation after euthanasia would only require a change in guidance, while in Belgium and the Netherlands, the laws on organ donation would need to be adjusted. Eurotransplant currently does not have a policy on directed deceased donation. Practically, allocation to the specific recipient(s) can be processed just as this would be done for living directed donation. Next to the directed donation of one organ, the recipients of other donated organs can still be selected based on the transplant waiting lists–while directed donation of more than one organ is possible as well. We concede that the proposed procedure of directed organ donation after euthanasia will be very rare, but nevertheless we need to discuss this topic and potentially adjust the law, since it would seem unjust if a patient who wants to donate to a specific relative following euthanasia does not get this chance because of legal requirements.

CONCLUSION

Directed organ donation after euthanasia is medically, legally and ethically feasible when robust and rigorous safeguards are established. Directed organ donation after euthanasia would fulfil the wish of the patient who is conscious, competent and able to provide first person consent, and it would be consistent with the same principles that permit directed donation for living donors. However, strict safeguards should be in place for the willing donor to protect this patient from any external pressure to request or continue a directed organ donation after euthanasia procedure.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JB initiated the research. JB, ND, and WM participated in the research design. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MINI REVIEW
published: 18 March 2022
doi: 10.3389/ti.2022.10084

Inequitable Access to Transplants: Adults With Impaired Decision-Making Capacity

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Inequitable access to deceased donor organs for transplantation has received considerable scrutiny in recent years. Emerging evidence suggests patients with impaired decision-making capacity (IDC) face inequitable access to transplantation. The "Ethical and Legal Issues" working group of the European Society of Transplantation undertook an expert consensus process. Literature relating to transplantation in patients with IDC was examined and collated to investigate whether IDC is associated with inferior transplant outcomes and the legitimacy of this healthcare inequality was examined. Even though the available evidence of inferior transplant outcomes in these patients is limited, the working group concluded that access to transplantation in patients with IDC may be inequitable. Consequently, we argue that IDC should not in and of itself be considered as a barrier to either registration on the transplant waiting list or allocation of an organ. Strategies for non-discrimination should focus on ensuring eligibility is based upon sound evidence and outcomes without reference to non-medical criteria. Recommendations to support policy makers and healthcare providers to reduce unintended inequity and inadvertent discrimination are set out. We call upon transplant centres and national bodies to include data on decision-making capacity in routine reporting schedules in order to improve the evidence base upon which organ policy decisions are made going forward.

Keywords: transplantation, ethics, capacity, law and policy, equitable access

OPEN ACCESS

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Received: *30 September 2021*
Accepted: *11 February 2022*
Published: *18 March 2022*

Citation:
Thom RL, Dalle-Ave A, Bunnik EM, Krones T, Van Assche K, Ruck Keene A and Cronin AJ (2022) Inequitable Access to Transplants: Adults With Impaired Decision-Making Capacity. Transpl Int 35:10084. doi: 10.3389/ti.2022.10084

Abbreviations: IDC, Impaired decision-making capacity; EBPG, European Best Practice Group; QoL, Quality of Life; QALY, Quality Adjusted Life Year; aHR, adjusted hazard Ratio; CI, Confidence Interval; OCEBM, Oxford Centre for Evidence based medicine.

INTRODUCTION

Issues of scarce resource allocation and inequitable access to medical treatment have long-since been the doctor's dilemma. Deceased donor organs for transplants are a scarce resource, and it is widely agreed that equitable access to transplantation must be prioritised. In recent years transplant professionals and advocacy groups have highlighted how those who may have impaired legal decision making capacity (IDC) have historically faced inequitable access to transplant waiting lists and organ allocation (1–3). This has led to multiple United States jurisdictions instituting specific legislation, however such changes are yet to be seen in Europe (1).

Those who may have IDC include patients with 1) intellectual disability, 2) a mental health condition, including for example disorders affecting reasoning such as psychosis, 3) cognitive impairment that may be due to neurological disease or a single acquired deficit (e.g., stroke or head injury) and finally 4) disorders or consciousness such as persistent vegetative or minimally conscious states. Cognitive impairment is of particular importance as up to 70% of patients aged over 55 receiving dialysis have moderate to severe cognitive impairment (4) and there is emerging evidence which suggests such patients have a lower likelihood of being listed for transplantation (5).

In this paper we interrogate the relationship between 1) apparent lack of mental capacity to make relevant decisions and 2) equitable access to deceased donor organ transplantation. We seek to explain why lacking the mental capacity to consent to transplant should not itself per se be a barrier to access to and allocation of an organ for transplant. We do this with reference to four key transplant outcome measures and specifically interrogate whether, and if so to what extent, the concerns raised by these four key transplant outcome measures are supported by published empirical evidence. We highlight ethical considerations and legal issues, and, finally, set out recommendations and guidelines for clinicians and policy makers to help overcome perceived barriers and avoid unintentional discrimination.

MATERIALS AND METHODS

The "Ethical and Legal Issues" working group of the European Society of Organ Transplantation undertook an expert consensus process between October 2020 and March 2021. This took the form of extensive online discussions between clinical transplant, ethics, and legal experts. Discussions were informed by a review of the published literature relating to transplantation in persons with IDC.

For the purpose of this paper relevant literature was identified by a search of MEDLINE accessed through PubMed. Search terms used were (organ transplantation) AND (mental incapacity OR intellectual disability) between September 2010 and September 2020. We included peer reviewed publications from scholarly journals. Our key purpose was to identify whether strong evidence existed to support the view that transplant outcomes are inferior in persons with IDC.

Our search generated 66 papers. The titles and abstracts of all English language papers were screened. 16 papers relevant papers were identified. One paper was excluded as it was a case study. Seven papers were primary research- six retrospective cohort studies and one online survey. The remainder were literature reviews, ethical analyses or editorials. Further sources were identified through cited materials. In addition, primary and secondary legal sources from LexisNexis and Westlaw databases and public policy documents were analysed.

TRANSPLANT OUTCOME MEASURES AND INEQUITABLE ACCESS TO TRANSPLANTATION

Four key transplant outcome measures emerge in the literature as relevant clinical concerns and to varying degrees cut across all the groups we have identified as at risk of lacking the mental capacity to make relevant decisions as regards to medical treatment and transplantation. These are 1) medication adherence, 2) graft outcome, 3) patient outcome and 4) quality-of-life (QoL). While medication adherence is not itself a transplant outcome measure, we observe that medication non-adherence is assumed to have a causal effect on transplant outcomes. As post-transplant medication non-adherence is taken to negatively impact organ and patient survival and quality of life, the *prognosis* of non-adherence is mentioned in the literature as a reason not to list a patient or not to allocate an organ.

We assessed whether, and, if so, to what extent, the concerns raised by these four inter-related key transplant outcome measures are supported or actively refuted by the published empirical evidence. We included outcome data relating to living donor transplantation because limited evidence was available on deceased donor transplant outcomes in persons with IDC. A summary of this empirical assessment is set out in table one (**Table 1**) and is followed by an ethical and legal analysis of the concerns raised by each transplant outcome measure and by their assumed causal dependency.

In the empirical and theoretical literature found to date disorders of consciousness and their implications for potential transplant recipients have not received attention. This lack of empirical evidence has led us to exclude them from our further discussion, although their position would benefit from further theoretical analysis as they seem to be a group who are subject to distinct concerns.

Medication Adherence

Non-adherence to prescribed medication is common, transplantation is no exception. The estimated prevalence of non-adherence in transplant recipients is between 36 and 55% (6). There are multiple factors which have been shown to be associated with non-adherence, including "youth (<50 years old), male, low social support, unemployment, low education, >3 months post graft, living donor, >6 comorbidities, >5 drugs/day, >2 intakes/day, negative beliefs, negative behaviour, depression and anxiety (7)"- however, many of these factors may

TABLE 1 | Summary of empirical evidence relating key transplant outcome measures to each group with potentially impaired decision making capacity.

Group with potentially impaired DECISION-MAKING capacity	Key transplant outcome measures			
	Adherence with medical therapy	**Graft outcome**	**Patient outcome**	**Quality of life**
Intellectual disability	Cohort studies suggesting adherence is comparable. OCEBM[a] level 3 (1, 17)	Multiple cohort studies suggesting graft outcomes are comparable. OCEBM level 3 (1, 13–19, 33)	Multiple cohort studies suggesting non-graft outcomes are comparable. OCEBM level 3 (1, 13–19, 33)	Evidence is that in general quality of life is improved by transplantation (25) OCEBM level 1 Small number of cohort studies showing QOL benefit in this group. OCEBM level 3 (26, 33)
Severe mental health conditions	Evidence of increased non-adherence in those with depression (7) OCEBM level 3 but not in other conditions in particularly in those with psychosis/mania (8, 9) OCEBM Level 3	Evidence of poorer outcomes in those with depression (24) OCEBM level 1. Otherwise conflicting evidence from cohort studies of other psychological conditions OCEBM Level 3 (2, 8, 9, 22)	Evidence of poorer outcomes in those with depression (24) OCEBM level 1 Otherwise conflicting evidence from cohort studies of other psychological conditions OCEBM Level 3 (2, 8, 9, 22)	Evidence is that in general quality of life is improved by transplantation (25) OCEBM level 1
Cognitive impairment	Evidence from cohort studies of reduced adherence in older age groups of transplant recipients OCEBM level 3 (11, 12)	Cohort studies indicate worse outcomes (23) OCEBM level 3	Cohort studies indicate worse outcomes (23) OCEBM level 3	Cohort study evidence that QoL benefit is consistent in over 65s (those most at risk of cognitive impairment on dialysis)(28) OCEBM level 3
Permanent disorders of consciousness	No concern as adherence would be assured by caregiver	No evidence available	No evidence available	Theoretical reason to believe QoL outcomes would be significantly different from the general population of transplant recipients

[a]*Oxford Centre for Evidence Based Medicine 2011 levels of evidence are included to indicate the degree of certainty with which the authors make these assertions.*
This table has drawn on evidence relating to intellectual disability from the paediatric literature. However in this paper we do not consider children as a discrete category, as they are treated differently where they are considered too young to have the legal capacity to make the relevant decisions, whether or not they have any intellectual disability or mental disorder.

be equally present in patients who have decisional capacity as in those who lack it.

Non-adherence is frequently linked to those with mental health disorders (2). However, in a study of 955 transplant recipients it was found that those with a pre-existing mental health diagnosis and those with pre-transplant non-adherence were not necessarily groups which overlapped (8). Studies looking specifically at adherence in severe mental health disorders which may result in IDC (e.g., psychosis) are scarce. However Molnar used percentage of days covered by immune suppression prescriptions for a cohort of 442 post-transplant patients with a history of psychosis and mania and found that these did not differ significantly between those with a psychiatric history and those without (9).

In contrast it could be argued that those with intellectual disability may already have strong social support networks and committed carers which act as protective factors against non-adherence (1, 10). Samelson-Jones in a case review of five adults with intellectual disability who received cardiac transplants found only one instance of significant non-adherence which was primarily due to a deterioration in the ability of the caregiver rather than the patient (10).

Finally, it is widely acknowledged that in the general population those with advanced age and co-morbidity face specific barriers to adherence. Polypharmacy, visual loss and cognitive impairment may all contribute to difficulty adhering with complex medication regimes. One study which attempted to assess if these general concerns were replicated in the transplant population showed non-adherence to be alarmingly high in older transplant recipients affecting 86% (11). With another showing that age >60 was found to be significantly associated with worse adherence (12).

The limited evidence available is inconclusive with regards to whether adherence in persons with IDC is reduced when compared to the general population. It is therefore not possible to assert that IDC can legitimately be used as a surrogate marker for post-transplant non-adherence. Concerns related to post-transplant medication non-adherence may be alleviated when committed caregivers and social support networks are available.

Graft and Patient Outcomes

Cohort studies have shown that patients with intellectual disability receiving a variety of solid organ transplants have equal survival to those without (1, 13–20). A literature review of transplant outcomes in those with intellectual disability found 18 published studies with a mixture of solid organ transplants included, mostly but not exclusively in paediatric recipients (1). The largest cohorts are found in kidney transplant recipients where 5-year graft survival ranged from 75 to 100% (1) and when compared to matched populations without intellectual disability there is no difference in acute rejection or graft survival (13).

Meta-analysis have shown depression to be associated with increased graft loss and all-cause mortality RR1.65 (CI:1.21–2.26) (21) although a causative factor is not considered and a large retrospective cohort study of 4582 patients in Ontario has shown a hazard ratio (HR) = 1.494 [95% confidence interval (CI) = 1.168–1.913] of post-transplant death in patients with a diagnosis of "psychological conditions" which was independent of age (22). However, this represents a very heterogenous group. In contrast cohort studies of patients with psychosis or mania do not reveal an association with increased rejection or graft loss (8, 9) although there is likely to be selection bias as those transplanted were likely stable prior to transplantation.

Cognitively impaired recipients in a retrospective study of 864 patients at two centres in North America showed that there was a substantially higher all cause graft loss than in those without impairment in living donor recipients- aHR 5.40 (CI 1.78–16.34, $p < 0.01$) and in deceased donor recipients with severe cognitive impairment aHR 2.92 (CI1.13–7.50, $p = 0.03$) but no statistically significant difference in those with any stage of cognitive impairment (23).

Quality of Life (QoL)

There is a wealth of evidence supporting the assertion than kidney patients' QoL is greatly improved by transplantation, particularly when compared to remaining on dialysis (25). This is the principal reason transplantation is considered to be the gold standard treatment of kidney failure. However, there remains considerable debate over the best measures to judge QoL. For example, a major criticism of the objective Quality Adjusted Life Year (QALY) measure, which gives weight to quantity and utility of life as well as quality, is that it is inherently biased against those with limited life expectancy and that the "Quality" factor is often not measured by self-assessment but by third-party assessment although it is widely recognized that QoL is a subjective rather than an objective dimension.

Chen et al. directly address this with regard to patients with intellectual disabilities and argue that there is "bias, subjectivity and stigma frequently associated with clinicians QoL assessments of patients with intellectual disability [which must] not be used to categorically exclude patients from lifesaving and life-enhancing surgery" (1). They go on to cite evidence that perceived QoL of recipients with intellectual disability and QoL of the principle carer improved post transplantation (26), showing that those with intellectual disability also benefit from transplantation. When considering psychological disorders while psychiatric comorbidity and particularly depression remain common in patients post transplant (27) it does not follow that patients with these diagnoses would be excluded from the benefit to QoL offered by transplantation. Similar criticisms of ableism may be levelled at clinician attitudes towards those with advanced age and cognitive impairment even though again limited evidence would show that QoL improvements from transplantation are consistent even in older age groups (28).

From available evidence on these four interrelated outcomes, one can conclude that there is very limited evidence on non-adherence of persons with IDC, only very weak evidence of worse outcomes of renal transplants with regards to graft and patient survival and QoL in persons with cognitive impairments and/or persons suffering from depression, but not in patients with intellectual disabilities and other psychological conditions.

ETHICAL ISSUES

Clinical decision-making regarding access to or allocation of deceased donor organs for transplant is constrained by scarcity, and so prompts considerations of justice. Justice implies that equals should be treated equally: when patients are similar in medically relevant respects, they ought to be treated equally, as all persons are considered as having the same right to life and health. However, reasonable persons may commit to different ethical theories on what equal treatment entails. Consequently, there is no consensus on the principles of fair allocation of scarce healthcare resources (29).

In living donation, by contrast, the issue of fair allocation does not usually arise, as the recipient brings his or her own donor and does not lay claim to a public pool of scarce organs. That is not to say that there are no ethical concerns regarding equal access in living donation. For instance, access to living donors may not be equally distributed among patients with impaired decision-making capacity. Also, our literature reveals data suggesting significantly inferior outcomes in living donor kidney transplantation in cognitively impaired patients. These concerns merit further investigation, but are beyond the scope of this manuscript.

The most prominent ethical theories of justice are utilitarian and egalitarian. Utilitarian principles aim to maximise the aggregated benefits produced by scarce resources, while egalitarian principles strive for equity or equal opportunity, regardless of aggregated outcomes, and/or for giving priority to the worst-off. These principles for allocation almost always stand in tension with each other, as giving priority to the worst-off often reduces overall utility, and vice versa.

Applying either theory, patients with IDC should be assessed and might even be prioritized, to ensure equal opportunity to a life-saving treatment. It seems reasonable to assume that for all potential recipients, regardless of decisional capacity, transplantation would offer significant QoL benefits, and that assumptions to the contrary may be subject to negative bias. Even from a utilitarian perspective, differentiated treatment of patients with and without relevant decision-making capacities is warranted only when there are (measurable) differences in transplant outcomes between the two groups. The evidence base would have to be as solid and the estimated risk of shorter survival or QoL would have to be as low as in other patients who are currently not being assessed for organ transplant, for example patients with significant cardiovascular or neoplastic disease. Given the current state of knowledge, we conclude that there is no sound ethical justification not to list patients with IDC who (presumably) want to be listed.

Further research is recommended to confirm whether graft or patient outcomes are inferior in patients with impaired decision-making capacity. Evidence on transplant outcomes is needed to guide decision-making about listing for transplantation.

However, as long as there is no evidence to conclude that transplant outcomes measures are (much) lower in persons with impaired decision-making capacity, there is no medical or ethical reason to exclude these patients from organ transplantation.

LEGAL ISSUES

The critical legal issue is how to secure individuals with IDC effective legal protection against discrimination on the basis of disability, as this is contrary to the United Nations Convention on the Rights of Persons with Disabilities (CRPD), the European Convention on Human Rights, and many national Constitutions. The CRPD explicitly imposes an obligation upon States party to it to prevent discriminatory denial of health care or health services on the basis of disability (Article 25(f)), as part of those States' recognition that persons with disabilities have the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability. Whilst the European Convention on Human Rights does not include an express right to health, it enshrines in Article 14 the right not to be discriminated against (including on the basis of disability) in the enjoyment of rights under the Convention, including the right to life (Article 2) and the right to physical integrity (Article 8). These obligations are mirrored in non-discrimination provisions enshrined in many national Constitutions. In some of these Constitutions, such as the German Constitution (Article 3 (3)), discrimination on the ground of disability is explicitly prohibited. In short, making eligibility for organ transplantation contingent upon the person's decision-making capacity would amount to unjustified differential treatment on the basis of intellectual disability, which would be in violation of non-discrimination obligations under human rights and constitutional law. However, existing international guidelines on transplantation do not expressly address the potential for discrimination upon the basis of disability (30–32).

Our concern is that when making decisions about listing or allocation, clinicians might look to the absence of decision-making capacity rather than to the possible relevant medical implications of that incapacity, and, no doubt inadvertently, risk discrimination. That a person may have an intellectual disability means that they may not ask to be put forward for transplantation, but it says nothing about whether they should medically qualify for it.

Therefore, we suggest that transplant wait listing and allocation decisions should take into account decisional incapacity only to the extent that it influences relevant medical criteria, such as the state of that person's health or the outcome of the transplantation. Also, clinicians should proceed on the basis that a patient without the relevant decisional capacity would wish to be considered for a transplant unless there is good reason to believe to the contrary. This means that focus is then placed upon whether there is a *medical* reason for not putting the person forward.

Further, securing the rights of those with disabilities requires tailoring of care plans, and identifying strategies to support their adherence. Ironically, many of those who lack decisional capacity are in fact in situations where adherence can be maximised, if not guaranteed: for instance those with profound impairments needing continued and intensive care. The most creative of these strategies may be required where a person has fluctuating capacity, for instance as a result of a mental health condition. In some jurisdictions, these strategies could include the approval by court of a care plan aimed at optimising outcome.

Crucially, adopting such strategies (and our recommendations below) will not mean that individuals with impaired decision-making capacity will automatically jump the allocation queue; rather, it means that they are given their proper place in the queue.

KEY RECOMMENDATIONS

The purpose of these recommendations is to promote equitable access to transplantation and ensure that patients without the relevant decisional capacity will be considered for transplantation.

1. That the person does not have the mental capacity to make relevant decisions ("the relevant decisional capacity") should not in and of itself be an absolute or relative contraindication to transplantation
2. There should be a general assumption that patients without the relevant decisional capacity should have equitable access to organs for transplant and would want to be considered for a transplant unless there is proper reason to believe to the contrary.
3. Decision-making regarding access to transplantation for patients with impaired decisional capacity should as far as possible include the potential recipient, their families and carers. Such decision-making should specifically include 1) identification of the wishes and feelings of the patient towards transplantation; and 2) where it is understood that the patient would wish access to transplantation, drawing up a care plan which would maximise the chances of a successful transplant outcome.
4. When it is being determined that a person without the relevant decisional capacity is not eligible for transplant this must be based on sound medical reasons and evidence. It should not be on the assumption that the lack of capacity in and of itself would affect transplant outcome measures.
5. When a patient without the relevant decisional capacity has been judged not to be suitable for a transplant it is the clinician's responsibility to inform them and their family/carers honestly and transparently about the basis upon which the decision was made.
6. In order to overcome perceived barriers and avoid unintentional discrimination, transplanting centres and national bodies should include data on decision-making capacity in their routine transplant reporting schedule in order to improve the evidence base upon which organ policy decisions are made going forward, and develop a suitable operational framework that facilitates

transplantation in persons with impaired decision-making capacity.
7. International guidelines on transplantation should include, in their provisions on prohibiting discrimination in organ allocation, an explicit reference to discrimination based on disability.

Conclusion

This paper arose out of a concern on the part of the expert group as to the place of decisional capacity in considerations of access to and allocation of organs for transplants, and, in particular, a concern that such capacity–a cornerstone of autonomy–could inadvertently give rise to unintended discrimination upon the basis of disability. In the paper, we have outlined the ways in which the evidence does not support some of the assumptions which on occasion appear to have underpinned thinking in this area, examined the ethical arguments, and framed matters by reference to international and regional human rights instruments.

We recognise that this paper is just a first start in identifying the problem. We tentatively suggest that our recommendations may assist both in delineating it fully and resolving it. A systematic review to interrogate the issues we have raised further alongside a programme of research investigating transplant outcomes would be useful. Finally, while our focus in this paper has been access to deceased donor organs for transplantation we would like to acknowledge that issues related to living donor transplantation also require attention. In particular, determining whether, and if so to what extent, patients with cognitive impairment have inferior transplant outcomes should be a priority and could help guide clinicians in identifying individuals who may not be suitable for transplantation.

AUTHOR CONTRIBUTIONS

All contributing authors have participated in the consensus process, design and writing of the manuscript. AC/RT led the manuscript and led on the transplant outcomes. AK and KA led on the legal section. AD-A, TK and EB led on the ethics section. All authors agreed on the categories of patients with impaired decision making. AC was senior author with oversight of the entire manuscript and is chair of the "ethical and legal issues" working group of ESOT.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

We thank the European Society for Organ Transplantation for facilitating the consensus process.

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ORIGINAL RESEARCH
published: 19 May 2022
doi: 10.3389/ti.2022.10289

Radiological Screening Methods in Deceased Organ Donation: An Overview of Guidelines Worldwide

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Organ transplantation is performed worldwide, but policies regarding donor imaging are not uniform. An overview of the policies in different regions is missing. This study aims to investigate the various protocols worldwide on imaging in deceased organ donation. An online survey was created to determine the current policies. Competent authorities were approached to fill out the survey based on their current protocols. In total 32 of the 48 countries approached filled out the questionnaire (response rate 67%). In 16% of the countries no abdominal imaging is required prior to procurement. In 50%, abdominal ultrasound (US) is performed to screen the abdomen and in 19% an enhanced abdominal Computed Tomography (CT). In 15% of the countries both an unenhanced abdominal CT scan and abdominal US are performed. In 38% of the countries a chest radiographic (CXR) is performed to screen the thorax, in 28% only a chest CT, and in 34% both are performed. Policies regarding radiologic screening in deceased organ donors show a great variation between different countries. Consensus on which imaging method should be applied is missing. A uniform approach will contribute to quality and safety, justifying (inter)national exchange of organs.

Keywords: screening, transplantation, ethics, organ donation, organ procurement, imaging, guidelines, transplant ethics

OPEN ACCESS

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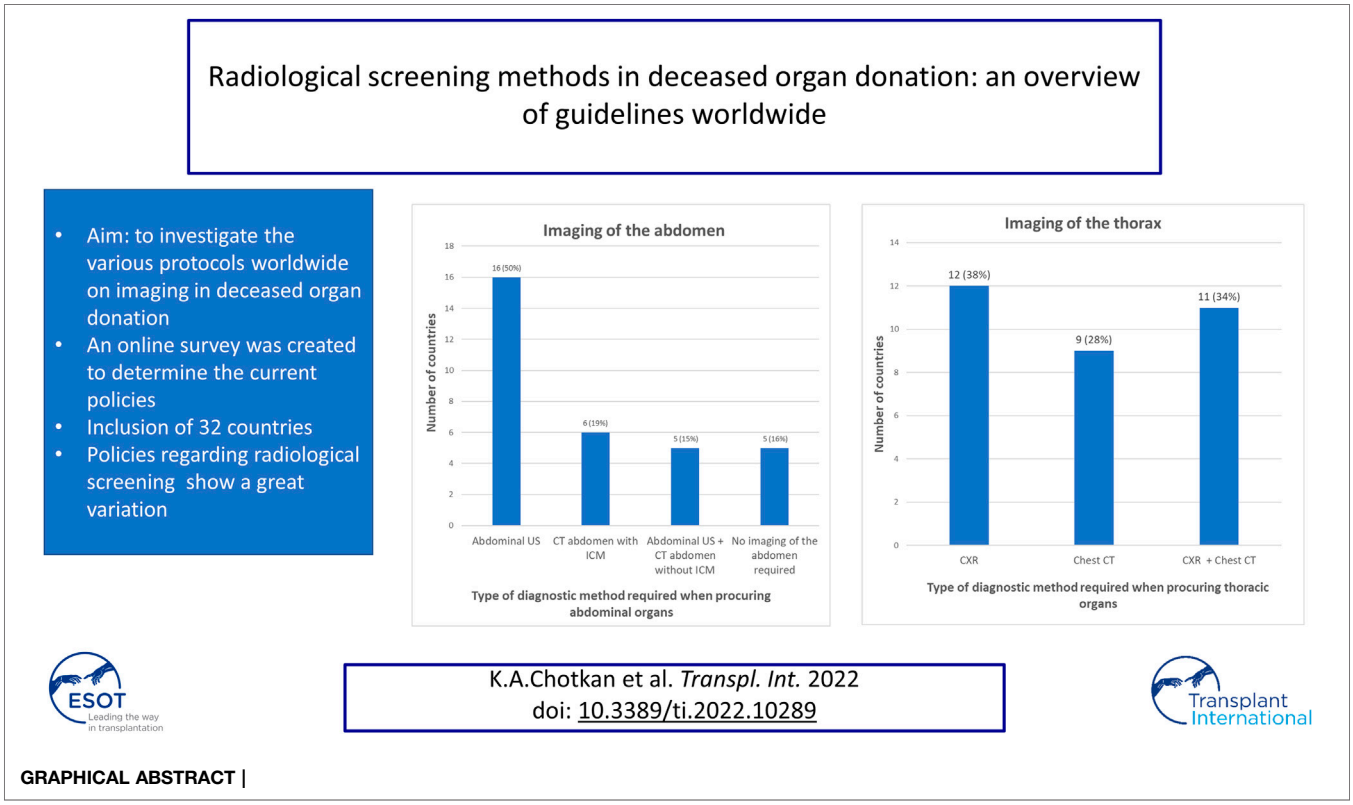
Received: *07 December 2021*
Accepted: *26 April 2022*
Published: *19 May 2022*

Citation:
Chotkan KA, Mensink J, Pol RA, Van Der Kaaij NP, Beenen LFM, Nijboer WN, Schaefer B, Alwayn IPJ and Braat AE (2022) Radiological Screening Methods in Deceased Organ Donation: An Overview of Guidelines Worldwide. Transpl Int 35:10289. doi: 10.3389/ti.2022.10289



GRAPHICAL ABSTRACT |

INTRODUCTION

Organ transplantation is a lifesaving treatment for patients with end-stage organ failure but is not without risk for the recipient. The comprehensiveness and quality of donor assessment contribute to adequate risk management, applicable to individual and vulnerable recipients. Optimal donor assessment provides important information on organ quality and anatomy. Donor assessment includes interviews with relatives, assessment of the medical and social behavior history, full physical examination, laboratory tests, and complementary tests (in particular imaging) (1). In Netherlands (part of the Eurotransplant region), radiological screening in deceased organ donors consists of at least a chest radiography (CXR) and abdominal ultrasound (US). Various studies in the past have advocated for the inclusion of the use of chest and abdominal Computed Tomography (CT) scans to optimally prepare a donor and identify risk factors (2–4). Possible advantages of the use of CT scans are more accurate screening for malignancies and other significant diseases, mapping of aberrant (vascular) anatomy, enhanced assessment of organ quality, and improved size matching in liver and lung transplantation.

More detailed imaging may also have a downside; incidental findings on chest and (un)enhanced abdominal CT scans have a prevalence ranging from 40% to 75%. Of these, 3%–20% findings require additional investigations (5–8). This could possibly lead to more (invasive) diagnostic procedures with potential risks and could delay the procurement and allocation process. On the other hand, when being informed pre-operatively of these findings, biopsies can be obtained before procurement.

Also, to perform an enhanced CT scan, intravenous contrast medium (ICM) must be administered, which leads to exposure of donor kidneys to a potential nephrotoxic contrast medium. A recent publication of Magnus et al., containing a retrospective analysis of 709 kidney donors who received ICM, showed no difference in serum creatine levels in the donor, delayed graft function (DGF) or graft loss in the recipients compared to 685 kidney donors who did not receive ICM (9). This group only contained Donation of Brain death (DBD) donors and no Donation after Circulatory Death (DCD) donors. The DGF rate in DCD kidneys is known to be significantly higher compared to DBD kidneys (10). The added effect of ICM may therefore have an even higher (negative) impact on outcome by inducing acute kidney injury (AKI). Finally, transport to the radiology department of a critically ill patient adds additional risks.

Although organ transplantation is performed worldwide, policies regarding donor assessment and imaging are not uniform. An overview of the policies and underlying arguments in different regions of the world could provide valuable information for countries who are thinking about changing their policy. A uniform approach will contribute to quality and safety, justifying (inter)national exchange of organs.

This study therefore aims to provide an overview on the various protocols for radiological screening in deceased organ donation worldwide.

TABLE 1 | Overview of the screenings method used in which country.

Country	Screening of the thorax when only thoracic organs are being procured	Screening of the abdomen when only thoracic organs are being procured	Screening of the thorax when only abdominal organs are being procured	Screening of the abdomen when only abdominal organs are being procured	Number of deceased donors PMP (per million people) in 2019	Guidelines used in the whole country
Australia/ New Zealand	Chest X-ray (for lung donors only if they meet certain criteria a chest CT is performed)	No Imaging performed of the abdomen	Chest X-ray	No Imaging performed of the abdomen	Australia: 20.10 New Zealand 12.40	Yes
Austria	Chest X-ray	Abdominal ultrasound	Chest X-ray	Abdominal ultrasound = minimal mandatory In daily practice abdominal ultrasound and CT	20.30	Unknown
Belarus	Chest CT	Abdominal ultrasound	Chest X-ray	Abdominal ultrasound	26.20	Unknown
Belgium	Chest X-ray and chest CT	Abdominal ultrasound	Chest X-ray and chest CT	Abdominal ultrasound	27.20	Yes
Canada	Chest X-ray	None	Chest X-ray	None (Abdominal imaging is only advised in those with age >50, comorbid conditions, high BMI or clinical history of malignancy)	21.87	Yes (But every transplant region can ask for additional examinations)
Croatia	Chest X-ray	→ very rarely only thoracic organs, but if it happens, abdominal ultrasound	Chest X-ray	Abdominal ultrasound	31.20	Unknown
Czech Republic	Chest X-Ray and Chest CT (→ due to COVID)	Abdominal ultrasound	Chest X-Ray and chest CT	Abdominal ultrasound + CT abdomen without ICM	24.98	Yes
Ecuador	Chest X-ray and chest CT	Abdominal US	Chest X-ray	Abdominal ultrasound + CT abdomen without ICM	7.78	Unknown
Estonia	Chest X-Ray and chest CT	Abdominal ultrasound + CT abdomen without ICM	Chest X-Ray and chest CT	Abdominal ultrasound + CT abdomen without ICM	18.87	Yes
Finland	Chest CT	None	Chest X-ray and CT thorax	CT abdomen with ICM	25.51	Yes (only one transplantation centre in Finland)
France	Chest CT	CT abdomen with ICM	Chest CT	CT abdomen with ICM	33.25	Yes
Germany	Chest X-ray (if CT/MRT is done, it is always covering thorax and abdomen)	Abdominal ultrasound	Chest X-ray (if CT/ MRT is done, it is always covering thorax and abdomen)	Abdominal ultrasound (CT/ MRT whenever possible, ICM depends on the individual situation)	10.8	Yes
Greece	Chest CT	Abdominal Ultrasound	Chest X-ray	Abdominal ultrasound	5.0	No
Hungary	Chest X-ray and Chest CT	Abdominal ultrasound	Chest X-ray	Abdominal Ultrasound	18.11	Yes
Iran	Chest X-ray and Chest CT	Abdominal ultrasound	Chest X-ray	Abdominal ultrasound	14.34	Yes
Israel	Chest CT	CT abdomen with ICM	Chest CT	CT abdomen with ICM	10.43	Yes
Italy	Chest X-Ray and Chest CT	Abdominal ultrasound	Chest X-ray	Abdominal ultrasound	22.80	Yes

(Continued on following page)

TABLE 1 | (*Continued*) Overview of the screenings method used in which country.

Country	Screening of the thorax when only thoracic organs are being procured	Screening of the abdomen when only thoracic organs are being procured	Screening of the thorax when only abdominal organs are being procured	Screening of the abdomen when only abdominal organs are being procured	Number of deceased donors PMP (per million people) in 2019	Guidelines used in the whole country
Japan	Chest X-ray	Abdominal Ultrasound	Chest X-ray	Abdominal ultrasound and CT abdomen without ICM	0.98	No
Netherlands	Chest X-ray	Abdominal ultrasound	Chest X-ray	Abdominal ultrasound	14.47	Yes
Norway	Chest X-ray and Chest CT	CT abdomen without ICM	Chest X-ray and chest CT	CT abdomen with ICM	18.18	Yes
Slovenia	Chest X-ray	Abdominal ultrasound	Chest X-ray and chest CT	Abdominal ultrasound	18.26	Yes
South Africa	Chest X-ray	No standard imaging of the abdomen required		No standard imaging of the abdomen required	1.29 (2016)	No
South Korea	Chest X-Ray and Chest CT	Abdominal ultrasound + CT abdomen without ICM	Chest X-Ray and CT thorax	Abdominal ultrasound + CT abdomen without ICM	8.68	Yes
Spain	Chest X-ray + Chest CT	Abdominal ultrasound	Chest X-ray	Abdominal ultrasound	49.61	Yes
Sweden	Chest CT	CT abdomen without ICM	Chest CT	CT abdomen with ICM	18.51	Yes
Switzerland	Chest X-ray + Chest CT (→ criteria defined by the lung expert group)	Abdominal ultrasound (→ when CT thorax is included, a CT abdomen is asked as well)	Chest X-ray	Abdominal ultrasound	19.30	Yes
Thailand	Chest X-ray	None	Chest X-ray	Abdominal Ultrasound (if indicated)	4.51	Yes
United Kingdom	Chest X-ray	No Imaging performed of the abdomen	Chest X-Ray	No Imaging performed of the abdomen	23.01	Yes
United States	Chest X-ray	Abdomen→ none	Chest X-ray	None	36.88	Yes (But every transplant region can ask for additional examinations)

Only the countries who gave permission to name their country were included in this table.

MATERIALS AND METHODS

To investigate whether an overview of the different policies in organ donor screening was available, a literature search of PubMed was performed, using Mesh terms; diagnostic imaging, tissue donors, tissue and organ procurement (**Supplementary Appendix S1**).

Additionally, an online survey was created in Survey Monkey to obtain country specific information (**Supplementary Appendix S2**). For information on countries with an active deceased organ donation program, and the annual number of (deceased) donors, the website International Registry in Organ Donation and Transplantation (IRODaT) was consulted (11). From 71 countries with a deceased organ donation program, transplant authorities were selected if they reported a total of at least 30 deceased donors per year (donation activity), based on the numbers of 2019, since 2020 is not representative due to the SARS-CoV-2 pandemic. This led to an inclusion of 48 countries. The value of a minimum of 30 deceased donors per year was chosen to include a large diversity of countries, including smaller countries, but to exclude countries which do not have deceased donation on a regular basis (and most likely do not have standardized guidelines for deceased organ donation). Contact information of these selected countries was obtained from Eurotransplant International, the Dutch Transplant Foundation and websites of the competent authorities of organ donation or donation professionals. Between May and July 2021, these contacts were approached by email to fill out the questionnaire.

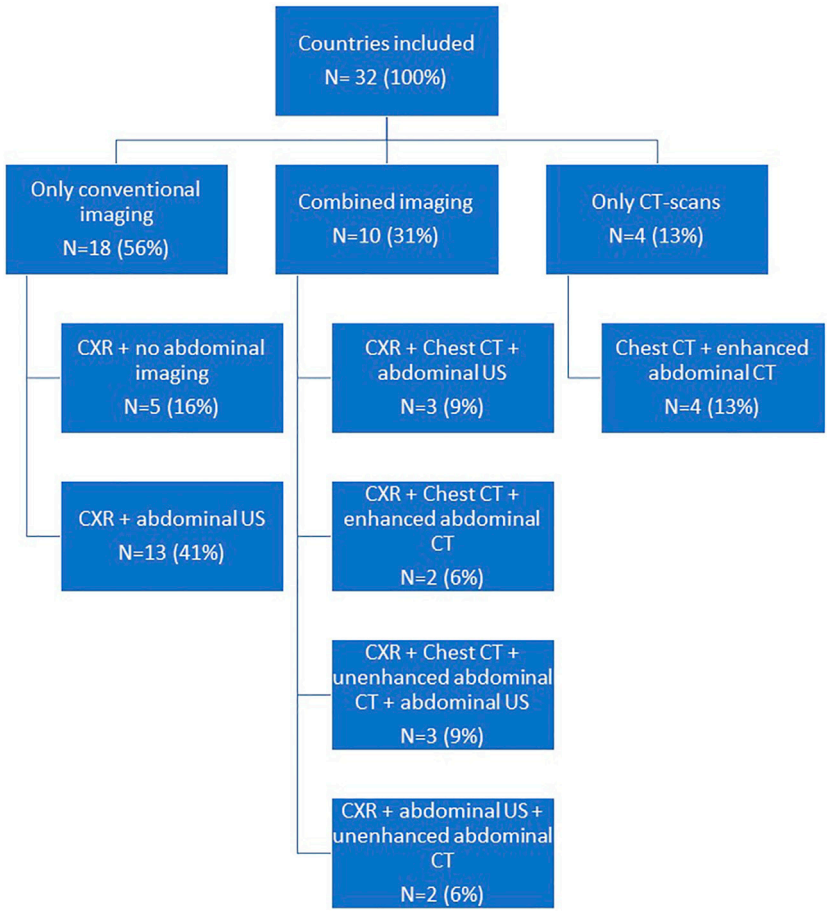


FIGURE 1 | Flow chart on imaging performed when procuring abdominal organs.

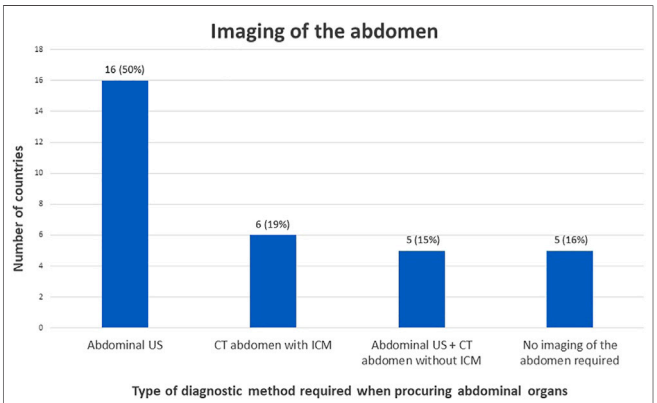


FIGURE 2 | Graphical view of number of countries in which a certain policy is applied regarding imaging of the abdomen.

To answer the question of whether imaging policies were associated with donor rate and donation activity, statistical analyses were performed using IBM SPSS Statistics for Windows (IBM Corp. Released 2017. Version 25.0. Armonk, NY). Shapiro-Wilk tests were used to assess the distribution of donor rate/donation activity between the imaging groups. To compare skewed numerical data the Kruskal Wallis test was used.

RESULTS

An overview of different guidelines regarding radiological screening in deceased organ donation was not found in PubMed. The Guide to the quality and safety of organs for transplantation from the council of Europe (1) has a specific chapter on donor imaging. In this chapter it is advised that at minimum, an up-to-date CXR and abdominal US should be included at the time of donation. Further radiological tests are advised to be performed when thorough donor evaluation is required, for example in patients with suspected malignancies or in donors in whom it is thought that appropriate intra-operative examination of the thoraco-abdominal cavities cannot be adequately carried out.

Thirty-two out of 48 countries on six continents responded to the questionnaire (response rate 67%). **Table 1** gives an overview of all the diagnostic screening methods reported in the survey, including the number of deceased donors PMP (per million

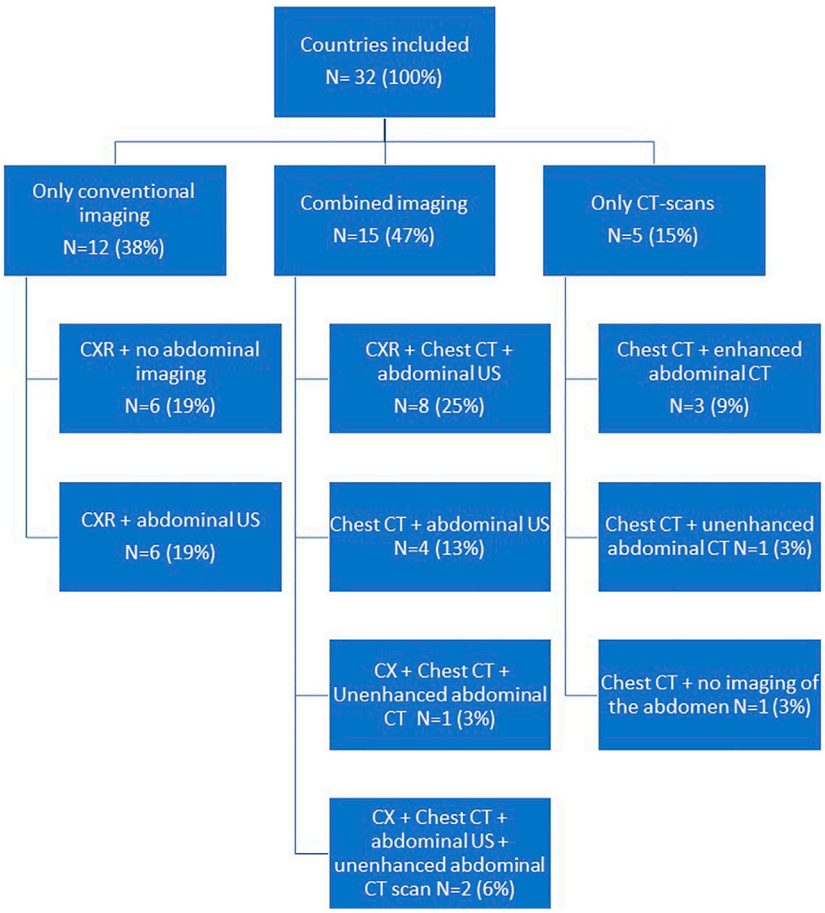


FIGURE 3 | Flowchart on imaging performed when procuring thoracic organs.

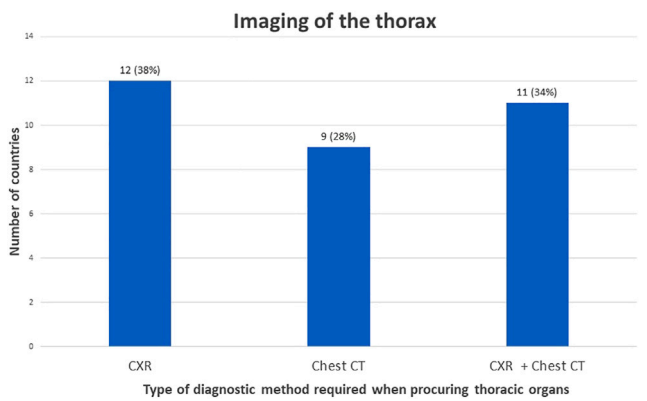


FIGURE 4 | Graphical view of number of countries in which a certain policy is applied regarding imaging of the thorax.

people) per country. **Supplementary Datasheet 3** provides an overview of how many countries per region have been approached and the response rate per region. Three organizations did not give permission to publish their answers. Although these are not included in **Table 1**, their answers were analysed anonymously. Some countries replied that the guidelines were region dependent and do not apply to the whole country. This is also included in **Table 1**. Also, three respondents mentioned that guidelines describe the minimal requirements and that the accepting transplant centre could ask for additional examinations.

Procurement of Abdominal Organs

For the assessment of abdominal organ quality, CXR and abdominal US is considered the preferred screening method in 41% countries (**Figures 1**, **2**). In 9% an abdominal US is performed in combination with a chest CT instead of a CXR. In 13% of the countries a chest and abdominal CT scan is part of the regular screening of deceased donors, in 6% next to these two imaging methods also a CXR is performed. In Finland, Norway, Sweden, France, and Israel an enhanced abdominal CT is made, excluding donors with existing or high risk for acute kidney injury (AKI). Unfortunately, the definition of what was considered a high-risk kidney donor was not further explained. In 15% of the countries an abdominal US as well as an unenhanced abdominal CT is performed. In 16% of the countries there are no minimal requirements regarding

abdominal imaging prior to procurement and only a CXR is considered necessary.

Procurement of Thoracic Organs

To determine suitability of thoracic donor organs only a CXR is required in 19% of the countries, with no requirements of imaging of the abdomen. (**Figures 3**, **4**). A CXR and abdominal US were considered the preferred screening method in 19% of the countries. In 25% a CXR, chest CT and abdominal US is performed. In 13% both a chest CT and abdominal US is carried out. In 9% of the countries chest CT and enhanced abdominal CT scan is performed. In 3% a CXR, chest CT and an unenhanced abdominal CT scan is made. A CXR, chest CT, an unenhanced abdominal CT scan plus abdominal US are performed in 6% of the countries. In 3% a chest CT and unenhanced abdominal CT scan was required, and another 3% required only a chest CT and no imaging of the abdomen.

Summary of Preferences

Most countries (81% of the respondents) report that there are no objections against using CT scans in the screenings process of deceased donor organ donation. The reasons CT-scans are preferred are to facilitate the detection of malignancies (76% of the respondents were in favour of CT scans), and provide information about (aberrant) anatomy of the donor (68%). Sixty-four percent also reported CT scans have a value in providing information about organ quality, for example liver steatosis, renal atrophy, severe atherosclerosis, or pulmonary embolism.

Six respondents (16%) replied that there are objections for the routine use of CT scans in the screening process but addressed concerns regarding incidental findings that would unintentionally lead to donor rejection. Other objections were the logistic challenges associated with performing a routine donor CT, i.e., transporting the donor to the CT and increasing costs of the donation process.

If an abdominal CT scan is not part of the standard screening protocol, 76% of the respondents replied that the main reasons for performing an abdominal CT scan is for the purpose of trauma screening, or suspected anomalies detected on the conventional imaging (24%).

If a chest CT scan is not part of the standard screening protocol, 45% of the respondents replied that the main reason for performing a chest CT scan is also for the purpose of trauma screening or suspected anomalies on the conventional imaging (36%). Two respondents replied that reasons for making a chest CT scan was intended for screening for SARS-CoV-2.

Donor rate versus imaging policy was plotted, to investigate whether there is an association between imaging policies before procurement and donation rate (**Supplementary Datasheet 4**). No clear association was seen between these two using eyeball estimation. Using the Kruskal Wallis test, since the data was not normally distributed, no significant difference in donor rate between the different imaging policy groups was found ($p = 0.37$).

Donation activity (the total number of deceased donors per year) versus imaging policy was also plotted, to investigate whether there is an association between imaging policies before procurement and donation activity (**Supplementary Datasheet 5**). No clear association was seen between these two using eyeball estimation. Using the Kruskal Wallis test, since the data was not normally distributed, no significant difference in donation activity between the different imaging policy groups was found ($p = 0.61$).

DISCUSSION

This study shows a large difference between policies regarding diagnostic screenings methods in deceased organ donation in different transplant regions. The current literature lacks a consensus regarding imaging of deceased donors. No significant association between donor rate and imaging policy groups before procurement was found, nor a significant association between donation activity and imaging policy groups. The donor rate of the countries included ranged from 1 to 50 deceased donors PMP. The donation activity of the countries included ranged from 44 deceased donors per year to 11.870 deceased donors per year.

In the Eurotransplant International region (including eight European countries), the age of the donor population is increasing and with it also the comorbidity rate (12). Since this has impact on the incidence of malignancies and organ quality, an intensified assessment using radiological imaging has become increasingly important (13). Also the proportion of DCD donors has increased through the years, a donor pool historically known for its comorbidity and a rapid and mainly cold dissection, without proper perfusion feedback, in which prior knowledge of the anatomy significantly aids to the operative plan (14, 15).

In Finland, Norway, Sweden, France and Israel imaging is performed using chest and enhanced abdominal CT scan. On the contrary, Australia, the United Kingdom and South Africa do not require imaging of the abdomen before procurement of abdominal organs. In the United States and Canada there is no national policy on imaging of the abdomen, but the different Organ Procurement Organisations do have their own policies. In South Africa there is no screening of the abdomen because of costs and logistic challenges, but in Australia this is a well-considered choice because the procuring surgeon always performs an examination of the abdominal cavity and organs. The idea is that the added yield of abdominal imaging is low and could potentially extend the donor work up time (due to evaluation of any abnormalities). The United Kingdom stated that, in their opinion, performing an abdominal US has no additional value. Detection of malignancies depends on exploration of the abdomen by the procuring surgeon, an approach that might work for large tumors but is expected to have a low sensitivity and specificity for smaller of intraparenchymal lesions. With the shift in the donor population towards more older and extended criteria donors, we as professionals should start asking the question of whether it is time for a paradigm shift. Furthermore, it is interesting to note that English-speaking countries tend to avoid imaging prior to procurement, which could suggest there might be a cultural or historical reason for this.

There were conflicting ideas reported regarding the risk of administrating ICM to potential kidney donors. France, Israel, Sweden, and Norway (all four using enhanced abdominal CT scans) are only reluctant giving donors with a marginal kidney function ICM. But what is considered a marginal donor is often poorly reported or defined. Except for Israel, which uses a specific definition, in which donors with an increase in serum creatinine of more than or equal to 50% from baseline, a creatinine level of >150 µmol/L or a reduction in urine output to less than 0.5 ml/kg/h for more than 12 h despite adequate hydration, are excluded. (Of note; this is slightly different from the AKI classification of AKI stage 1/2) (16). None of these four countries have reported any data regarding negative effects on graft function in the recipients of the kidneys exposed to ICM. Estonia performs an unenhanced abdominal CT scan and abdominal US on all their donors. The idea behind this policy is that with an unenhanced abdominal CT the donor is being screened for any abnormalities or pathological findings (and if indicated, this is supplemented with an enhanced CT scan), while doppler ultrasound is used to assess renal vascularization.

Since the introduction of CT scans in the 1970s, it has become an important tool offering fast and reliable diagnosis of various diseases, which accelerated the application within a broad framework in daily medical practice (17–20). The technique of ICM was introduced even before the invention of the CT scanner, but the chemical properties changed through the years; high osmolarity contrast media were replaced, because of its nephrotoxic properties, by low osmolarity contrast and iso-osmolar contrast agents (21).

In donor assessment, the use of CT scans has several (potential) advantages, namely an accurate detection of malignancies and more accurate assessment of organ quality (i.e., liver steatosis, renal atrophy, severity of atherosclerosis, or pulmonary embolism) compared to conventional modalities. In 2019, Mensink et al. performed a retrospective study to assess the additional value of CT scans in donor screening and concluded that, if a CT scan was added to the screening protocol, at least 7 unnecessary procurements (0.5% of all procurements) could be prevented, over a 5 year period, due to the identification of malignancies (22).

Also, in detecting aberrant (vascular) anatomy, for example the kidney and the liver, CT scans will provide valuable information. Multiple renal arteries are not a rarity with a reported incidence of 24%–28% and their presence causes a higher risk of potential complications at procurement with subsequent graft loss or DGF (23–26). The incidence of variants in hepatic arteries is even higher and ranges from 25% to 45%, insufficiently recognized aberrant anatomy could increase the risk of surgical injury during procurement (27–29). In living donor liver and kidney transplantation CT-scans are already routinely performed and proven essential for measuring total and residual liver volume and assess the anatomy (30). These same advantages could be gained in deceased donors and improve transplant outcome and graft survival (30–33). In lung transplantation, matching of the donor lung and recipient thorax is important to prevent size mismatch. Performing a chest CT results in better prediction of the total lung capacity, which therefore benefits the optimal matching and preoperative planning (4, 34).

However, every advantage has its disadvantage. If more accurate imaging is applied, the risk of incidental findings increases, resulting in additional tests and thereby prolonging duration of donor assessment or even cessation of a donor procedure. The extent of this risk is currently unknown and must be weighed against the likelihood of malignancy transmission. On the other hand, not performing a CT scan because of the fear of finding anomalies of unknown significance and a chance of leading to cessation of the donor, means the physicians are taking a calculated risk for transplanting a malignancy. From an ethical perspective, this could raise the question of whether it is safe to transplant these organs.

Also, transporting a potential donor that might be hemodynamically unstable to the CT could also be a challenge. In case of a DCD II (unsuccessful resuscitation) and DCD IV (cardiac arrest in a patient who is brain dead), performing a CT scan is probably in most of the cases impossible.

A CT scans is associated with higher costs compared in comparison to CXR and abdominal US; a chest and abdominal CT scan in Netherlands cost approximately €400 together, while the costs of a CXR and abdominal US together are less than €150 (35). But despite the extra costs, it could be more cost effective by timely cessation of a donor procedure in case of malignancy. Yet this assumption should also be considered in future studies.

This study has a few limitations that need to be addressed. First, not all countries approached replied to our survey and the majority of the countries were from Europe. However, several large and influential transplant organizations did respond. The response rate was 67%, which is in accordance with the response rate in patient and health care professional surveys in surgery (the average response rate was 53%, SD 25%) (36). Since only the countries that replied to the survey could be included, a certain selection bias should be considered. The survey was created by the author itself and reviewed by several procuring surgeons, which could have led to missing questions. For example, the survey did not contain the option to fill out whether chest CT is performed with or without ICM. Nevertheless, none of the respondents commented chest CT was performed using ICM. To define the countries to be approached the IRODaT registry was used instead of the international figures from the Global Observatory on Donation and Transplantation WHO-ONT, since the author was familiar with the IRODaT Registry. After comparing the data from both databases, in 80% of the countries the number of deceased donors was the same in both databases. In 20% of the countries the numbers differed by only a few numbers.

In conclusion, this overview shows that policies regarding radiologic screening in deceased donor organ management are quite different between various countries and transplant organizations throughout the world, based on different views on (the safety of) organ transplantation. Future research should focus on interviewing specific transplant centers or Organ Procurement Organisations regarding their policies. This study shows there is a need to prospectively investigate the value of CT scans in deceased organ donation. In such a study, we would suggest the following outcome measurements; changes in acceptance of

the grafts based on the diagnostic imaging, better matching of donor-recipient (size measure for long and/or liver transplantation) and the incidence of detecting malignancies before procurement. This type of research could contribute to making decisions on policy changes evidence-based and well considered.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AB, RP, WN, BS, and KC participated in designing the survey. KC participated in data collection. All authors participated in construction and critical revision of the article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors gracefully acknowledge all competent transplant authorities for replying to the survey and giving permission to publish the results of the survey.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10289/full#supplementary-material

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ESOT | Transplant International

POINT OF VIEW
published: 13 May 2022
doi: 10.3389/ti.2022.10461

Comparing Deceased Organ Donation Performance in Two Countries that Use Different Metrics: Comparing Apples With Apples

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Organ donation networks audit and report on national or regional organ donation performance, however there are inconsistencies in the metrics and definitions used, rendering comparisons difficult or inappropriate. This is despite multiple attempts exploring the possibility for convergently evolving audits so that collectives of donation networks might transparently share data and practice and then target system interventions. This paper represents a collaboration between the United Kingdom and Australian organ donation organisations which aimed to understand the intricacies of our respective auditing systems, compare the metrics and definitions they employ and ultimately assess their level of comparability. This point of view outlines the historical context underlying the development of the auditing tools, demonstrates their differences to the Critical Pathway proposed as a common tool a decade ago and presents a side-by-side comparison of donation definitions, metrics and data for the 2019 calendar year. There were significant differences in donation definition terminology, metrics and overall structure of the audits. Fitting the audits to a tiered scaffold allowed for reasonable comparisons however this required substantial effort and understanding of nuance. Direct comparison of international and inter-regional donation performance is challenging and would benefit from consistent auditing processes across organisations.

Keywords: transplantation, organ donation, performance, auditing, reporting, metrics, definitions

Point of View

OPEN ACCESS

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Received: *24 February 2022*
Accepted: *25 April 2022*
Published: *13 May 2022*

Citation:
Milross L, Brown C, Gladkis L, Downes K, Goodwin M, Madden S, McDonald M, Barry L, Opdam H, Manara A and Gardiner D (2022) Comparing Deceased Organ Donation Performance in Two Countries that Use Different Metrics: Comparing Apples With Apples. Transpl Int 35:10461. doi: 10.3389/ti.2022.10461

INTRODUCTION

Organ transplantation is a lifesaving, life-transforming intervention which often is the only effective treatment available to patients with end-stage organ failure. Such patients rely on a limited supply of organs and experience high mortality and significant morbidity whilst waitlisted (1). Supply is influenced both by the size of the potential donor pool and critically the efficacy of its conversion into actual donors (2). Conversion broadly depends on healthcare system resources and cultural factors and is facilitated through donor identification, referral and approach, community attitudes to donation, donor physiological support and transplant unit acceptance practices. Countries with advanced donation systems have organ donation organisations which lead in the assessment of national/regional donation

TABLE 1 | Critical pathway for deceased donation definitions—adapted from Dominguez et al. (2011)[6].

Common term	DBD component	DCD component
Potential	Potential DBD donor: A person whose clinical condition is suspected to fulfil brain death criteria	Potential DCD donor: A. A person whose circulator and respiratory functions have ceased and resuscitative measures are not to be attempted or continued, or B. A person in whom the cessation of circulatory and respiratory functions is anticipated to occur within a time frame that will enable organ recovery
Eligible	Eligible DBD donor: A medically suitable person who has been declared dead based on neurological criteria as stipulated by the law of the relevant jurisdiction	Eligible DCD donor: A medically suitable person who has been declared dead based on the irreversible absence of circulatory and respiratory functions as stipulated by the law of the relevant jurisdiction, within a time frame that enables organ recovery
Actual	Actual DBD donor: A consented eligible donor: A. In whom an operative incision was made with the intent of organ recovery for the purpose of transplantation, or B. From whom at least one organ was recovered for the purpose of transplantation	Actual DCD donor: A consented eligible donor: A. In whom an operative incision was made with the intent of organ recovery for the purpose of transplantation, or B. From whom at least one organ was recovered for the purpose of transplantation
Utilised	Utilised DBD donor: An actual donor from whom at least one organ was transplanted	Utilised DCD donor: An actual donor from whom at least one organ was transplanted

conversion performance, collecting data to identify barriers to donation, direct interventions and measure the effect of their implementation.

Meaningful comparison of national/regional donation metrics might allow for sharing of best practice and overall improvement of donation performance. Countries with low conversion rates could learn from practices of countries with better performance (3). However, difficulties exist in comparisons due to inconsistencies in the definitions and metrics used as performance indicators (4). Indeed, a recent US study showed significant variability in the performance rankings of organ procurement agencies depending on which donation metrics were used (5).

The "Critical Pathway for Deceased Donation," the outcome of a multi-national initiative held between 2008–10, was aimed to provide a solution to this issue by providing a set of common definitions to guide consistency in reporting of donation performance (6). However, while the Critical Pathway was welcomed, the goal of common international definitions has not been realised and many nations have witnessed divergent evolution in the audit of donation performance. We aimed to explore this issue through a collaboration between the national donation organisations of the United Kingdom and Australia, both countries which contributed to the development of the critical pathway. In this point of view, we will outline the critical pathway for deceased donation, the history of the development of our individual auditing tools and finally, investigate the degree of comparability between our donation definitions and metrics.

THE CRITICAL PATHWAY FOR DECEASED DONATION

The critical pathway for deceased donation was developed by a multi-national collective at the Madrid Resolution on Organ Donation and Transplantation (7) and published by Dominguez et al. in 2011 (6). It outlines a series of definitions which enable all "possible deceased organ donors" to be quantified, including definitions for "potential" donors, "actual" donors and "utilised" donors. A similar template was recently suggested for European tissue donation (8). The value of this structured approach to donation networks is its ability to pinpoint where unrealised donation opportunities occur along the pathway. Where cases of avoidable unrealised donation are identified, interventions can be targeted to increase rates of donation.

Inclusion in the "possible deceased organ donor" pool is defined by the critical pathway as "A patient with devastating brain injury or lesion or a patient with circulatory failure and apparently medically suitable for organ donation"(6). The pathway then splits into two components, separating into donation after brain death (DBD) and donation after circulatory death (DCD) pathways. There are four major steps to each pathway (**Table 1**); "Potential," "Eligible," "Actual" and "Utilised" DBD/DCD donors.

THE DEVELOPMENT OF THE UK AND AUSTRALIAN DONATION AUDITS

The development of the potential donor audit (PDA) in the UK followed the publication of a study auditing DBD potential in intensive care units (ICUs) which estimated a possible 20% increase in deceased kidney donation based on prompt testing for brain stem death (9). Following this publication, the first UK PDA, auditing the DBD pathway, was established in 2003. Since then, the PDA inclusion criteria have been extended, firstly in 2009 to also audit the potential for DCD donation and include deaths in emergency departments (EDs), and next in 2013 when the age criteria were extended from 75 years and under to 80 years and under. Enhancements to the PDA were made in 2020 to capture more informative data on the medical suitability of eligible DCD donors and further detail on the donation

TABLE 2 | Differences in audited deaths included in the UK and Australian donation audits.

	United Kingdom	Australia
Inclusion criteria	Deaths under 80 years old occurring in intensive care OR emergency department (excluding deaths in neonatal ICU)	Deaths under 80 years old or >28 days old occurring in intensive care or emergency departments OR occurring anywhere in hospital within 24 h of presence in intensive care OR emergency department where irrecoverable brain injury present. Additional inclusion of patients >80 yr if formal request for consideration of donation placed by family and donation considered feasible by attending staff
Data pathway structure	DBD and DCD data audited separately	DBD and DCD data combined in audit
Network Organisation	National, centralised service: "Statistics and Clinical Research department, NHS Blood and Transplant"	National, centralised service: the "Organ and Tissue Authority" (OTA) which maintains a web-based auditing tool capturing approx. 98% of deceased donation activity in Australia
Data Collection and input	Specialist Nurses in Organ Donation embedded in individual hospitals	Nurse donation specialists embedded in individual hospitals or through outreach roles in smaller hospitals without permanent embedded staff

decision conversations. Since this time, data are collected via an app and can be entered in real time. Data are input and validated by Specialist Nurses in Organ Donation (SNODs), employed by NHS Blood and Transplant (NHSBT), who are embedded in the individual hospitals.

Early audits of hospital deaths occurred in several states in Australia with the aim of quantifying the potential for organ donation, focusing on identifying missed donor cases (10-12). Most missed opportunities for donation occurred in severely brain injured patients who, due to poor prognoses, had treatment withdrawn in the ED or ICU. The first national audit occurred during a National Organ Donation Collaborative from 2006–09. In 2009, a national reform began that included the establishment of a national agency, the Organ and Tissue Authority and the state-based DonateLife Network. The DonateLife Audit was developed as a monitoring tool with retrospective review of all hospital patient deaths with donor potential. A new web-based tool was implemented in 2012 that included fields for donor physiology and organ function, providing more detailed information about donor organ suitability for transplantation. The audit provides a means of optimising clinical practice both at a local and national level, identifying cases with learning points for local case review and providing national, jurisdictional and hospital level data on measures such as the donor pool, and rates of consent and donation (13). Regular internal reporting enables monitoring of clinical practice improvement including the routine referral to donation services of patients at medical consensus of end-of-life and utilisation of a best practice approach to offering donation to families (14). The audit is completed by donation specialist staff and is undertaken in most Australian hospitals with donor potential.

A COMPARISON OF UK AND AUSTRALIAN DEFINITIONS AND METRICS USED IN DONATION REPORTING

Over 2020–2021, we conducted a series of virtual meetings aiming to compare national methods, definitions and metrics used for data collection and reporting of national deceased donation performance. Tables were created outlining the definitions used in DBD and DCD pathways set out by the "Critical Pathway for Deceased Donation" (6) in the first column, with further columns left blank for population by nearest equivalent definitions from Australian and UK official reference documents. These included the "Potential Donor Audit Report 2019–20" from NHS Blood and Transplant, UK and the "DonateLife Audit Standard Operation Procedure" used by the Organ and Tissue Authority in Australia. Side-by-side definitions allowed for in-depth discussion within the group surrounding similarities and differences between definitions used. Minutes were taken and differences and similarities synthesised through discussion across subsequent meetings.

General differences between the auditing structures were immediately apparent (**Table 2**). Estimating the potential donor pool is essential to any donation audit and the first challenge is that the two national audits cast differently sized nets in the denominator of audited deaths. In the UK, deaths are only audited if they physically occurred within the ICU or ED. In Australia, this is extended to deaths due to irrecoverable brain injury occurring anywhere in hospital within 24 h of being in an ICU or ED. The audits also differ slightly in age at death range captured. Both audits capture deaths from 28 days to 80 years, however the Australian audit also includes patients who were referred for consideration of organ donation outside these criteria, for example those above 80 years old where a family request was made and where donation was considered feasible by attending staff. Differing inclusion criteria mean that when it comes to comparing the possible donor pools between countries, we could only proceed by restricting inclusion to death in ICU alone.

The basic structure of the audit also differed. In the UK, when DBD and DCD cases are audited they feed into separate streams of data collection (similar to the Critical Pathway) whereas in Australia these streams are combined (**Figure 1**).

Despite some differences in terminology used between countries, both audits could be fitted to seven major tiers (**Figure 1**). The general inclusion criteria (Tier 1) already represented an uneven starting point for comparisons, and differences continued throughout the tiers. **Table 3** outlines

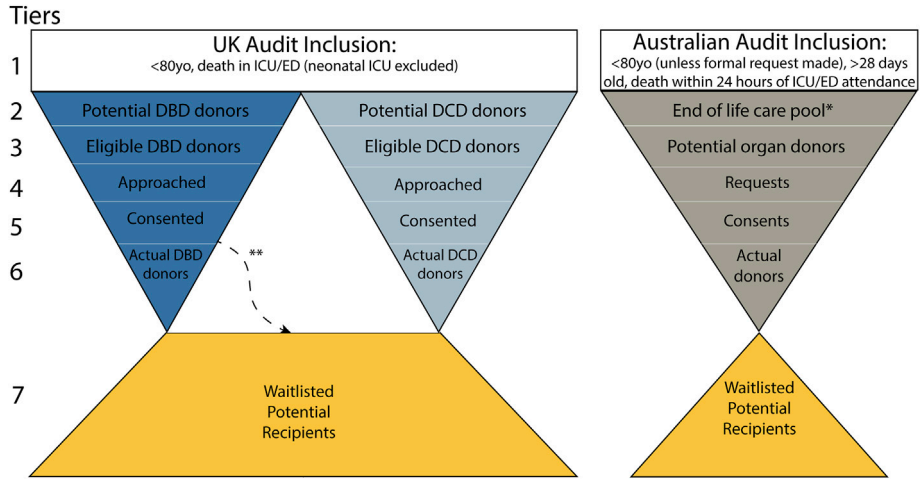

FIGURE 1 | Structure of donation performance audits in the UK (left) and Australia (right). *Not publicly available, **refers to "Actual donors: DCD," a small subset of those who are brain dead who enter a DCD pathway by specific request of family.

specific differences in the UK and Australian donation audits in Tiers 2–6. Tier 2 represents the first group in each audit which is deemed to have donation potential, thus warranting inclusion for further evaluation. In the UK, potential DBD and DCD donors are separate and feed down the audit as such whereas in Australia these groups are combined into an "End-of-Life Care Pool." The Australian end-of-life care pool contains patients confirmed brain dead (or likely to have fulfilled criteria for brain death), or had treatment withdrawn and where death was anticipated, thus combining the DBD and DCD streams.

There were differences in the inclusion criteria of potential DBD- and DCD-pathway patients. For DBD in the UK, Tier 2 contains those suspected of brain death and meet criteria for formal neurological death testing whereas in Australia Tier 2 captures both suspected and confirmed brain dead patients. For DCD in the UK, a timeframe is applied to the potential DCD donor definition with inclusion if death was anticipated within 4 hours of withdrawal of life-sustaining treatment whereas Australia includes deaths which actually occurred within 6 h of withdrawal (or longer if DCD was planned but death did not occur within 6 h).

Tier 3 represents those in Tier 2 who are then deemed medically suitable with no absolute contraindications to donation. The UK refers to these patients as "Eligible DBD/DCD donors" as per the Critical Pathway (6) whereas Australia uses the term "Potential donors." For inclusion of those in the brain death pathway in Tier 3, confirmation of brain death by formal neurological testing is essential to both audits. Data is impacted at Tier 3 due to differences in exclusion criteria outlined by nationally accepted lists of absolute contraindications.

Tier 4 refers to the interaction between donor families and healthcare staff including donation coordinators, nurses and hospital doctors. In the UK, donation coordinators are referred to generically as Specialist Nurse-Organ Donation (SNOD) and in Australia the term Donation Specialist Nurse encompasses a number of slightly varying roles. At this tier, differing semantics are used, however both "Approach" (UK) and "Request" (Australia) are used in the audit which refers to family approaches to offer donation. Where these definitions do differ is in their denominator, with only those deemed eligible included in the UK whereas in Australia it is all discussions held, including those which may have been raised by families or led by ICU staff where donation was initially considered feasible although ultimately the person was not suitable.

Tier 5 is the consent rate of those families approached or requested for donation. The combined DBD/DCD Australian figure means comparison of specific consent, between the two types of deceased organ donation, cannot be readily achieved such as in the UK.

Tier 6 counts where donation is considered to have taken place. In the UK, "actual donor" status is defined by organ retrieval with the intention to transplant whereas in Australia cases are included at the point of "knife to skin" of the donor, both irrespective of actual utilisation (implantation) of organs. A final difference in audit structure occurs here as the UK reports on the small proportion of those included in the DBD pathway who actually proceed down a DCD pathway due to specific requests from the family to be present when the heart stops beating. Such cases also occur in Australia in practice.

COMPARISON OF REAL DATA—WHAT CAN BE REASONABLY COMPARED?

We next examined real data collected by both national audits (**Table 4**). The 2019 calendar year was chosen as this was the most recent year where donation activity was not impacted by the COVID-19 pandemic. To proceed, the DBD and DCD streams in the UK audit needed to be totalled for equivalence to the corresponding Australian tiers. We were able to compare figures for the possible donor pool (Tier 1) by adjusting the catchment to include only deaths occurring within ICUs.

TABLE 3 | Specific differences in the UK and Australian donation audits.

Tier	UK—DBD	UK—DCD	Australia	Comments
2	"Potential DBD donor" A patient who meets all four criteria (coma, ventilated, fixed pupils, apnoeic) for neurological death testing excluding those not tested due to reasons "cardiac arrest despite resuscitation," "brainstem reflexes returned," "neonates—less than 2 months post term"	"Potential DCD donor" A patient who had treatment withdrawn and death was anticipated within 4 hours	"End-of-life care pool" Any patient who meets the following criteria: -Confirmed or suspected brain death -Withdrawal of one or more of mechanical ventilation, artificial airway, mechanical circulatory support prior to death as part of the process of end-of-life care -A decision was made regarding organ donation	-Differing terms -DBD: Australian audit combines suspected brain dead and those confirmed via testing DCD: UK places time restriction of anticipated to 4 hours -"End-of-Life Care Pool" data not publicly available
3	"Eligible DBD donor." Patients for whom death was confirmed following neurological tests and who had no absolute medical contraindications to solid organ donation	"Eligible DCD donor" Patients who had treatment withdrawn and death was anticipated within 4 hours, with no absolute medical contraindications to solid organ donation	"Potential donor" Any of the "End-of-Life Care pool" who were medically suitable/had no absolute medical contraindications to solid organ donation	-Differing terms -Neurological tests to confirm brain death for inclusion in category in both countries -Inclusion subject to differences in lists of absolute medical contraindications/ medical suitability
4	"Approached DBD donors." Eligible DBD families approached for consent/ authorisation for donation	"Approached eligible DCD donors." Eligible DCD donor families approached for consent/authorisation for donation	"Requests" Count of all cases where organ donation was discussed with the family and a final decision of consent or decline was made. Includes all requests, regardless of age or potential donor status, except cases where family was advised of lack of donor suitability	-Differing terms -Differing denominators with UK using eligible DBD/DCD donors only -UK also uses both terms "consent" and "authorisation" owing to different legislation in Scotland
5	"Consented DBD donors." Families or nominated/appointed representatives of eligible DBD donors approached for formal organ donation discussion where consent/authorisation was ascertained	"Consented eligible DCD donors." Families or nominated/appointed representatives of eligible DCD donors approached for formal organ donation discussion where consent/ authorisation was ascertained	"Consents" Consent for organ donation is given by the family or next of kin. Cases where the family is advised of lack of donor suitability are not included	-Congruent in inclusion of actual family donation conversations in cases which had no absolute or prior identified medical contraindications
6	"Actual donors: DBD": Consented, eligible DBD pathway patients who became actual DBD donors as defined by organ retrieval with the intention to transplant (unless returned to donor where considered unsuitable)	"Actual DCD donors": Consented, eligible DCD pathway patients who became actual DCD donors as defined by organ retrieval with the intention to transplant (unless returned to donor where considered unsuitable)	"Actual donors": A person for whom the organ retrieval procedure commenced in the operating room (with surgical incision) for the purpose of transplantation. This includes donors who may have been deemed medically unsuitable during surgery or after the removal of organs	-Actual donation defined at "knife to skin" of donor in Australia and "organ retrieval with the intention to transplant" in UK. -Select few in DBD pathway in UK who became DCD donors due to specific requests of family reported in audit. This does occur in Australia however is not publicly reported

However, this by necessity, excluded deaths associated with other locations such as EDs and wards and thus underestimates the true donor pool (11). Where appropriate, data was provided in absolute numbers as well as in per million population (pmp) however we note population age distribution impacts national donation potential (15). This figure is also impacted by proportion of donation-compatible deaths, for example differing due to variable cerebrovascular disease and traffic accident mortality (16).

DISCUSSION

Direct comparison of UK and Australian deceased organ donation data was challenging due to differences in the metrics and definitions used by the national donation networks. A tiered structure allowed approximations at each step of the pathway and subsequently, certain comparisons could be cautiously made. Interpretation of comparisons requires detailed understanding of the way data is derived, collection methods, flow and the relationships between data points.

Difficulties in comparing national donation performance is not a new issue. Jansen et al. (2009) found significant heterogeneity in definitions used for "potential organ donor" and "refusal rate" across 11 European countries (4). They concluded non-uniform definitions meant that comparisons were not appropriate and called for shared definitions. In the United States, non-standardised, inconsistent, self-reported metrics reported by Organ Procurement Organisations (OPOs)

TABLE 4 | Comparison of 2019 donation activity data in the UK and Australia across tiers. Population estimate used for per million population (pmp) calculations were 66.8 million in the UK and 25.37 in Australia for 2019.

Tier	Corresponding metric	UK (DBD + DCD)	Australia
1	Deaths in chosen location (ICU)	22688 (339 pmp)	5990 (234 pmp)
2	Potential donors (UK) or EOL care pool (Aus)	Not included	Not included (not publicly available)
3	"Eligible" (UK)/"Potential" (Aus)	5844 (87 pmp)	1309 (51 pmp)
4	"Approached" (UK)/"Requested" (Aus)	3351 (50 pmp)	1224 (48 pmp)
5	Consents	2276 (34 pmp)	756 (30 pmp)
	Consent rate	67.9%	62%
6	Actual donors	1624 (24 pmp)	548 (22 pmp)

TABLE 5 | Immediate actions and future directions.

- The most meaningful comparisons between the UK and Australian donation organisations begin at "Tier 4," or the number "approached" or "requested" for donation. Further collaborations between our organisations should focus on downstream data comparisons including consent and conversion rates
- Invite and encourage dialogue between other organ donation organisations interested in updating or evolving their audits by establishing a working group which would routinely meet at a recurring international conference such as the International Society for Organ Donation and Procurement (ISODP) Congress
- The use of standardised definitions and metrics by databases which collect and publish data on organ donation and transplantation activity such as the Global Observatory on Donation and Transplantation (GODT)
- Encourage the use of side-by-side descriptive information alongside data points in publications which aid the reader in understanding how each data point was derived

also make interregional performance assessments problematic (5,17,18). As pointed out by Goldberg *et al.* (2019) this is an issue of fairness as these metrics inform interventions which could improve access in truly underperforming states. Canada also has difficulties with a lack of standardisation possibly due to its provincially-administered healthcare system (19).

Many initiatives have attempted to establish and promulgate a set of standard definitions and metrics which measure donation performance. Most notably, the multi-national collaborative led by Dominguez et al. (2011) established the "critical pathway for deceased donation" which played an important role in providing a universal framework for the process of deceased organ donation (6). However, donation practices constantly evolve, necessitating continuous reassessment of benchmarking practices. A recent 'call to action' from the European Kidney Health Alliance argued there is work to be done and recommended establishing appropriate comparative tools (3).

Our group attempted to take up the mantle of this work. From our minutes, "The goal is the concept of potentially using our two databases and trying to bring them together so that we can actually have comparative metrics." It was noted that the two audits, ". . .have probably evolved in different directions." When comparing our audits, we first noted there were several significant general differences in their structure. The starting points varied due to differing inclusion criteria in estimating the "possible" donor pool. We also note that not all ICUs and EDs report all deaths where organ donation is possible in a consistent and standardised way. To identify the full depth of this pool would require an audit of all hospital deaths nationally (11). For the purposes of our review, we approximated our data by only considering deaths in ICU though this is inconsistent with our actual practice and underestimates the donor pool. Our second major difference was that when DBD and DCD cases are audited they feed into separate streams of data in the UK whereas in Australia they are reported in a combined fashion. A strength of separate reporting is the ease in external assessment of DCD implementation. DCD has been shown as a way to increase donation activity and contributes substantially to overall donation numbers (20) and therefore may benefit from separate monitoring. However, a weakness in stream separation lies in accounting for the small number of potential donors where the donation process was stopped prior to the point where the pathway was completely differentiated or, in the data collection phase, where it was not possible to allocate them retrospectively to a pathway.

We developed a tiered system based on the critical pathway for deceased donation to compare the definitions and metrics used by our audits. At almost every tier there were different uses of terminology and nuance in metrics. It was felt that much of the differences found were in the way data was reported rather than collected and that internal data could be produced which would more readily match the counterpart organisation's data. Undertaking this work itself did help with interpreting each counterpart's figures and some comparisons were felt to represent reasonable approximations.

There are several limitations with auditing donation performance in general. The audits attempt to simplify the messy real world of variably unfolding patient scenarios and different clinician practices and record-keeping. Difficulties arise in capturing scenarios outside of the expected 'order of events', for example where families are approached at earlier stages such as prior to brain death testing. Furthermore, the audits variably combine elements of retrospective data collection as well as data collection which is actively and purposefully collected during the donation process. For example, when recording potential DCD donors, the UK approach would be to include "A patient who had treatment withdrawn and death was anticipated within 4 hours", this relying on the clear recording of "anticipation" of death during the donation process for later retrospective data

collection. In other words, this element of the audit is conducted prospectively but collected retrospectively. In Australia, the observation that death occurred within 6 h of withdrawal of cardio-respiratory support (or beyond 6 h if donation had been planned) is the trigger for inclusion which necessitates the retrospective approach.

We also discussed the mutual development of "quality metrics", including tracking characteristics of the donation conversation, from formalised pre-discussion planning sessions to presence of donation specialise staff. Notably, donation coordinator nursing staff involvement in donation conversations is implicated in increasing DBD and DCD consent rates (21).

Clearly, moving towards a shared reality, "international language" and uniform metrics is desirable. **Table 5** outlines our suggestions for the immediate steps and future directions which can be taken which include further work between our organisations and others. In the future, international donation networks could audit a standardised pool of potential donors, capturing all deaths using a global coding system integrating digital time stamps and in a digitalised, user-friendly system. Metrics could then be generated from shared definitions and reported in multiple formats including absolute numbers, adjustments made for per million population and even considerations for adjustments made for population age distribution and "mortality profiles" (16).

We found that comparison of deceased organ donation data between two countries, which at first glance have similar culture and donation practice, was extremely challenging due to differences in our metrics and definitions. This would be compounded when comparing with even more countries and organ donation organisations. However, this work is essential if we are to search widely for solutions and learn from our partners when addressing the shortage of organs for transplantation. We do know that our goal is the same: the minimisation of unrealised potential donors. We therefore encourage, invite and hope to foster larger collaborative efforts from this international audience towards the goal of convergent evolution of definitions and metrics. This work will become increasingly relevant as practices in organ donation and transplantation evolve with society and time. It's time to compare apples with apples when reporting donation performance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualisation—LM, AM, and DG; Literature search—LM; Figure and table development—LM, CB, LG, KD, MG, SM, and MM; Writing—original draft—LM; Writing—review and editing, including verification of data—CB, LG, KD, MG, SM, MM, LB, HO, AM, and DG.

FUNDING

At the time of writing, LM was supported by a General Sir John Monash Foundation scholarship (2020) for a Master of Research (Immunobiology) at Newcastle University.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW AND META-ANALYSIS
published: 02 February 2023
doi: 10.3389/ti.2023.10913

Anonymity in Kidney Paired Donation: A Systematic Review of Reasons

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The objective of this study was to investigate reasons for or against anonymity that are pertinent to kidney paired donations (KPD). We conducted a systematic review of reasons using PubMed and Google Scholar until May 2022 and through snowballing. Inclusion criteria were publications that: 1) discussed organ donation anonymity; 2) was peer-reviewed; 3) presented at least one reason on anonymity. Exclusion criteria: 1) not published in a scientific journal; 2) grey literature and dissertations. Four researchers independently reviewed and selected papers based on the criteria, extracted text passages and coded them into narrow and broad reason types, selected reasons that were valid for kidney paired donations. 50 articles were included, 62 narrow reasons (n = 24 for; n = 38 against) and 13 broad reasons were coded. Broad reasons were: protection against harm, general benefits, gratitude, curiosity, unrealistic to implement, fundamental rights, respect people's wishes, professional neutrality, timing is important, information disclosure, altruism, reciprocity and donation pool. We did not find reasons that justify legal prohibition of donor-recipient interactions for KPD, if they consented to meet. Professional counselling, follow-up and careful evaluations to prevent potential harm.

Keywords: ethics, anonymity, organ transplantation, systematic review, kidney paired donation

INTRODUCTION

For decades, anonymity has been a core principle in ethical practice of organ donations. The World Health Organization recommends that "personal anonymity and privacy of donors and recipients are always protected" (Guiding Principle 11), and Council of Europe states "anonymity of the donor and of the recipient must be respected" (art. 2.2). Given the intricacies of potential donor-recipient interactions, however, anonymity regulations vary between nations. For instance, Swiss laws on anonymity for paired donation is maintained until pre-surgery, with the possibility of revoking it afterwards, should all concerned persons consent to do so (RS.810.212.3, art. 18). In contrast, anonymity is legally mandated before and after the surgery in European countries, such as Netherlands (1), Spain (Ley 30/1979, art. 4.d) and Sweden (2).

Anonymity legislations are generally applicable to all organ transplant contexts, including unspecified, otherwise known as "non-directed," "altruistic" or "Samaritan" organ donations, and deceased organ donations. For both types, donors and recipients are unrelated and unknown to each other. In specified donations, also known as "directed" organ donations (the organ is intended for a specified recipient), generally a kidney, the donor-recipient relationship can be of genetic or affective nature, such as associations by partnership, friendship or marriage. For specified donations, when a donor is immunologically incompatible to the intended recipient, kidney paired donation (KPD) programs allow donors to give a kidney in exchange of a compatible one from another donor to their intended recipient. Paired organ donations are thus considered a variant of direct organ donation.

OPEN ACCESS

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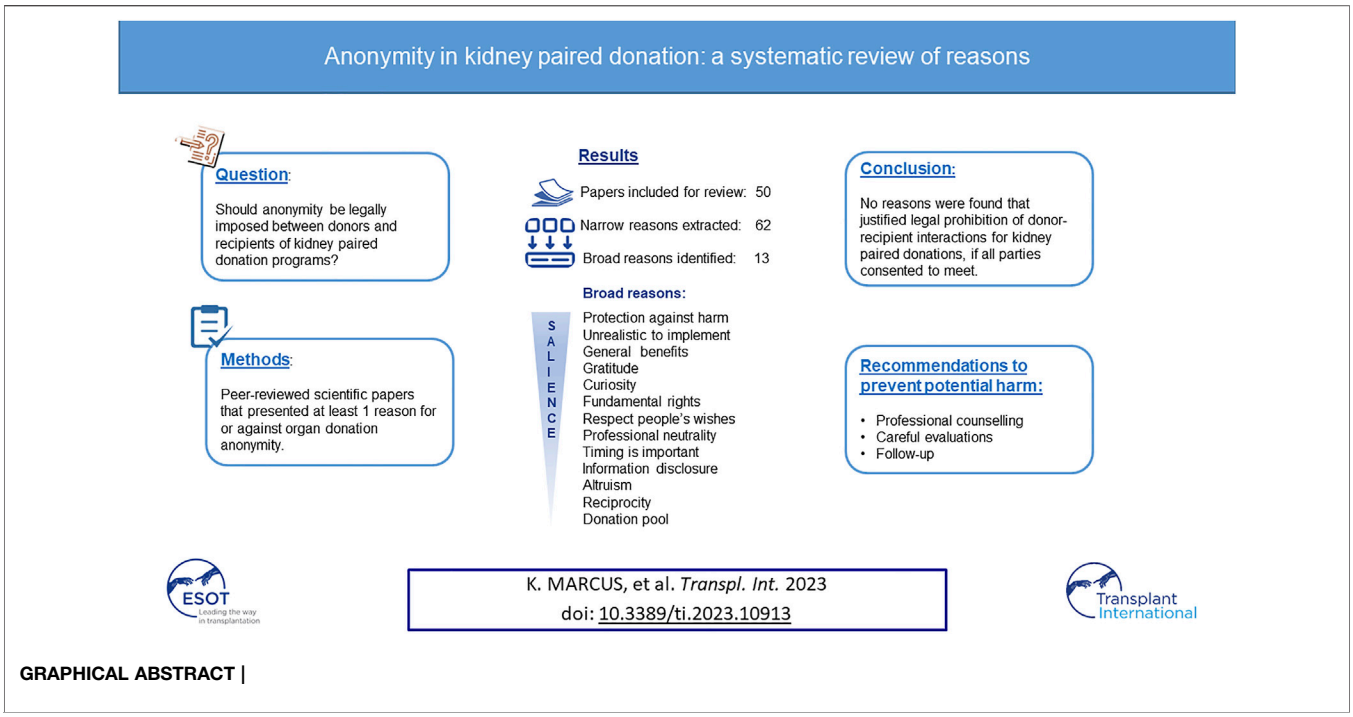
Received: *19 September 2022*
Accepted: *11 January 2023*
Published: *02 February 2023*

Citation:
Marcus K, Berner D, Hadaya K and Hurst S (2023) Anonymity in Kidney Paired Donation: A Systematic Review of Reasons. Transpl Int 36:10913. doi: 10.3389/ti.2023.10913



GRAPHICAL ABSTRACT |

While donor-recipient anonymity is defined by national policies, it is still a subject of debate. The Italian Committee for Bioethics, for instance, petitioned to allow deceased donor families and recipients to make contact, if given explicit consent (3). For KPD, other circumstances further complicate the subject. First, because this donation type involves at least two donation pairs, an individual's choice to meet the other pair may lead to undesired relationships for the partner involved. Second, in contrast to deceased donor or unspecified donations, a KPD donor's intent is not entirely altruistic, since both donation pairs have a gain from participating the exchange.

Further, anonymity between organ donation pairs is arguably a question that requires considerations on the reasoning of ethical concerns, to help the policy decision-making process (4). While policy discussions on anonymity persist, reason-based literature on the issue remain scarce.

Therefore, the objective of this study is to investigate the reasonings of whether anonymity should be legally imposed between donors and recipients of KPDs. To do so, we conducted a systematic review of reasons, by investigating reasons presented in peer-reviewed papers for organ donations. We determined those that may be applicable in KPD context, to recommend whether anonymity should be legally imposed, or that it may be relinquished based on free decisions by the donation pairs.

MATERIALS AND METHODS

This systematic review of reasons was conducted based on the model by Strech and Sofaer, a method developed for studies that aim to improve argument-based bioethic concerns and to identify gaps that calls for further research (4, 5).

We searched scientific journals in PubMed and Google Scholar databases until May 2022. First, we scanned the databases to identify the appropriate index terms. The search strategy was deliberately wide to broaden the capture of publications, which included editorials, opinion pieces and papers on anonymity for organ donations. We used the string of key terms: ("anonymity" OR "anonymous" OR "confidentiality") AND ("transplantation" OR "organ donation") AND ("kidney" OR "renal" OR "liver" OR "hepatic"). Snowballing technique was also applied.

Inclusion and Exclusion Criteria

A publication was only included if it: 1) presented discussion on donor-recipient anonymity; 2) was peer-reviewed; 3) presented at least one reason for or against anonymity. Papers that were not published in a scientific journal, dissertations, non-peer reviewed publications and grey literature were excluded. No language restrictions were placed, we used DeepL Translator for non-English publications. KM, DB and SH independently reviewed titles and abstract, papers were only included if they met the inclusion criteria. Papers were excluded if at last two reviewers agreed to do so, discrepancies were resolved through discussions.

Data Synthesis

KM and DB carried out full text analysis to extract text passages that described a reason for or against anonymity, then coded them into "narrow" reasons based on their context. For example, "good relationships were formed" was assigned to passages that

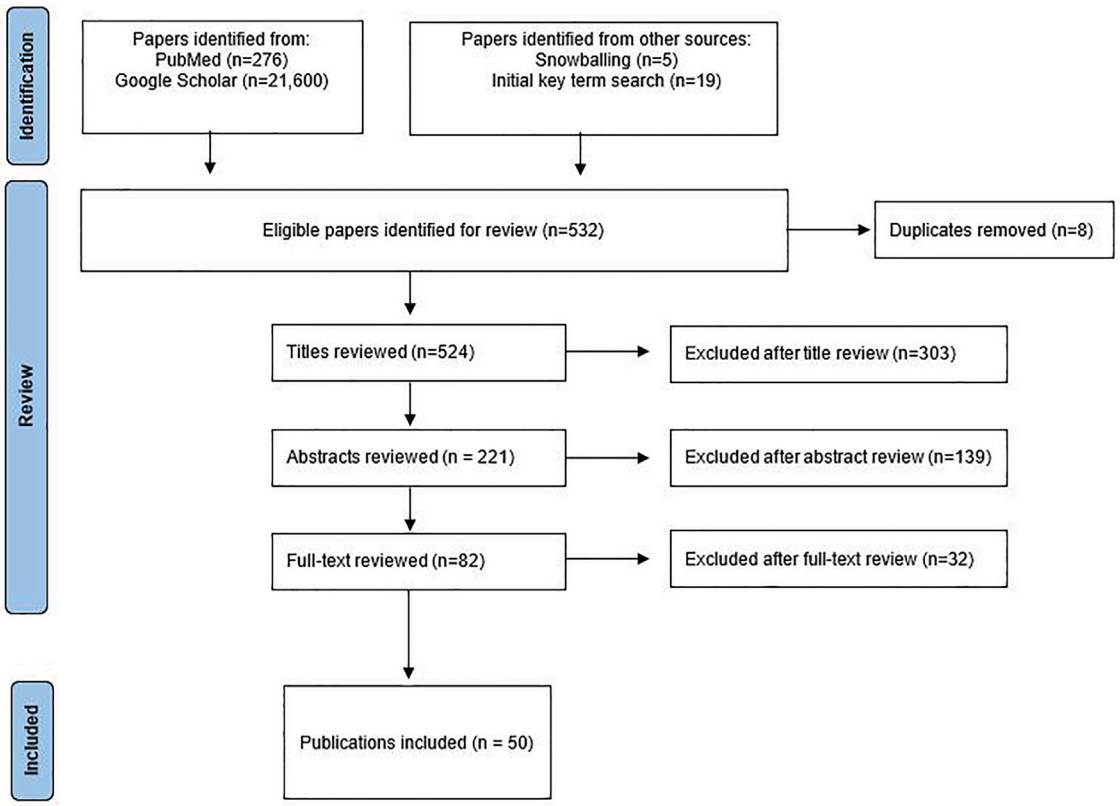


FIGURE 1 | Publication search and selection process.

described the context of a positive relationship from donor-recipient interactions.

Each "narrow" reason was then coded into "broad" reasons, which gives an overview of the type of reasons in few words. For instance, narrow reasons "donors and recipients are naturally curious about each other" and "direct contact satisfied donor families' curiosity" were coded as "curiosity" broad reason. For complex text passages that could be assigned more than one "broad" or "narrow" reason types were reassessed based only on the paper's context to minimize bias. The coded reason types were reviewed by KM, SH and KH for validity, then identified those that were applicable for KPD.

Publications were classified by type and country, based on where the research was conducted or where the donation program took place. For editorials, opinion pieces and essays, the country was determined by the authors' affiliation. Opinion pieces and essays were coded as "discussion paper"; reports on organ donation programs under "program report"; research studies, editorials and conference reports were coded accordingly.

RESULTS

Figure 1 shows the PRISMA flow diagram of the paper inclusion and exclusion process. The review yielded 50 eligible publications for full-text analysis; 36 were either program reports or studies, of which 14 were from the United States. The rest were carried out in West European countries, as well as one study from Israel and one from New Zealand. **Table 1** presents a précis of the selected publications.

Table 2 shows the reason types coded for and against anonymity. The first column shows the broad reason types, the "Side" column represents whether the narrow reasons were for ("pro") or against ("con") anonymity. The third column contains the narrow reasons, those that we did not find pertinent to paired donations are marked with an asterisk (*). The fourth column shows the donation context in which the narrow reasons were found: unspecified, deceased donor (Deceased) or KPD (Paired). Reasons showing more than one donation type indicate that they were found in more than one circumstance. For instance, while the reason "anonymity is the standard that protects donors and recipients" was only found in papers that reported unspecified donations, reason "shields burden of knowledge in case of negative outcomes in the other party" was found stated in all three donation types.

In total, we identified 62 narrow reasons and 13 broad reasons. There were 24 narrow reasons in favor of anonymity and 38 against. Further, the most frequently cited narrow reason for anonymity were those coded under the "protection against harm" broad reason type (n = 12). In reasons against anonymity, we identified eight narrow reasons that were coded "respect people's wishes" broad reason type, four narrow reasons for

TABLE 1 | Included papers by author, year, type and country.

Authors	Year	Type	Country
Bailey et al.	2016	Qualitative interview	United Kingdom
Goetzmann et al.	2009	Cross-sectional survey	Switzerland
Tong et al.	2012	Qualitative interview	New Zealand
Fortin et al.	2008	Qualitative study	Canada
Ross	2010	Pilot study proposal	United States
Mamode et al.	2013	Systematic review	United Kingdom
Kranenburg et al.	2007	Mixed method study	Netherlands
Kranenburg et al.	2004	Discussion paper	Netherlands
Maple et al.	2014	Cross-sectional survey	United Kingdom
Lima et al.	2012	Program report	Portugal
De Klerk	2010	Program report	Netherlands
Jacobs	2004	Program report	United States
Slaats et al.	2018	Retrospective observational study	Sweden and Netherlands
Wadström et al.	2019	Longitudinal study	Sweden
Woodle et al.	2010	Program report	United States
Ross et al.	1997	Editorial	United States
Lennerling et al.	2007	Case studies	Sweden
Ghent et al.	2019	Interview study	Canada
Hanto	2007	Discussion paper	Canada
Azuri et al.	2013	Mixed methods study	Israel
Lewino et al.	1996	Exploratory descriptive study	United States
Dobbels et al.	2009	Cross-sectional survey	Belgium
Henderson et al.	2003	Cross-sectional survey	Canada
Annema et al.	2015	Cross-sectional survey	Netherlands
Albert	1998	Program report	United States
Ono et al.	2008	Cross-sectional survey	Brazil
Pronk et al.	2017	Longitudinal study	Netherlands
Dor et al.	2011	Terminology assessment	Netherlands
Adams et al.	2002	Conference report	United States
Morrissey et al.	2005	Program report	United States
Patel et al.	2011	Discussion paper	United Kingdom
Clayville	1999	Qualitative interview	United States
Mark et al.	2006	Program report	United States
Corr et al.	1994	Discussion paper	United States
Matas et al.	2000	Program report	United States
Gohh et al.	2001	Case study discussion	United States
Colaneri	2004	Discussion paper	United States
Erim et al.	2010	Program report	Germany
Jendrisak et al.	2006	Program report	United States
Thiel et al.	2001	Discussion paper	Switzerland
Gilbert et al.	2005	Program report	United States
Wallis et al.	2011	Program report	United States
Durand et al.	2014	Qualitative interview	Canada
Olbrisch	2001	Discussion paper	United States
Hilhorst	2005	Discussion paper	Netherlands
Rodrigue et al.	2011	Cross-sectional survey	United States
Landry	2006	Discussion paper	United States
Lucan	2007	Program report	Romania
Duvoux	2019	Program report	Canada

"fundamental rights" and four narrow reasons for "timing is important" broad reason types.

Protection Against Harm

We found that anonymity as a preventive measure against potential harm was a frequently given reason for those in favor of its legal imposition. This included safeguarding donors from "burden of knowledge in case of negative outcomes," protecting recipients from "feeling indebted, guilt and expected to say thanks," as well as preventing possible "awkwardness," "emotional stress" and fears of bias overall.

Several papers reported negative donor-recipient interaction experiences, due to bias related to social and religious differences, or unmet expectations of the other person (18, 22, 29). Two studies reported cases of unintended donor-recipient meeting during hospitalization. In one study, two donors had intentionally breached anonymity without their recipient's consent (17); the other study reported two accidental donor-recipient meetings (31). In both studies, one person reported discontent and regretted the meeting, while another was pleased despite the initial awkwardness.

Further, we found concerns regarding risk of financial extortion, blackmail or expectations of secondary gains from

TABLE 2 | Reasons for and against anonymity.

Broad reasons	Side	Narrow reasons	Donation type	Source
Protection against harm	Pro	Feelings of guilt from meeting the donor family can affect organ integration[a]	Deceased	(6, 7)
		Anonymity is the standard that protects donors and recipients	Unspecified	(8, 9)
		Shields burden of knowledge in case of negative outcomes in the other party	Paired, unspecified, deceased	(9–16)
		Anonymity can protect donors from being pressured or coerced to donate	Paired, unspecified, deceased	(6, 14, 17–21)
		People are protected from feeling indebted, guilt and expected to say thanks	Paired, Unspecified, Deceased	(6, 8, 9, 18, 22–28)
		Contact with the other party can lead to great emotional stress	Paired, unspecified, deceased	(1, 12, 18, 22–25, 29, 30)
		Meeting may lead to unequal relationships between parties[a]	Unspecified	(31)
		Awkwardness and discontent when anonymity was breached by the other party	Unspecified	(17, 31)
		Meeting the donor family can lead to recipients feeling pressured to nurture the organ[a]	Deceased	(22)
		Prevents risks of financial extortion, abuse, blackmail, organ trafficking or expectations of secondary gains	Paired, unspecified, deceased	(18, 25–27, 32, 33)
		Bias or disappointed expectations of the other party	Paired, unspecified, deceased	(8–10, 17, 18, 22, 23, 28, 29, 31, 32, 34)
		Donor families became too involved in the recipient's life	Deceased	(29)
	Con	Disadvantages were reported due to the lack of contact[a]	Deceased	(22)
		Signs of distress were found in parties in the absence of expressed thanks[a]	Deceased	(16, 17)
		Donors reported the experience to be lonely, business-like and impersonal[a]	Paired or unspecified	(18)
		There is no evidence of ulterior motives, exploitation or expectations of reciprocity to organ donation	Unspecified	(9, 35, 36)
General benefits	Pro	The benefit of meeting does not justify the workload involved in facilitating it	Unspecified	(23)
		Anonymity gives people closure, relief and opportunity to focus on their own lives	Paired, unspecified, deceased	(10, 22)
		Meetings have been positive and beneficial	Paired, unspecified, deceased	(2, 14, 17, 19, 22, 29, 37, 38)
		Good relationships were formed	Paired, unspecified, deceased	(9, 17, 22, 23, 30, 31, 39, 40)
	Con	Expressing gratitude in person can help establish a bond	Unspecified	(36)
		Receiving gratitude can have a healing effect for the donor family[a]	Deceased	(1, 22, 25, 29, 40, 41)
		Removing anonymity helps people achieve closure, better quality of life and promote wellbeing	Paired, unspecified, deceased	(17, 18, 40)
		Seeing the positive outcome in a recipient confirms the meaningfulness of the act	Paired, unspecified, deceased	(17, 22, 29–31, 38, 41, 42)
		Anonymity prevents donors from the satisfaction of seeing the benefits of their act[a]	Unspecified	(42–45)
		Helps maintain transparency on the quality and origin of the organ	Paired	(39, 46)
Gratitude	Pro	Recipients can say thanks anonymously	Unspecified	(8, 23)
		Recipients for alcoholic liver disease and those with higher education felt no need to say thanks	Deceased	(1)
	Con	The primary reason to contact is to personally say thanks	Unspecified, deceased	(1, 11, 24, 25, 29, 31)
		Anonymity prevents people from their natural desire to express gratitude	Unspecified, deceased	(18, 23, 41)
		The opportunity to give thanks through a meeting should not be wasted	Paired, unspecified, deceased	(24, 36, 38)
Curiosity	Pro	Initial curiosities about the other party dissipate with time	Unspecified	(11, 19)
	Con	Donors and recipients are naturally curious about each other	Paired, unspecified, deceased	(1, 6, 12, 18, 25, 30, 31)
		Direct contact satisfied donor families' curiosity	Deceased	(22)
Unrealistic to implement	Con	Strict anonymity can be difficult or impossible in some circumstances	Paired, unspecified	(10, 32, 39, 46, 47)
		People would try and manage to find each other despite restrictions	Paired, unspecified	(8, 48)
		Inapplicable when pairs are genetically or already emotionally involved with each other	Paired	(46)
Fundamental rights	Con	Making decisions for oneself is a fundamental right	Paired, unspecified, deceased	(1, 18, 24, 25, 29, 30)
		Donors have a right to know to whom their organ was donated	Unspecified	(8, 18)
		People are capable of making the best decisions for themselves	Deceased	(22, 30)
		People are responsible for the consequences of their own decision	Unspecified	(18)

(Continued on following page)

TABLE 2 | (*Continued*) Reasons for and against anonymity.

Broad reasons	Side	Narrow reasons	Donation type	Source
Respect people's wishes	Pro	Donors and recipients wish to remain private to prevent problematic relationships	Paired, unspecified, deceased	(1, 8–10, 12, 18, 22, 23, 25, 26, 32, 41)
		Donors and recipients do not feel the need to contact the other party	Paired, unspecified, deceased	(1, 8, 11, 15, 19, 22, 24, 27)
		Donors and recipients agree with anonymity	Paired, unspecified, deceased	(1, 11, 15, 18, 19, 27, 31)
		Donors want to feel like the donation was made to their loved one	Paired	(11)
	Con	Donors and recipients want to meet each other	Paired, unspecified, deceased	(1, 19, 22, 24, 25, 29, 30, 36, 39, 49, 50)
		Some would agree to meet because it could be important to the other person	Unspecified	(31)
		Anonymity should be lifted if everyone agreed to meet	Paired, unspecified, deceased	(2, 18, 24, 25, 29, 47, 51)
		Donors and recipients want to share the experience with each other	Paired, unspecified, deceased	(29, 31)
Professional neutrality	Con	Medical professionals should remain neutral	Deceased	(29)
		Medical teams should respect and facilitate people's wishes to meet	Deceased	(22, 24, 29, 30)
Timing is important	Con	Anonymity during the early stages of the operation is important, but can be reassessed afterwards if others agree to meet	Paired, unspecified, deceased	(2, 8, 21,37, 42, 47, 52)
		A professional is needed to facilitate and give counselling to both parties before the meeting	Deceased	(1, 24, 29, 40)
		There is a preference to meet within 1 year of the transplantation	Deceased	(22)
		Gradual preparations before the meeting is needed	Deceased	(22, 24, 25, 29, 40)
Information disclosure	Con	Donors worry that the recipient's lifestyle or non-adherence may cause a negative outcome	Unspecified	(34)
		Fear of acquiring the donor's bad traits or personality through the grafted organ, and would like to have these traits pre-disclosed	Deceased	(6)
Altruism	Pro	Donate anonymously is true altruism[a]	Paired, unspecified	(8, 18, 26, 27, 42)
Reciprocity	Pro	The reciprocity principle of organ donation can be achieved despite anonymity[a]	Deceased	(53)
Donation pool	Pro	Direct living donation may lead to a decrease in the organ donation pool[a]	Unspecified	(8)
	Con	People with positive experience about organ donation can become strong advocates pro new donors[a]	Unspecified, deceased	(1,9,17,24,25)
		Anonymity might discourage people who need a personal story from becoming donors[a]	Unspecified	(18)

[a]*Reasons that are not applicable for paired donations.*

donors to recipients, or that potential donors may be coerced into donation if anonymity was not maintained. However, a study on motivations for unspecified donations found that donors commonly thought the act would "make a huge difference to someone else's [life]" (15). Other studies showed no evidence of ulterior motives, expectations of reward from organ donors (9, 35, 36). We did not find any report of forced donations.

Some narrow reasons in favor of anonymity were less clear. For instance, Azuri et al. (22) argued that meeting the deceased donor family might lead the recipient to feel an "extra sense of responsibility to nurture the donated organ," but we found no further clarifications on this reasoning.

General Benefits and Gratitude

In the "general benefits" broad reason, we identified two narrow reason types for anonymity and eight against. One reason that supported anonymity was that it allowed donors or donor families and recipients to achieve their own closure and to focus on their own lives (10, 22). The other was that the benefits of the meeting do not justify the resource cost of facilitating them (23).

In narrow reasons against anonymity, we found observed benefits of the donor-recipient meeting: people were able to achieve closure together, good relationships were formed and meetings were generally reported as positive and beneficial. Further, donors reported that seeing the positive effects of the transplantation brought a sense of satisfaction and meaningfulness to their act. Two studies argued that lifting anonymity in KPDs can help maintain transparency on the quality and origin of the organ (39, 46).

In "Gratitude" broad reason, we identified five narrow reason types, two in favor of anonymity and three against. In narrow reasons against anonymity, one was cited in six papers, arguing the primary reason for people to wish contact was to personally say thanks. Other narrow reasons against anonymity argued that it prevents people's natural desire to give thanks, and the opportunity to do so through a meeting should not be wasted. In reasons for anonymity, two papers stated that gratitude can be expressed anonymously. In addition, one paper found that liver recipients in particular felt no need to express gratitude.

Curiosity

For broad reason type "Curiosity," we identified three narrow reasons, one for anonymity and two against. Whereas donors and recipients stated curiosity being a reason for wanting to relinquish anonymity, two studies that presented an argument against suggested that these curiosities tend to dissipate with time (11, 19).

Unrealistic to Implement

We identified three narrow reasons that argued strict anonymity would be unrealistic, nearly impossible to maintain under certain circumstances: when the transplantations take place in the same institution and carried out by the same team (46), or when donors and recipients had to be hospitalized on the same floor (32). Authors from two papers stated in countries where conditions allow, people would try and succeed in finding each other, despite anonymity restrictions (8, 48).

Fundamental Rights, Respect People's Wishes and Professional Neutrality

Under "Fundamental rights," we identified four narrow reasons that were against anonymity, of which two that we found closely related to several narrow reasons under "respecting people's wishes." For instance, donors and recipients of Slaats et al. study stated that people should be free to make choices on their own anonymity, and be responsible for the consequences of such decision. Other papers argued that anonymity should be lifted if both parties agreed to do so (18, 24, 25, 29, 47, 51).

Further, two narrow reasons that were identified under the "professional neutrality" broad reason were presented under similar contexts to those coded under "respect of people's wishes." Deceased donation families and recipients expressed that medical professionals should remain neutral, respect and facilitate people's wishes to meet (22, 24, 29, 30).

Timing Is Important

For broad reason "Timing is important," we identified four narrow reasons, all were against maintaining anonymity after the operation. We found an emphasis on the importance of maintaining pre-transplantation anonymity, but the donor and recipient's decision to meet can be reassessed by the medical professionals afterwards (8, 37, 42, 47, 51, 52).

Further, findings from studies in deceased donations showed participants had a preferred delay period between time of surgery and time to meet. For instance, Azuri et al. (22) found two preferred post-surgery delays: within a month or at least 1 year after.

DISCUSSION

Overall, we found that the most frequently given reasons in favor of anonymity were concerns for potential harm that may arise from donor-recipient interactions, whereas reasons against anonymity were argued based on the observed benefits associated with the organ donor-recipient interactions. While frequency is not the prime objective of our study, it suggests nonetheless that potential harm being a common concern, despite the lack of empirical evidence, and that further research may be required. Other main findings from our study were concerns for respecting people's "Fundamental rights." Interestingly, these were often argued along with "Respect people's wishes," "Professional neutrality" and "Timing is important," which suggests people perceiving them as being closely associated with the respect of people's decisions as a fundamental right.

In terms of "Protection against harm," we found few studies that reported "harm" observed from the donor-recipient interaction, including two reports of discomfort, awkwardness and regret having met the other party, when anonymity was breached without their consent.

For concerns of blackmailing, extortion or coercion, we did not find any evidence of ill-intents in our review. While our findings do not rule out their potential occurrence, it is unlikely to be frequent. First, most countries have signed the WHO Guiding Principles that condemn commercialization of organs (54), in addition to national legislations against monetary procurement of organs. Second, ill-intents and wrongdoings are arguably possible if meetings occur before the donation, not after it. Further, risks may be disclosed to KPD pairs before the operation, and preventive measures against concerns of harm can be implemented by the medical team afterwards.

In contrast to concerns for potential harm, we found reports of observed donor-recipient interaction benefits, including good relationships being formed; for donors, seeing the positive outcome in the recipient reportedly affirmed the meaningfulness of their act.

In unspecified and deceased donations, some authors argued that the donated organs were often seen as the "gift of life" (41)—which explains recipients who were reportedly keen to express gratitude for receiving the "gift." In these donations, recipients reported strong, positive emotions that motivated them to do so personally. For KPDs, circumstances may differ, since anonymity reportedly allowed some donors to keep the procedure as though the organ was donated to their intended recipient (12). In this case, it would be justifiable to respect the donors' wishes, but not as a reason to legally impose anonymity.

Indeed, legally mandated anonymity excludes donors from all possibility of seeing the positive impact of their act, or recipients to form a good relationship with their donor, especially if both pairs wish to make contact. These elements should be considered, since it is arguably human nature for donors to wish seeing the positive outcome of their act, upon explicit agreement from the recipients.

Another possible outcome to consider is the fear of bias. Participants from studies reported stress due to people seeing or fearing unmet expectations of their donor or recipient, including social or religious bias. The donation pairs should thus be informed of such risk, that the other pair may or may not possess their expected characteristics and *vice versa*, allowing people to decide whether they would make contact.

Given the scarce evidence of harm found in donor-recipient interactions, as well as the observed benefits amongst those who

did meet, versus concerns for potential harms, findings of our study suggest that the strict anonymity policy should be reconsidered. This echoes the statement by Pronk et al. (2), that "discussion on the risks and benefits of anonymity in anonymous donation, has long been more speculative than evidence-based," which we found equally applicable to the KPD context.

Therefore, we argue that revoking anonymity should be made possible, if all concerned persons made explicit and independent decision to do so, to "preserve the ethical principle and morality of autonomy" of the decision-making individual (30). This argument is in line with the *Directive 2010/53/EU,* which recommends the possibility of revoking anonymity after transplantation. In practice however, this is generally not allowed by the domestic laws of European members States.

On the other hand, the free-decision approach is already in practice in many countries, where post-operation anonymity may be relinquished if all parties agree, such as the United States, Switzerland and the United Kingdom. In addition, studies in the Netherlands, Sweden and the United Kingdom showed respecting one's decision to revoke anonymity to be well received by organ donation pairs: participants expressed satisfaction in the decision to remain anonymous, and donation pairs who opted to meet generally reported positive experience from their interaction (2, 18).

In this light, the decision approach should maintain the requirement for all persons of the donation pairs to consent, in the objective of upholding the principle of respecting people's decisions. If one person in the paired donation wishes to maintain his or her anonymity, then that wish should be fully respected and upheld for both donation pairs.

We found papers that went one step further and stressed the importance of professional neutrality, with respect to the donors and recipients' wishes—that professional follow-up plays a key role in regulating and maximizing the safeguard of the couples' wellbeing in carrying out their decisions.

What could this look like in practice? First, we found that medical professionals, donors and recipients in general agreed that anonymity should be upheld before the operation. Prior to the surgery, however, donation pairs may already be informed of their right to revoke their anonymity afterwards, if everyone gives their independent and explicit consent. The discussions between medical professionals and each individual is thus critical to allow informed decisions.

Second, during and after the transplantation process, counselling and advice as a preventive measure against potential harms. These sessions may inform donation pairs the possible risks and benefits of interaction, as well as the possibility of a negative outcome. The informed knowledge of unequal outcomes is already in practice in the United States, mandated by the Organ Procurement and Transplantation Network policy for KPDs (art. 13.4.c.11).

Third, ensuring sufficient time between the surgery and moment of decision on anonymity can allow people to reflect, discuss and seek further professional advice if needed. The time delay is likely to be important, since studies suggest that initial curiosities about the other party tend to dissipate with time (11, 19). A time delay would allow initial curiosities to wane, so those who are truly keen on making contact may benefit from its advantages.

Despite the positive effects reported from donor-recipient interactions, Ghent et al. (23) argued that successful meetings do not justify the resource cost of facilitating them, because they could be used on transplantation work instead. This brings to question how effectively the resources were allocated in staff time and other resources attributed to the task. Since revoking anonymity by consent is already in practice in multiple countries with reported positive outcomes, we argue that finding the appropriate resource needed may be worthwhile, so people may enjoy and share the benefits of the act.

In addition, we noted that publications on anonymity between donation pairs were relatively scarce in Europe and other countries, compared to the United States. This may due to cultural differences, as theorized by authors who noted differences in opinions on anonymity between study participants of different countries. Cultures with blurred personal boundaries may have stronger wish for solidarity over personal privacy (22). Further, whereas European cultures favor following a "collective norm," American societies appreciate individual opportunities (1). This suggests that anonymity merits further investigations, so that each national policy caters to its domestic needs.

STRENGTHS AND LIMITATIONS

To our knowledge, this is the first systematic review of reasons that investigated applicable ethical reasonings regarding anonymity for paired organ donations. Further, this paper highlights the disadvantages and advantages of maintaining or lifting paired organ donation anonymity from ethical practical perspectives.

Our review also has several limitations. First, coding text passages into narrow and broad reason types had a risk of bias. To minimise this, researchers worked independently, and text passages were reviewed based on their context during coding, to avoid interpretations outside the contextual scope of the paper from which it was extracted. However, as with all subjective interpretations, this method is not entirely free of reviewer bias. Second, we perceived a loss of detailed information during the coding process.

Third, despite the deliberate broadened search, nearly all of our findings were in English, with more eligible papers from the United States than any other country, which could have led to cultural bias in the findings of the eligible papers. This could be due to the search being conducted in English prominent databases. While this was addressed by placing no language restrictions, which generated two non-English articles, there may be other country or region-specific search engines that could have generated more results from non-anglophone countries with different cultural and legal views.

Fourth, while we broadened our search in the key terms used, we noticed certain papers that were pertinent to our review could only be found by applying the snowballing technique.

Consequently, there may be papers that are pertinent to this review but did not show up in our search.

CONCLUSION

In sum, while we found a wealth of reasons for and against anonymity in organ donations, those that supported anonymity were primarily based on speculation without supporting evidence. In contrast, we found reasons against anonymity that were based on observed benefits. Therefore, we did not find reasonings that justified legally imposed anonymity for donation pairs who wish to make post-operation contact. In fact, we found that the most ethically convincing reasons to be those that emphasized the respect of an adult person's capacity and right to make informed decisions for oneself, with professional support, careful evaluations and appropriate delay between times of operation and contact. This was supported by positive outcomes reported from donor-recipient interactions, where such practice was allowed. We thus deem that future research will be useful, to investigate the best timing for donors and recipients to make informed decisions on their anonymity, as well as the best clinical and medical practice to help prepare donation pairs to meet, if they so choose.

We also noted that countries that enacted regulations to allow relinquishing anonymity by consent, such as Switzerland, the United Kingdom and the United States, show a recognition and intent to preserve an individual's autonomy. In contrast, other countries, including European states, maintain strict anonymity with no possibility of revoking donor-recipient anonymity. In light of our findings and of ethical considerations for best practice, we encourage policymakers to reconsider strict anonymity regulations for paired donations, to help maximizing donors and recipients' benefit from their organ transplants.

AUTHOR CONTRIBUTIONS

SH and KH conceived the study, KM drafted the first version of the manuscript. SH and KH contributed to drafting sections of the manuscript. All authors participated in the study design, contributed to the interpretation of data, read and approved the final manuscript.

FUNDING

The project was funded by the Institute for Ethics, History, and the Humanities, Geneva University Medical School, Geneva, Switzerland.

ACKNOWLEDGMENTS

KM would like to thank Mr. Chia-chen Huang for his support through the research.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 28 February 2023
doi: 10.3389/ti.2023.10959

Twenty Years of Unspecified Kidney Donation: Unspecified Donors Looking Back on Their Donation Experiences

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The Netherlands was the first European country to implement unspecified kidney donation in 2000. This qualitative study aimed to evaluate the experiences of unspecified kidney donors (UKDs) in our transplant institute to improve the care for this valuable group of donors. We conducted semi-structured interviews with 106 UKDs who donated between 2000–2016 (response rate 84%). Interviews were audio-recorded, transcribed verbatim and independently coded by 2 researchers in NVivo using thematic analysis. The following 14 themes reflecting donor experiences were found: Satisfaction with donation; Support from social network; Interpersonal stress; Complaints about hospital care; Uncertainty about donor approval; Life on hold between approval and actual donation; Donation requires perseverance and commitment; Recovery took longer than expected; Normalization of the donation; Becoming an advocate for living kidney donation; Satisfaction with anonymity; Ongoing curiosity about outcome or recipient; Importance of anonymous communication; Anonymity is not watertight. The data reinforced that unspecified kidney donation is a positive experience for donors and that they were generally satisfied with the procedures. Most important complaints about the procedure concerned the length of the assessment procedure and the lack of acknowledgment for UKDs from both their recipients and health professionals. Suggestions are made to address the needs of UKDs.

Keywords: kidney transplant, anonymity, non-directed altruistic donation, qualitative studies, unspecified kidney donation

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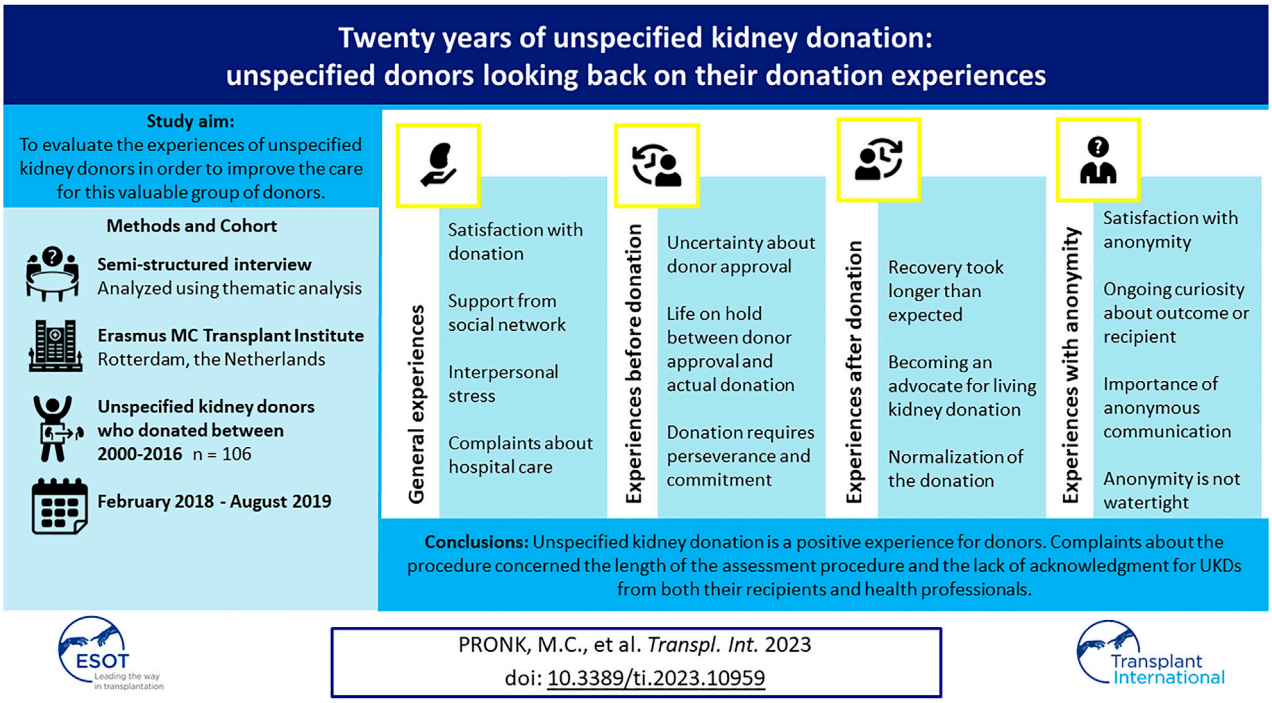
Received: *07 October 2022*
Accepted: *30 January 2023*
Published: *28 February 2023*

Citation:
Pronk MC, Zuidema WC, Weimar W, Van De Wetering J, Ismail SY and Massey EK (2023) Twenty Years of Unspecified Kidney Donation: Unspecified Donors Looking Back on Their Donation Experiences. Transpl Int 36:10959. doi: 10.3389/ti.2023.10959

INTRODUCTION

Living donor kidney transplantation is the treatment of choice for patients with kidney failure, because it affords the best patient and graft survival (1). Over the past 2 decades several strategies have been employed to expand the living donor pool, including the introduction of unspecified kidney donation. Unspecified kidney donation refers to living donation whereby an organ is donated by a healthy person to an unknown recipient, i.e., someone they do not know or have ever met. Unspecified kidney donors (UKDs) are also known as non-directed, anonymous, Good Samaritan or altruistic donors (2). An UKD can donate directly to a patient at the top of the waiting list or donate into a kidney-exchange program to trigger a chain of donations (3).



GRAPHICAL ABSTRACT |

The Netherlands was the first European country to implement unspecified kidney donation in 2000 and since 2005 UKDs have been incorporated into the national kidney exchange program (called domino-paired donation). Currently, the Netherlands and the UK have the highest number of living donor kidney transplants in Europe as well as the highest proportion of UKDs in the living donor pool (4). In the past 5 years, UKDs accounted for 7%–11% of all living donors in the Netherlands (5). The living donor evaluation in the Netherlands follow articles 3–8 of the Dutch Donor Act (6) and guidelines for (anonymous) living kidney donation from the Dutch Transplant Society (available at www.transplantatievereniging.nl/richtlijnen). All living donors in the Netherlands undergo medical and psychosocial screening and compatibility testing. In addition, all UKDs are referred for a mental health assessment by a psychologist or social worker. To ensure privacy of both donor and recipient, the UKD and the recipient remain anonymous before and after the donation. After the transplantation recipients and donors have the possibility to send an anonymous card to each other (*via* the transplant coordinators).

As UKDs currently make an invaluable contribution to the living donor pool, it is important to take good care of this group of donors. Previous literature on the experiences of UKDs worldwide has shown that their donation experience is generally very positive (7-11). Nevertheless, it has also been reported that the donation was experienced as life interrupting or as a source of interpersonal stress (8-12). In addition, some UKDs complained about the intensity and length of the donor assessment procedure and the long waiting time before the actual donation (9-14). Although the aforementioned studies have provided reassuring evidence with regard to the experiences of UKDs, they cannot simply be generalized to the Netherlands, because of different healthcare systems across countries. In addition, there is a need for studies with a longer follow-up time after donation. In our transplant institute we have one of the longest running donation programmes of Europe and as such have one of the largest cohort of UKDs, with a longer follow-up time than reported in previous studies. Therefore, the current study aimed to evaluate the experiences of the cohort of unspecified kidney donors in our transplant institute, which can help to improve the education and care for this valuable group of donors.

MATERIALS AND METHODS

Participants

All UKDs who donated a kidney at the Erasmus Medical Transplant Institute between 2000–2016 were eligible for participation. All donors were above the age of 18 years. Donors were included if they had donated anonymously to the waiting list or through a domino-paired exchange programme. Exclusion criteria were death, therapeutic donors (who underwent nephrectomy for medical reasons) or donation anonymously through the paired exchange program (donors from an incompatible donor-recipient couple). All donors underwent medical and psychological screening, as part of the standardized living donor work-up in our transplant institute.

TABLE 1 | Socio-demographic and medical characteristics (N = 106).

Socio-demographic characteristics	
Female gender: N (%)	57 (53.8)
Age (years) at donation: median (range)	59 (21–89)
Age (years) at study: median (range)	67 (25–94)
Ethnicity: n (%)	
European	105 (99.1)
Asian	1 (1)
In paid employment: n (%)	56 (52.8)
Highest level of education	
Primary school	5 (4.7)
Secondary/high school	48 (45.3)
Further/higher education	53 (50.0)
Marital status: n (%)	
Married/living together/partnership	61 (51.9)
Single/divorced/widowed	51 (48.1)
Has children: n (%)	65 (61.3)
Has religious affiliation: n (%)	46 (43.4)
Medical characteristics	
Time (months) since donation: median (range)	71.50 (23–153)
Registered in deceased donor register: N (%)	92 (86.8)
Registered to donate body to science: N (%)	2 (1.8)

Procedures and Measures

All eligible UKDs received a letter from the Erasmus MC Transplant Institute with information on the study. They were called 2 weeks later to assess willingness to participate. If applicable, an interview appointment was made. Between February 2018 and August 2019 donors participated in a semi-structured interview that lasted approximately 45 min. The interview guide (see **Supplementary Material**) was developed by a multidisciplinary research team consisting of the authors (3 psychologists, 2 nephrologists and 1 former unspecified donor coordinator). Questions covered participants' experiences with the donor-work up, the hospital admission and recovery period, the reactions from their social environment, and their opinion about the anonymity of the procedure. We also asked whether participants would, in retrospect, make the decision to donate again. Interviews were conducted by the second author (WZ), who was known to all participants through her previous role as unspecified living donation coordinator; however, during the study, she was not involved in the clinical care pathway. Most interviews took place in the out-patient clinic (combined with the yearly check-up). In some cases, data was collected at the donors' home, depending on participants' preference, mobility and health. In all settings data was collected individually to ensure privacy. Informed consent forms were signed at the beginning of the interview. Socio-demographic and medical characteristics were obtained from patients records or donor database and checked for accuracy at the beginning of the interview. Ethical approval for the study was obtained from the institutional review board (METC -2017-1180).

Analysis

Interviews were audio-recorded and transcribed verbatim. Each transcript was anonymized and given a unique study number which was used to identify quotes in this publication. NVivo 12 supported data management and coding. The analysis and reporting of the results conform to the COREQ checklist (see **Supplementary Material**) (15). Transcripts were coded independently by the first and second author (MP). The first author is a female psychologist (MSc.) with experience in qualitative research. The background of the second author (interviewer) has been described above. An inductive thematic analysis of the transcripts was conducted, in which we followed the six steps described by Braun and Clarke (16). After careful (re) reading of the transcripts, we started with assigning descriptive codes to sections of text that appeared relevant to the research topic. This resulted in an extensive initial code framework. Next, we considered how different codes could be combined into overarching themes or subthemes. Through this process the descriptive codes were redefined and condensed into more meaningful and analytical categories. The data and the code framework were repeatedly scrutinized to ensure that all the significant responses were extracted and allocated to appropriate themes. We carefully reviewed the themes to evaluate if they were coherent and distinct from each other. Each phase of the analysis was extensively discussed by the two coders (MP, WZ) and coding discrepancies were discussed until agreement was reached. When necessary, a third author (EM, psychologist) was consulted. Finally, the themes were described in a narrative form to provide an accurate illustration of each theme. We used words as "many" and "few" to identify the relative frequency of the theme within the study population and to draw attention to (ir)regularities in the data. These words are not meant to convey generalizability beyond the study population.

RESULTS

Participants

During the study period 142 UKDs had donated a kidney, either to a patient on the deceased donor waiting list or in an exchange procedure. Eight donors were excluded because they were therapeutic donors and at the time of inclusion 8 donors had died. Cause of death was unrelated to living donation and occurred after a median of 52 months (range 31–164) after donation. Of the 126 remaining eligible donors, 106 gave consent to participate (84%). Reasons for non-participation are outlined in the **Supplementary Material**. Both positive reasons, such as closure, and negative reasons, such as dissatisfaction, were reported. Socio-demographic and medical characteristics can be found in **Table 1**.

Themes

The analysis suggested fourteen themes. We have divided the themes in four categories: general donation experiences, pre-donation experiences, post-donation experiences and experiences with anonymity. Further elucidation of the themes is provided below and an overview of the themes is presented in **Figure 1**. **Tables 2–5** present quotations illustrating the themes.

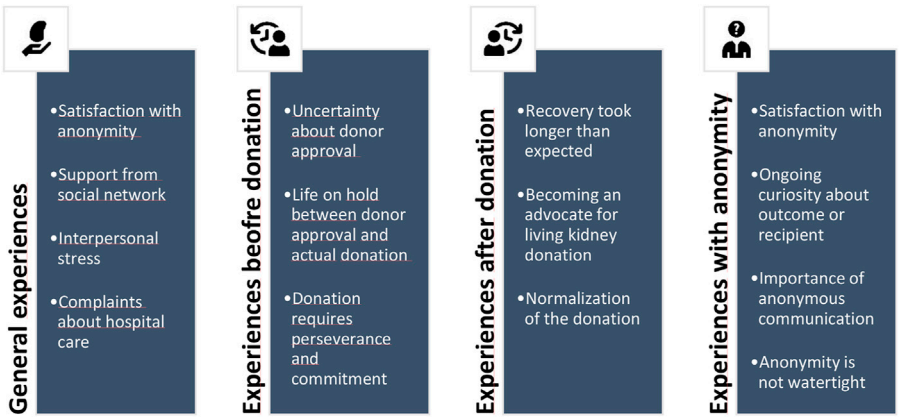


FIGURE 1 | Overview of themes representing the experiences of unspecified kidney donors.

TABLE 2 | Illustrative quotations reflecting donors' general experiences with UKD.

Theme	Quotations[a]
Satisfaction with donation process	"It (the donor work-up) was very well organized. Until the moment of surgery I could say 'stop!'. I never considered that, but it was all well taken care off." 110 "(The donor workup) gave me a feeling of safety; that everything was examined so thoroughly." 117 "I found it quite funny and interesting; the whole medical scene. I've been operated only once when I was a child, so to experience this whole procedure once is fascinating." 466 "To this day it (the kidney donation) has been a very good decision and I never regretted it." 23 "I find it wonderful that I got to do this [the kidney donation], I felt like I won €100.000, that's how happy I was about that I could be an altruistic kidney donor." 291 "I never regretted it [the kidney donation] and if my kidney would grow back, I'd do it again." 103
Support from social environment	"After the donation I stayed with my sister for 6 weeks. Everyone wanted to help me, but they also do that when I have a normal flu." 44 "Before everyone said 'gosh, wat are you doing?' and after the donation they found me very brave and I received a lot of flowers and cards." 292 "I like to be by myself, so I did not really get much support and I did not want it, I could manage by myself. I bought groceries beforehand and my son went shopping for me once, but more help I did not get." 414 "At work they did not cooperate at all. I work in the healthcare sector, but they were not supportive. (. . .) It made me very sad." 337
Interpersonal stress	"My wife first thought I was joking. She did not come to the hospital after I donated. She left the house as a direct consequence of my kidney donation, because I did not give in at all. I told her that even though we were married, my kidney is no part of that." 136 "I gave my parents a DVD and leaflets about altruistic donation, but they did not even watch it. I distanced myself from my parents a few weeks before the donation, we had no contact for a while. My parents threatened to sell my horse trailer, they were desperate to stop me from donating." 486
Negative experiences with hospital care	"No one in the hospital said to me 'wow, nice that you have done this!'. They said nothing kind, nothing friendly. One nurse said something nice to me and I suddenly got emotional, but the others only chatted among themselves about their private life. I find that very unprofessional." 193 "They were very kind before the donation, but after the donation they were like 'shut up and stay away'. That's how I felt it." 173 "Only the financial compensation was strange. Why does it have to take so much effort to get my travel costs reimbursed? A living kidney donor saves the health insurance companies almost €50.000. So why do they care about a few euros?" 220

[a]*The numbers at the end of the quotations are identifiers and represent the participant numbers.*

General Donation Experiences

Satisfaction With Donation

For most donors, the donation was a positive experience. Some called it "interesting" or "amazing." Donors were generally satisfied with the hospital care and did not experience the donation process as stressful, although they mentioned feeling somewhat nervous before surgery. For some it was reassuring to know that they could withdraw from the process at any time. Most donors experienced a smooth recovery and 98% would make the decision to donate again. The two donors who regretted their decision to donate were dissatisfied about the hospital care they received and criticised the lack of empathy from the hospital

TABLE 3 | Illustrative quotations reflecting donors' pre-donation experiences.

Theme	Quotations[a]
Uncertainty about donor approval	"It was nice to be turned inside out in preparation for the donation. Other people have to pay for that kind of check-up." 426 "At times it was stressful, because you're afraid they will find something you do not wanna know'" 106 "I really hoped I would be allowed to donate, because I saw it as a lifesaving act. My major thought was, that I hoped I could do it, that I hoped to pass the tests, despite my mild hypertension." 298 "I was only a little nervous about the psychological screening, because the psychologist was hard to read and I did not know what they thought of me." 397 "The psychologist asked me a lot of strange questions. He started out with asking why I wanted to donate, if I was sure I did not want it just to receive attention etcetera. I'm not easily taken aback, but the conversation with this psychologist did not feel good." 193
Life on hold during donor work-up	(Donor who had to wait several months before an operation date): "I mean, you made the decision to donate, you've passed the tests, medically and psychologically all is fine. I got the feeling I got stalled, while so many people are waiting for a kidney. Why did it have to take so long?" 424 "I hoped I would donate in summer, so that I could recover in the garden, but then it got autumn. I felt a little inpatient, that it took longer again. I looked forward to it and then again it did not happen." 45 "On the day of admission I felt relieved, it is finally happening, the waiting is over." 46
Donation requires perseverance and commitment	"The reactions (from the social environment) were mainly positive. Or 'good that you do that' and 'I'd never do it.'. My sister was vehemently against it, because 'you have two kidneys not without reason, what is something happens with the other kidney?'. But it did not make me doubt my decision or whatsoever, no." 111 "People said: 'Girl, at your age? You're crazy!'. My kids had lost their dad already, how would it go with their mum? I can imagine that." 322 "I constantly had to defend myself, when I told others about my plans to donate. That was hard for me. Not only in my social network, but also in the hospital. When I got my blood drawn and we started chatting, the nurse said: 'wow, why do you do this? For a stranger?' It felt like I had to go in defense-mode." 124 "I encountered resistance from people. Some people even got angry, so I stopped talking about it. I feel like more education about living donation is needed." 262 "Before the donation I had not told many people, because I knew that my sister would not agree. So I thought, I'm not gonna talk about it, because people will only make a fuss about it." 369 "I never doubted my decision. I always felt like, this is something personal. I want this and what others think of it, is their opinion. This is my choice and I do not care what others think." 486

[a]*The numbers at the end of the quotations are identifiers and represent the participant numbers.*

TABLE 4 | Illustrative quotations reflecting donors' post-donation experiences.

Theme	Quotations[a]
Recovery took longer than expected	"I got problems with the wound and I had to take it slow for a few months. At that point I pitied myself: I donated my kidney, I do not deserve this." 103 "I only started to work again after 3 months. I had a lot of pain in my stomach, probably due to scar tissue, and I kept on getting bladder infections, but I recovered. I see other donors who could cycle again after one or 2 weeks, but not me." 193
Becoming an advocate for living kidney donation	"The reason that I share my donor experience with others is because I want to draw people's attention to the possibility of becoming a living donor." 256 "I'm an active member of my church and together with the pastor I have organized two services about kidney donation. (question for the interviewer): Do you know anything else I could do or participate in?" 102 (Donor who got featured on several TV channels and in newspapers): "In retrospect I'd have done it differently. I'd have never cooperated with TV, an anonymous newspaper article would have been enough, because I'd have control over that. Looking back on my feelings about the media, it was a media storm. On the other side it has triggered a lot, but I would not work with too many media channels again." 23 "I shared a story about my kidney donation of Facebook, to spread the word about living kidney donation." 339
Normalization of the donation	"I'm surprised that to me it (the unspecified kidney donation) is the most natural thing in the world and others find it extraordinary. I do not understand that people do not do it, to me it is so very logical to donate. I'd prefer to donate another kidney, so to speak." 102 "I do not see it like wow I'm such a good person, because I donated my kidney. I do not think about it anymore. I once donated that thing, it's finished. It's history." 268 "It was a piece of cake. The surgery was on Friday, I was discharged on Monday. I did not notice anything from the surgery or the scar." 424 "Being down to earth, I'd say: it's not that special. Just do it, it's no effort and you derive a lot of satisfaction in return." 449

[a]*The numbers at the end of the quotations are identifiers and represent the participant numbers.*

TABLE 5 | Illustrative quotations reflecting donors' experiences with anonymity.

Theme	Quotations[a]
Satisfaction with anonymous procedure	"I was happy with the anonymity, because the recipient does not have to bother about giving something in return. I rather give than receive presents." 224 "I see only advantages of anonymity. If I'd hear the kidney had been rejected by the recipient, I'd be so sad for that person, I'd very upset to hear that." 226 "I absolutely do not want to know my recipient. If I'd know, I'd watch that person. If he lives good, eats healthy, and I do not have the right to interfere with another person like that. But if I knew, I might do that." 372 "To me anonymous kidney donation is the purest form of donation. No personal interests played a role in my donation. Anonymity has been the force behind my donation." 23
Ongoing curiosity	"I'd only like to know if the kidney still functions. I do not need to know an age or anything about the recipient, because then the anonymity would be gone." 23 "Honestly, I'd like to know who got my kidney. I'd like to know if he/she is doing fine, and if the recipient would want that, I'd like to meet him/her. I regularly think about my recipient and it's a pity that I do not know anything about the outcome of the donation" 45 "It's a pity that you do not get to know if the donation has been successful, because if you do not hear anything, for what did I do it? It's a shame that I do not know if my goal [helping someone] has been achieved." 217
Importance of receiving anonymous communication	"I've always found it a shame that I did not hear anything. How on earth it is possible that someone receives a kidney and does not even send a postcard or a soap bar or just something, a gesture, I do not understand it." 268 "It has struck my mind that I'd have written a card if I'd been the recipient. I'd have been so happy and I'd have wanted to express that. I just find it a little strange. Was receiving my kidney so ordinary for them? Did the transplantation not go well?" 339 "I received a letter from my recipient. It was very touching and beautiful. I read the letter to my friends and family while celebrating new years eve." 424 "It received a card twice. I know it was a young chap and he had been on holiday for the first time in his life, because he was off dialysis. Receiving a postcard from Tenerife was just great!" 369
Anonymity is not watertight	"I was at a donor-day from the patient association and another donor mentioned the date of his donation and I said 'me too!'. I told him that I received a letter, and then he said 'it was me writing that letter' (the other donor participated in a domino-paired donation together with his wife who needed a kidney). I was shocked and touched. His wife was not ready for knowing about me, so we had no contact after that. But I now know that I donated to a mother of four children." 247 "I had to wait in a doctor's room and there were 4 cups on the table. I saw two identical surnames, one foreign surname and my own surname. I just knew that two names belonged to an exchange pair. When I came back for a check-up, that exchange couple was in the waiting room as well for the same check-up!" 424 "I checked my electronic patient record and at the 'relatives section' I suddenly saw a name I did not know. It was the name of my recipient. I could not restrain my curiosity and googled her name. I found everything: how old she was, where she lived and how she was doing at the moment. It is just a coincidence. I mean, I only had the name and decided to google the name. So I have a part in it as well." 403

[a]*The numbers at the end of the quotations are identifiers and represent the participant numbers.*

staff and/or the reimbursement procedure for donation related expenses.

Support From Social Network

The majority of donors felt supported by their relatives and friends during the donation process, despite the resistance they also encountered. During the recovery period participants received both psychological support, (e.g., post-cards), and practical support (e.g., people bringing groceries). Some donors said that they did not need extra support during the recovery, while others would have wanted more support than they received. A few donors reported that contact with other donors *via* patient societies was helpful to them. Only a minority of participants reported on the reaction and support of their employer. Most of them felt supported by their employer, but a few employers did not agree with the decision to donate or donors felt they had to return to work too soon after donation.

Interpersonal Stress

A small group of donors mentioned that their choice to become an UKD impacted their relationships, because some loved ones strongly opposed their decision to donate and could not understand it. A few donors said they broke up with their partner, because he or she could not accept the donors' decision. Several others mentioned conflicts in the parent-child relationship, which led to a temporary loss of contact or a continued estrangement.

Complaints About Hospital Care

Despite of the general high satisfaction with the donation process, many participants also had some complaints about their hospital experience. Concerning the donor work-up, some participants mentioned that attending all the appointments caused them inconvenience (some patients had many appointments on 1 day, others had to come to the hospital on multiple days). Concerning the admission for the nephrectomy and the hospital stay, some complained about a level of hygiene, the quality of the

food or fellow patients in their shared hospital room. Some participants complained about the responsiveness of and communication with the hospital staff. They felt that their needs (physical or emotional) were unseen or missed genuine interest or empathy from the hospital staff with regard to their donation to a stranger. Some donors felt that they were discharged too soon. A few donors felt frustrated about donation related expenses, such as travel costs, and were dissatisfied about the financial compensation they received. Also, a few donors complained that their family doctor (GP) did not seem to be aware of them only having one kidney.

Pre-Donation Experiences

Uncertainty About Donor Approval

Concerning the donor work-up, donors reported to be happy with the medical check-up. It felt good to be examined so thoroughly. Nonetheless they were nervous about receiving the final test results, because they feared that a reason (medical or psychological) would be found that would prevent them from becoming a UKD. A small group of donors found the psychosocial evaluation strange or intrusive, because of the kind of questions that were being asked (e.g., why they wanted to donate, or if they expected to be praised for their donation by others).

Life on Hold Between Donor Approval and Actual Donation

After being approved, donors felt excitement about the upcoming donation, but they still had to wait before a final donation date was set. Some donors reported that the period between the donor work-up and the actual donation was long, which caused problems with the scheduling of work or holidays. A few were anxious something would happen to them in this period of waiting, for example getting ill. Donors were relieved when the donation finally took place.

Donation Requires Perseverance and Commitment

When informing others about their decision to become an UKD, donors received both positive and negative responses. People admired them for their remarkable choice to donate, but would not do it themselves. Some loved ones said donating a kidney fits the personality of the donor and, in some cases, friends or family got inspired to become an UKD themselves. For all participants, however, the choice to donate was also met with some resistance and/or concern. Other people found it a risky, or even selfish decision (what if a loved one would need a kidney) and donors were regularly called "crazy" for wanting to become an UKD. Participants reported that they had to constantly justify their decision to donate. To avoid negative reactions, or to protect their loved ones against worrying, many donors waited long to share their decision to donate with others or informed very few people. This sometimes made the donation a lonely process. Despite the negative reactions they received, almost all participants reported that they never doubted their decision.

Post-Donation Experiences

Recovery Took Longer than Expected

Even though the majority of donors, in retrospect, reported that their recovery was smooth and as they expected it to be, for some donors the recovery took longer or was more stressful than expected. Some developed complications, of which wound infections were the most common, or suffered from ongoing pain or exhaustion. A few donors were very unhappy with their scar and underwent scar revision surgery at their own expense.

Normalization of the Donation

Many donors mentioned that others perceived their donation as a remarkable act, while for them it was a natural thing to do. They reported that they do not feel special for being an UKD and do not regularly think about the donation anymore. Some do not talk about it anymore, because they do not want or need to be praised for their donation. In retrospect, some donors feel like the donation was not a big deal and that the donation was no effort for them.

Becoming an Advocate for Living Kidney Donation

Some participants actively shared their story to create awareness about unspecified kidney donation. When they get the chance, they tell colleagues or other people about the donation. A few others shared their donation experience on social media or participated in educational activities organised by patient foundations. Some donors were asked to share their story on national TV or in a newspaper.

Experiences With Anonymity

Satisfaction With Anonymity

In general, participants were happy with the anonymity of their donation and they understood the advantages of anonymity. They believed that anonymity protected them against an unequal relationship with the recipient or a continued sense of obligation from the recipient to the donor (and *vice versa*). Some donors reported that they did not want gratitude. Donors also said that not knowing the recipient protected them against disappointment if the transplant failed or when the recipient would turn out to be different than they imagined. Finally, participants believed that anonymity ensures an unconditional gift and a fair allocation of organs, based on medical considerations rather than on prejudices. A small group of donors did not agree with anonymity and criticized the secrecy around the recipient, especially after the introduction of the General Data Protection Regulation (a regulation issued by the EU in 2016 to harmonize data privacy laws across Europe).

Ongoing Curiosity About Outcome or Recipient

Even though the majority of participants were happy with anonymity, many of them also experienced a level of ongoing curiosity. This curiosity mainly concerned the outcome of the transplantation (does the kidney still function? How is my recipient doing?), but some donors were curious to know (more details about) their recipient. A few would really like to meet their recipient and one donor did actively try to find her recipient. Some participants (repeatedly) called the hospital to inquire about the status of their kidney. During the interview some participants again tried to obtain more information about "their" kidney or about the recipient.

Importance of Anonymous Communication

Some donors were informed by their medical doctor that the transplantation had been successful. Knowing that the recipient was doing well meant a lot for these donors and made them happy. Some donors were told some details about their recipient, such as age and/or gender, which was valuable information for them. Only a minority of donors received one (or more) anonymous card(s) from their recipient. They reported that it was satisfying to hear something about the impact of the kidney donation on the recipient's life. A few donors mentioned that they received a small gift from the recipient, such as a fruit basket or a small amount of money in cash or on a gift card (the highest reported amount was €35). One person received a horseshoe charm, but returned this to the recipient, because he had ambivalent feelings about this gift. Most donors who did not receive an anonymous card from the recipient were not bothered by that, but some would have appreciated a (thank you) letter and were disappointed about not getting one. Some of them were upset, because in their opinion it is the least a recipient could have done to express his or her gratitude through such a card/letter.

Anonymity is not Watertight

A few donors had found out who their recipient is, in most cases due to carelessness of health organizations, such as the hospital or health insurance companies. One donor saw the name and address of her recipient in her electronic patient records and another donor was left alone in a doctor's room with four cups with names on it and could easily figure out who her recipient was. A few others found out the name of their recipients, because they got their travel expenses refunded by the health insurance of the recipient and the insurance companies were not aware of the anonymous nature of the donation. In some cases, donors could make an educated guess about who their recipient was, based on what they saw on the ward or heard from fellow patients (e.g., when sharing a room with the exchange donor in a domino-paired donation).

DISCUSSION

This large qualitative study summarized the experiences of UKDs in the Netherlands up to on average 7 years after donation and highlighted valuable implications for education and guidance of UKDs throughout the donation process. The donation was predominantly a positive experience for participants and 98% of donors would, if possible, make the same decision again to donate. Most donors were satisfied with the living donor evaluation, with the hospital care they received in the pre-donation and follow-up period, and experienced a smooth recovery and no unexpected or lasting consequences of their donation. These findings are in line with previous research on the experiences of UKDs in the Netherlands and in other countries (7-11). We also found that all participants, to a greater or lesser extent, faced resistance to their choice to become an UKD from friends, relatives or employers, because of a lack of understanding. Similar struggles have been reported by UKDs in other countries, such as the UK (11, 12), Sweden (10), the US (16), and New-Zealand (9). Like in these previous studies, we found that participants responded to the abovementioned struggles by determination and commitment to their decision. A detailed description of the motivation of these donors and the, overwhelmingly positive, impact of the donation on the lives and mental health of this cohort of UKDs can be found elsewhere (17).

Even though we conclude that the donation was generally a very positive experience for the UKDs in our centre, participants also revealed some negative experiences that call for adjustments and improvement of certain aspects of the donation process. Some participants criticized certain procedural aspects, such as the lengthy assessment procedure or the complicated procedures to get a refund for donation-related expenses. Similar complaints are reported by UKDs in other countries (9, 10), but also apply to living related kidney donors as well. It is important to highlight, that participants all donated before 2016 and subsidy regulations in the Netherlands have improved since then. Currently, all living kidney donors are entitled to compensation for donation related expenses (including parking costs, costs for additional medical or homecare, flowers for helpers, travel and accommodation costs for one caregiver) and to partial compensation for loss of income(18). Concerning the length of the living donor assessment procedure, one could try to optimize and shorten the assessment process (although the matching process will always take time, especially when UKDs are included in a kidney exchange program). For example, Northern-Ireland has implemented a one-day assessment process, which resulted in an increase of the living kidney donation rate and in an enhanced overall donor experience (19). Finally, some donors found the psychosocial evaluation disturbing, because they had the impression that their motivation was being questioned, which has also been reported by UKDs in the United Kingdom (13). To prevent these negative experiences, the goal of the psychosocial evaluation should always be explained to the donors. In accordance with the ELPAT living organ donor Psychosocial Assessment Tool (EPAT) (20), currently used in our transplant institute, we stress the importance of emphasizing that the psychosocial assessment is not a test, but an evaluation of how best to prepare for the donation and care for the individual.

On a psycho-social level we found that some donors experienced a lack of social support, an increased tension in relationships during the donation process (e.g., a break-up or estrangements) or a lack of acknowledgement for their donation (from the recipient or from the hospital staff). These are important findings that ask for improvements in the care for these donors, because they might lead to unfavourable psychological outcomes (21, 22). Firstly, assessing the social resources of UKDs should be part of the psychosocial screening for UKDs to identify concerns about a lack of social support or conflicts caused by donation (20, 23). In the EPAT-tool (20) the absence of social support is seen as a red flag for donation and as a signal that education on the impact after donation or additional support from the transplant team is needed. In addition, we recommend to include the social network in the education for and guidance of UKDs throughout the donation process as much as possible (i.e. by actively inviting friends and relatives to accompany the donor to hospital appointments). Although our UKDs were generally happy with the anonymity of their donation, many experienced a level of ongoing curiosity

towards the outcome of the transplantation, and, to a lesser extent, towards the identity of the recipient. This curiosity is common among UKDs worldwide (7, 9, 24, 25). While anonymous communication between donor and recipient is allowed in the Netherlands, only a minority of the included donors had received an anonymous card from their recipient. This gesture meant a lot to these donors, because they realized the impact of their act and felt a connection to the recipient (without rescinding anonymity). Some donors who did not receive a card experienced negative feelings about this. Previous studies have also described the importance of receiving acknowledgement from the recipient (9, 10, 12). Although there can be many reasons for recipients not to reach out (ranging from just forgetting about the possibility to a failed transplant), efforts should be made to make recipients of an anonymous living donor kidney more aware of the meaning of anonymous correspondence for their donor. Recipients should be informed about the possibility of sending an anonymous card at least once before the transplantation and once after the transplantation. Finally yet importantly, some participants were disappointed in the attitude of the hospital staff towards UKDs and missed empathy and understanding for their special kind of donation. As also described by Zuchowski and colleagues, who studied UKDs in the UK, the extensive work-up process was in sharp contrast with the treatment donors received after surgery. Although most donors did not want special treatment, they did look for some kind of recognition from the hospital staff (11). 'It's like delivering a package, after that you're just dismissed', one of our donors said. The disappointment about the lack of this recognition caused some donors to have lasting negative feelings about the donation (17). It should be noted that this feeling of "abandonment" after the donation has also been described by directed living kidney donors (26-29) and has been associated with lower satisfaction rates and a negative influence on quality of life (26). We agree with others in the field that healthcare professionals should "give explicit attention to living kidney donors after the donation"(27-29). Transplant centres should consider how they wish to acknowledge the contribution of anonymous donors, not only through something tangible (such as a card) but also through the attitude of staff. We believe that small actions such as a kind word or a compliment to a living donor will enrich the donor experience, of UKDs in particular. It therefore is important that transplant professionals are educated about the motivations and expectations of UKDs to increase understanding and empathy for this group that makes a major contribution to our public health. The themes found in this study can contribute to the content of such education.

Limitation of the Present Study and Future Directions

Firstly, a limitation of the study is the retrospective design, whereby findings may be subject to memory lapses or recall bias. Moreover, there is a wide variation in time since donation which we did not take into consideration in the analysis. On the other hand, we believe that we captured the most important experiences of our donors that remained active even years after the donation. It should, however, be kept in mind that participants donated over a long time-frame, in which policies and approaches toward UKDs have changed. Nevertheless we believe that the majority of experiences still apply and should be used as indicators to improve care for these donors. Secondly, the fact that the interviewer was known to the participants, based on her previous role as unspecified donor coordinator, could have introduced bias, for example in an attempt to avoid disappointment or embarrassment. On the other hand this may have boostered study participation and honesty. Given the high level of disclosure we did not feel this relationship negatively influenced participants' responses. Thirdly, as nearly all study participants had a European ethnicity, further research seems warranted to investigate whether the experiences of this group of donors can be generalized to other ethnic and cultural groups. We acknowledge that the results might not fully represent the experiences of donors from other transplant centres in the Netherlands and beyond. Future studies should ideally be prospective and should include potential donors who withdrew themselves or were not accepted for donation. In addition, it is important to assess whether the transplant professionals perspectives and experiences with regard to unspecified living kidney donation are in line with the donor perspective, in order to create support among transplant professionals to further improve the care for this group of donors.

Conclusion

In summary, this study showed that our UKDs are generally very satisfied with their donation and, if it were possible, would donate again. Most important complaints about the procedure concerned the length of the donor evaluation and the lack of acknowledgment or resistance for UKDs from both their recipients and health professionals. We call for efforts to optimize the assessment procedures, the education and guidance for UKDs throughout the process, and for more education for transplant professionals about unspecified kidney donation to increase their empathy towards UKDs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethis Review Committee Erasmus MC (2017-1180). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP Participated in project administration, data curation, data analyses, and writing of the paper. WZ Participated in study design, data collection, project administration, and review and editing of the paper. WW Participated in study design, supervision, and review and editing of the paper. JW Participated

in study design, supervision, and review and editing of the paper. SI Participated in study design, data collection, supervision, and review and editing of the paper. EM Participated in study design, data collection, supervision, and review and editing of the paper.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors acknowledge Louiza van Raalten for help with conducting interviews.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.10959/full#supplementary-material

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ESOT | Transplant International

POINT OF VIEW
published: 21 April 2023
doi: 10.3389/ti.2023.11139

Living Donor Kidney Transplantation in Older Individuals: An Ethical Legal and Psychological Aspects of Transplantation (ELPAT) View

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Living donor transplantation is the optimal treatment for suitable patients with end-stage kidney disease. There are particular advantages for older individuals in terms of elective surgery, timely transplantation, and early graft function. Yet, despite the superiority of living donor transplantation especially for this cohort, older patients are significantly less likely to access this treatment modality than younger age groups. However, given the changing population demographic in recent decades, there are increasing numbers of older but otherwise healthy individuals with kidney disease who could benefit from living donor transplantation. The complex reasons for this inequity of access are explored, including conscious and unconscious age-related bias by healthcare professionals, concerns relating to older living donors, ethical anxieties related to younger adults donating to aging patients, unwillingness of potential older recipients to consider living donation, and the relevant legislation. There is a legal and moral duty to consider the inequity of access to living donor transplantation, recognising both the potential disparity between chronological and physiological age in older patients, and benefits of this treatment for individuals as well as society.

Keywords: older recipients, access to transplantation, older living donors, age-related bias, inequity in living donor transplantation

Point of View

OPEN ACCESS

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Received: *15 December 2022*
Accepted: *12 April 2023*
Published: *21 April 2023*

Citation:
Courtney AE, Moorlock G, Van Assche K, Burnapp L, Mamode N, Lennerling A and Dor FJMF (2023) Living Donor Kidney Transplantation in Older Individuals: An Ethical Legal and Psychological Aspects of Transplantation (ELPAT) View. Transpl Int 36:11139. doi: 10.3389/ti.2023.11139

BACKGROUND

Kidney transplantation is the optimal form of renal replacement therapy for suitable patients with end-stage kidney disease (ESKD).

Notably, the demographic profile of the ESKD population is changing, with older patients (≥65 years) representing the fastest growing incident group starting maintenance dialysis therapy in many countries (1–4). Therefore, there is increasing interest in recent years in the outcome of transplantation compared to chronic dialysis treatment in this cohort, as a proportion of older patients will gain significantly in terms of quality and quantity of life with successful kidney transplantation (5–10).

The outcomes of kidney transplantation from living donors (LD) consistently exceed those from deceased donors (DD) in terms of patient and graft survival (11–13). However, the opportunity for kidney transplantation from a living donor is inconsistent across age categories; in the UK, for example, the likelihood of having a LD rather than a DD transplant is almost 90% lower in those aged 65 years or older at time of transplant, compared to young adults (14–17).

The scope of this paper is to explore the inequality of access to living kidney transplantation for the older recipient (defined as >65 years old).

Advantages of living donor transplantation in older patients

One of the objectives of the current deceased kidney offering scheme in the UK is to maximise the utility of DD organs, in part by preferentially matching kidney life expectancy with recipient life expectancy (18). This mirrors the principles of the Eurotransplant Senior Programme instigated in 1999 (19). Thus if reliant upon deceased donors, older patients are more likely to be offered a kidney from an older donor with associated comorbidity. There is a higher incidence of delayed graft function with such organs (20), requirement for biopsy with attendant hazards, and consequent need for prolonged hospital stay with associated risks of deterioration in functional ability and independence.

There are short-term advantages in receiving a LD organ over a DD organ, particularly in older patients. Transplants (even if coming from older donors) typically work immediately, facilitating early discharge and resumption of normal activities. Additionally, there are particular advantages to elective rather than emergency surgery in older individuals who are more likely to be comorbid than younger patients. Indeed, in some centres there are patients considered suitable *only* for living donor transplantation, where the risk:benefit ratio (considering the combined physiological stress of emergency surgery and a delayed poorly functioning kidney) of a DD transplant is so unfavourable as to be prohibitive. An additional benefit of LD transplantation in the older cohort is the opportunity for minimisation of, or no time on dialysis, i.e., pre-emptive transplantation. Dialysis duration prior to transplantation is arguably the strongest independent modifiable risk factor for kidney transplant outcomes, and this is likely to be of even greater significance in older patients, when decline in functional capacity (including cognitive function) and death on dialysis are accelerated compared to younger age groups (21–27). Thus, older individuals have a more limited window of opportunity for transplantation before the risks are considered excessive.

However as the prevalent age of the ESKD population rises, so does the age of the potential LD pool of siblings, spouses, and friends. There are two areas of potential concern with transplanting from older donors:

- the outcomes for the living donor—is the peri-operative risk unacceptably increased compared to young donors?
- the outcomes for the recipient—is the older transplanted kidney going to provide useful function for an acceptable period of time?

There is widespread acceptance of older DD for older patients with ESKD (19, 28), yet in some centres there is reluctance to consider transplantation from older LD, despite the reassurance of a healthy kidney with no peri-mortal injury.

Given that LD transplantation is the optimal treatment for ESKD in suitable patients, and has particular benefits for older individuals, what are the factors hindering this in practice? Is there inherent age discrimination? Are there ethical and psychosocial barriers within the transplant community that contribute to the discrepancy of access to this healthcare for older individuals?

Clinical Cases

Table 1 summarises two clinical scenarios with potential LD options for older transplant candidates, and raises challenging questions for healthcare teams.

SYSTEMIC BARRIERS

Transplant Professionals

Younger Donor

The physical risks to a donor are unaltered by the age or health of, or relationship with, the intended recipient. If the potential donor in case 1 was wishing to donate to his 5-year-old daughter, rather than 71-year-old mother, the surgical procedure, recovery, and long-term outcomes from a physical perspective will be identical. Yet, it is likely that few would dispute the appropriateness of proposed donation from the father to the child. The opinion on his donation to his elderly mother however will be considered differently in at least some transplant centres.

This may result from the difference in "value" that society assigns with certain relationships (29) and reflect the influence of the beliefs of the transplant professionals on the perceived "benefit" of his gift. If it is considered of more value to the child than to the parent, the identical physical risks are *relatively* greater when considering donation to the older individual. Is this valid? Is it reasonable that the transplant team makes a judgment call on the value of the transplant outcome for the recipient? (30). And is there account taken of the non-physical benefits to the donor from a successful transplant for the recipient?

Aside from value, there is another potential difference since the obligations that a parent may have to their child are not necessarily replicated in reverse, i.e., a child (even when an adult) does not necessarily have a corresponding duty to their parents. There are arguably certain things that a parent may be morally obliged to do for their children that a child is not obliged to do for their parents. But this cannot provide a compelling difference here, since talk of obligation in LD is itself potentially problematic when it comes to freely given consent. Moreover, given the value of autonomy in LD, it is not obvious that obligation arising from a particular relationship should make a donation more acceptable

TABLE 1 | Potential donors for older patients with end-stage kidney disease.

		Case 1	Case 2
Potential donor	Age	33 years	77 years
	Gender	Male	Male
Potential recipient	Age	71 years	75 years
	Gender	Female	Female
	Cause of ESKD	Obstructive uropathy	Vasculitis
Relationship		Son to mother	Husband to wife
Questions		Is this appropriate? How would this offer be considered if he wished to donate to his 5-year old daughter?	Is this appropriate? What are the alternatives for the potential recipient?

than an autonomously motivated donation without underlying obligation (30).

Aside from these considerations, it is inevitable that the culture of a transplant centre is influenced by the personal beliefs of its leading professionals (31–33), potentially based on single cases they once experienced (positively and negatively). Additionally, it may reflect a reluctance to change or deal with uncertainty (34). This impacts on the information given to potential donors and recipients, and the enthusiasm with which LD transplantation for older individuals is presented as an option, if at all. Inevitably such differences account, at least in part, for the discrepancy in access to LD transplantation.

Older Donor

Donor Considerations

Conversely to younger donors, where the concerns relate to long-term rather than short-term risks to health, for people donating at an older age the "long-term" is, by definition, limited but there is a greater potential risk of peri-operative morbidity. It is crucial that transplant teams have confidence in their assessment process in evaluating older volunteers.

An early suboptimal donor outcome, irrespective of age, has a much greater psychological impact on the transplanting team than poor kidney function two or three decades after donation in a younger individual. In the latter scenario, most probably an alternative medical practitioner will then be responsible for care of the donor.

It is likely that such psychological factors, and concern about the possibility of peri-operative events, are contributory to the subconscious assessment of risk. This is reflected in the attitude amongst transplant professionals in Europe towards extended criteria living donors: almost half (43%) reported an upper age limit for LD in one survey, and in another report a third would not consider donation from individuals over 70 years old (31, 33).

Such concerns however are not evidence based. The available literature supports the safety of nephrectomy in older donors assessed according to protocol: 1-year survival in donors aged ≥70 years (in the US from 1990–2010) was 99.5%, comparable to matched controls from the general population (99.1%) (35, 36).

The scenario in case 2 is common: couples that have retirement plans together where the quality of life of the "healthy" partner is substantially negatively impacted by the ESKD of the other. Undoubtedly, giving such individuals the opportunity to donate is transformational for the donor as well as the recipient. The early quality of life reports for the older donor may exceed that of younger contemporaries (37). Imposition of the fears and prejudices of a reluctant, risk-averse transplant team on the decision-making process will impact on achieving the best outcomes for the patient.

Recipient Considerations

Another consideration in relation to older potential donors is the likely outcome for the *recipient* in terms of graft function and survival. Younger kidneys are associated with better outcomes. However, there has been a progressive increase in the age of deceased donors over the past four decades. The persistent relative shortage of deceased donor organs, which has driven this, has of course been exacerbated by increasing willingness to consider older healthy patients for transplantation.

It is counter-intuitive therefore not to consider older potential living donors for older recipients, when the alternative is an older DD kidney, or no opportunity of transplantation. The reported outcomes for LD are better than for DD of not only comparable age, but also younger, with the benefits of established good health and function, and avoidance of the physiological catastrophe of death (37–40). The reality for the older recipient is that prolonged survival is not anticipated and therefore a single LD transplant, even from a comparably aged donor, is typically adequate.

Transplant Patients

Older patients with ESKD have a range of emotional and psychological responses when the possibility of a transplant, particularly from a living donor is discussed (41–43). The seriousness with which this option will be considered will be influenced by the attitude of the transplant team (44)—any reticence will typically translate into a reluctance from the patient to discuss the possibility with potential donors. Common with other specialties, the beliefs of the professional characteristically have a substantial impact on the health choices of the patient.

Even when there is genuine support from the clinicians for LD transplantation, however, the potential recipient often expresses reluctance (45). The feelings of guilt and unworthiness are well

described (46), however in relation to the older patient, there are specific issues.

Younger Donor

With a younger donor, most commonly a son or daughter, there can be a feeling of "disorder." In a comparable way as the death of an adult child is felt contrary to the natural cycle of life, so receiving the "gift of life" from a "child" can also feel counterintuitive and inappropriate. Being persuaded that the donor ultimately will also benefit—often this can only be conveyed convincingly by the potential donor—is usually necessary to overcome this barrier. Undoubtedly, considerable advantages to the donor can exist, not just emotionally but often practically in terms of the extended family support. Withholding an opportunity to donate may have a detrimental psychosocial impact on the potential donor (47). When a patient is unwilling to consider younger volunteers, it is important that, rather than simply accepting that there are "no LD options," the healthcare team enquire about possible volunteers and explore the reasons for decline.

Older Donor

When the LD volunteer is older, the reluctance may stem from not wishing to "put the donor at risk." In this scenario the depth of the emotional relationship may be the most influential factor, along with perhaps the enthusiasm of a partner who has the most to benefit (apart from the recipient themselves), from a successful transplant.

ETHICAL ISSUES

Since LD transplantation is the best treatment option for the patient with ESKD, to state that it is desirable to have more living donation would seem *prima facie* uncontroversial. But there are other perspectives, not just those of the recipient, which must be considered from an ethical perspective and a LD brings additional complexity.

If living donation is considered to bring overall benefit to the potential *donor*, then the argument to provide information about living donation to older patients is stronger. Giving more donors and recipients the opportunity to enjoy the benefits of successful transplantation, with additionally reducing reliance upon the scarce deceased donor pool and the economically draining maintenance dialysis programme, are good things. If living donation is considered not to provide so much benefit to the donor and given that benefits to the donor are possibly lower with older than younger recipients (as inevitably more time-limited), then the argument that living donation should be presented as an option to older recipients is somewhat weaker.

Part of the reason for reluctance to use living donors for older recipients may relate to the principle of utility, with the goal of maximising this for each organ. It could be argued that giving an excellent kidney from a young LD, which may function for at least 20 years in a comparably aged recipient, to an older patient who will only live for another 10 years fails to make full use of that kidney, as 10 years of transplanted kidney function would have been squandered. This argument is flawed because if the living donation never goes ahead in the first place, then all transplanted kidney function is squandered.

Another notable difference between living and deceased donors is that the former can articulate their choice of recipient, which is not possible in deceased donation. The principle of donor autonomy must therefore be in equipoise with utility, in contrast to the situation with deceased donation. Balancing this additionally with healthcare professionals' paternalistic "protection" can be challenging (48, 49).

LEGAL ISSUES

The right to health, generally defined as "the right to the enjoyment of the highest attainable standard of health," is enshrined in international human rights law and many national constitutions worldwide (50–52). Arguably, LD transplantation is the best option to achieve this for ESKD patients.

Denying older patients the opportunity to be considered for living kidney transplantation may be a violation of non-discrimination obligations under human rights law. The European Convention on Human Rights stipulates that individuals should not be discriminated against on any ground, including on the basis of age, in the enjoyment of the guaranteed rights such as the right to life and the right to physical integrity. Although health is not explicitly stated in the European Convention, the right to health is expressed in the European Social Charter, which includes a similar anti-discrimination clause.

Importantly, international human rights law has recently emphasised that countries ought to ensure the availability, accessibility, and affordability of healthcare for older persons, and that barriers should be eliminated that deny older persons their rights on an equal basis with other persons (53, 54). More generally, combatting age discrimination in access to healthcare has become a major human rights issue with the adoption in 2015 by the United Nations General Assembly of Sustainable Development Goal 3: Ensure Healthy Lives and Promote Wellbeing for All at All Ages (55).

Although international guidelines on transplantation do not yet explicitly focus on potential discrimination of recipients based on age, they do require provision of equitable access to transplantation services for patients. This means that "all people, whatever their condition or background, must be equally able to be assessed by whatever transplant services are available" (56). Moreover, these guidelines also recommend that organ transplantation services are determined by medical criteria, such as compatibility, medical urgency, and expected outcomes. Age considerations should not in and of themselves therefore be a contraindication to transplantation.

It is also widely accepted in healthcare that for consent to treatment to be valid legally, the patient must be given all relevant information about what the proposed treatment involves, the alternative treatments, and the consequence of not having the treatment. Most countries in Europe have, in their Law on Patient

Rights (e.g., Belgium, Netherlands, Sweden—*Patientlag* 2014:821 (57)) or in case law [e.g., for the UK see *Montgomery v. Lanarkshire Health Board* (58)], shifted away from the "reasonable physician standard" towards a "reasonable patient standard" in deciding what counts as relevant information to be disclosed to patients. At least in countries where LD is a well-established treatment option, it can be anticipated that ESKD patients would reasonably expect to be informed of this possibility. Reluctance to present living kidney transplantation as a therapeutic option to this cohort might therefore constitute a breach of legal duty.

It can be argued that LD transplantation cannot be considered an "available" treatment if the patient has a degree of responsibility to "source" a willing donor. However, if donors spontaneously offer to donate they have not necessarily been "sourced" by the recipient. It is of course impossible for anyone to volunteer for something about which they know nothing, so a person has to be made aware by some means, that they can volunteer to be considered as a donor.

In conclusion, older people do not have a legal right to have a living donor transplant, but do have a right to be informed of this possibility where it is an available therapeutic option that would be otherwise be offered to them if they were younger.

SOCIAL ISSUES

The inequity of access to transplantation and LD transplantation in particular within and between countries, is well recognised, but identifying and then overcoming the barriers is more challenging (59). There are undoubtedly social factors that impact on the ability to access this treatment though published work specifically in relation to older patients is limited; one report suggests there is no association between age and socioeconomic factors (60).

The relatively low LD rate in older age groups, despite obvious advantages suggests that socially this is not an accepted "norm". Potential older LD and recipients may assume that they are "too old" to be considered and therefore are less likely to volunteer as a donor or be self-active as a potential recipient. Society more broadly has to gain from LD in the older age group with restoration of "normal for age" activities and daily function allowing contribution again to family and societal life. Although the position statement from the European Renal Association-European Dialysis and Transplant Association Descartes Working Group in 2016 stated that elderly patients should be encouraged to consider living donation (61), barriers remain.

CONCLUSION

Living donor transplantation offers superior outcomes to both deceased donor transplantation and maintenance dialysis. There are particular advantages for older patients, yet this cohort is significantly less likely to access this treatment option compared to younger age groups. The reasons appear varied and complex. However this inequality cannot always be justified for clinical or ethical reasons, thus there is an age-based inequity of access to transplantation. There is a legal and moral duty to address this with recognition of the potential disparity between chronological and physiological age.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AC wrote the manuscript. AL and FD coordinated the group and supervised the work. All other authors contributed to discussions and writing the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

We acknowledge the support of the European Society for Organ Transplantation for ELPAT. ELPAT is a section of the European Society for Organ Transplantation.

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ORIGINAL RESEARCH
published: 21 February 2023
doi: 10.3389/ti.2023.10795

Changes in Awareness Toward Minor's Organ Donation Through Structured Information; Survey

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This study analyzed survey results regarding awareness of living minors' organ donation. The questionnaires focused on changes in how respondents felt about donations by living minors after eliciting the uncertainty of long-term outcomes for living donors and recipients. The respondents were categorized as minors, adults affiliated with non-medical jobs (Non-Meds), and adults affiliated with medical jobs (Meds). The rates of awareness of living organ donation were significantly different; minors at 86.2%, non-Meds at 82.0%, and Meds at 98.7% ($p < 0.001$). Only 41.4% of Minors and 32.0% of Non-Meds were aware of organ donation by minors, while 70.3% of Meds were ($p < 0.001$). The response rate of opposition to organ donation by minors was highest for Meds and remained the same before and after (54.4%–57.7%, $p = 0.311$). However, the opposition rate in Non-Meds significantly increased (32.4%–46.7%) after learning about the uncertainty of long-term outcomes ($p = 0.009$). The study found that Non-Meds lacked adequate knowledge regarding organ donation by minors and their potential lethal outcomes. Their attitudes toward organ donation by minors could be changed by giving structured information. It is necessary to provide exact information and raise social awareness regarding organ donation by living minors.

Keywords: living donor liver transplantation, living donor kidney transplantation, minors, long-term complication, informed consent, awareness, organ donation

OPEN ACCESS

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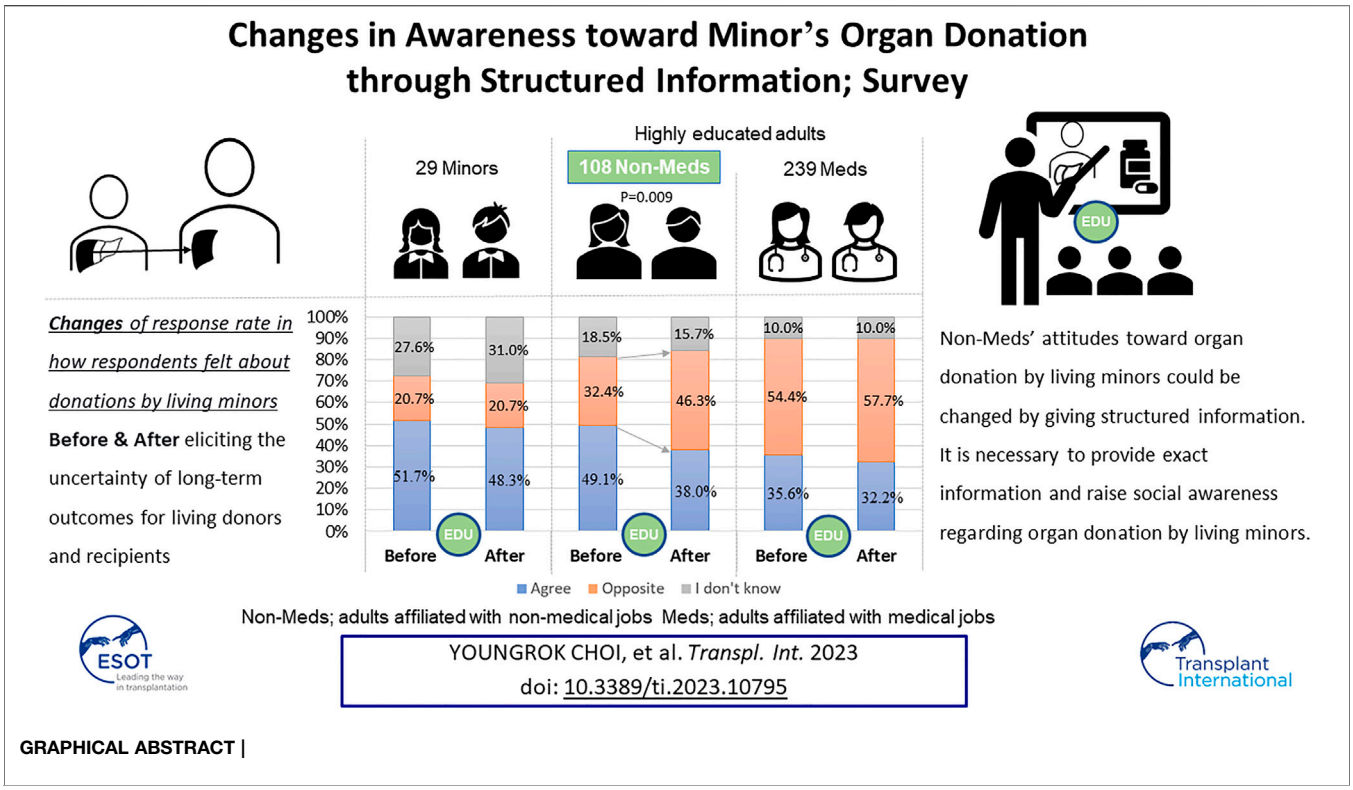
***Received:** 25 July 2022*
***Accepted:** 31 January 2023*
***Published:** 21 February 2023*

Citation:
Choi Y, Lee S, Lee Y, Cho MH, Ihn K, Yoon KC, Kang J-M, Kim SH, Kang HG and Yi N-J (2023) Changes in Awareness Toward Minor's Organ Donation Through Structured Information; Survey. Transpl Int 36:10795. doi: 10.3389/ti.2023.10795

INTRODUCTION

Solid organ transplantation has become a safe and effective treatment option for patients with end-stage renal failure, end-stage hepatic failure, metabolic liver disease, and malignancy. Further, living organ transplantation has been introduced to fill the gap between organ demand and supply, and reduce the high death rate of patients on the transplant waiting list. Living donor organ transplantation is more frequently performed than deceased donor organ transplantation,

Abbreviations: KT, kidney transplantation; LT, liver transplantation; n, number; Q, Question.



GRAPHICAL ABSTRACT |

particularly in Asia and South Korea (1). Nevertheless, organ transplantations have not been performed in sufficient numbers to fulfill the high demand for organ transplants, which is growing every year. As a result, both marginal donors and minors are now legally considered potential organ donors to expand the donor pool (2–6).

The World Health Organization guiding principles on human cells, tissue, and organ transplantation recommend that live organs should not be removed from minors for transplantation. However, several states in the United States and countries such as Canada, Belgium, Luxembourg, Norway, Sweden, the United Kingdom, and Indonesia legally allow the donations of minors under exceptional circumstances (7–12). In South Korea, 30 (2.5%) minors donated their liver in 2019 and 7 (0.5%) minors donated their kidneys in 2018 according to the annual report of the Korean Network for Organ Sharing (**Figure 1**) (1).

Although the number of minors donating livers and kidneys has decreased in recent years, the practice continues. Minors' organ donation may be influenced by cultural components that differ from those in Western countries. However, data on the lifelong effects of living donation on live donors as well as minors are lacking. Moreover, the issue of instability, which occurs when minors decide to donate their organs, has to be addressed. Therefore, there is a need to reassess the organ donation of minors (13, 14).

This study aimed to evaluate the knowledge of and attitude toward liver and kidney transplantation (LT and KT) from minor donors in Korea. Moreover, we assessed if receiving structured information on the outcomes of living organ transplantations and donations may change the attitude toward LT and KT from minors.

MATERIALS AND METHODS

From June-September 2020, ten professors (five pediatricians and five surgeons) in the Pediatric Committee of the Korea Society of Transplantation created and critically assessed the survey questionnaires and methods. The Institutional Review Board of Seoul National University Hospitalapproved the study protocol (IRB No. 2101-178-1193). Between 1 October and 30 November 2020, the cross-sectional ramdom survey was conducted using a Google form.

The survey link was referred by email to eleven National Universities, ten medical societies, the Korean Bar Association, and three high schools. Data of respondents' characteristics and responses were collected.

Minors were defined as persons younger than 19 years according to the Korean national regulation. The survey included a structured set of 27 questions. Korean and English-translated versions of the questionnaire were added as Supplementary documents 1 and 2.

The questionnaire was divided into three stages, as shown in **Figure 2**:

(1) Pre-survey stage: Respondents' basic attitudes (Question 1) toward minors' organ donation were investigated prior to the main survey.
(2) Survey stage
    (1) Respondents' characteristics and basic knowledge: The survey stage entails the collection of respondents' demographic data (Questions 2–8) and investigates

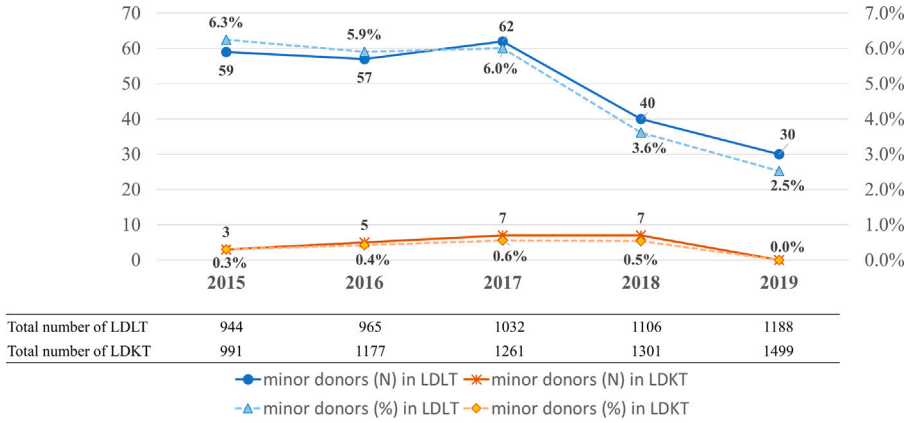


FIGURE 1 | The annual number of living donor transplantations and minor donors in Korea.

their basic knowledge of organ transplantation and minors' organ donation (Questions 9–10). The purpose of questions 25–26 was to examine respondents' expectations of the minimum age at which individuals can donate their organs after being made aware of the Korean law governing minors' organ donation, and the severity grade of donors' and recipients' complications following transplantation.

(2) Respondents' perception and attitude toward the donation and reception of minors' organs was further investigated after basic information and additional explanations were provided: The survey in which respondents were educated using structured material was divided into basic and additional explanations. Adults were informed of the overall outcomes and complications associated with the living donation before being asked if they would accept a liver or kidney graft from a family member or minor (Questions 13, 20). Following that, the same questions (Questions 16, 23) were asked after the lack of data, the uncertainty of outcomes associated with living liver donation in minors despite their long-life expectancy, and long-term complications in living kidney donors associated with living with one kidney had been explained to them. Minors among the respondents were also given the same explanations and asked whether they would be willing to donate their liver or kidney to their parents or siblings (Questions 11–12, Questions 18–19, Questions 14–15, and Questions 21–22). Finally, whether providing additional structured explanations influenced respondents' attitudes was also determined. Questions from 17 to 24 were included to ascertain why respondents altered their decisions after receiving additional explanations.

(3) Post-survey stage: After the survey stage, Question 27, the same question as Question 1, was asked to investigate whether there was any change in respondents' attitudes toward minors' organ transplantation following the questionnaire with additional information.

Statistical Analysis

Data are mostly presented as numbers and percentages in parenthesis (%), and descriptive statistics summarize the survey data. Answers from respondents were recoreded as categorical variables in the Google form.

Responses to each question were analyzed by categorizing respondents into three groups: minors (Minors), adults affiliated with non-medical jobs (Non-Meds), and adults affiliated with medical jobs (Meds). Pearson's chi-squared test was used to analyze diffrences between these groups and McNemar's chi-square test used to analyze diffrences within groups. A p-value less than 0.05 were considered statistically significant. The statistical analyses were conducted using SPSS version 25 for Windows (IBM Corporation, Armonk, NY, United States).

RESULTS

During the study period, 376 people responded. Potenetially eligible respondenst recieved an invitation by email form their institution. All respondenst filled out the questionnaire on a voluntary basis. The basic characteristics of the respondents are detailed in **Table 1**. There were 347 (92.2%) adults and 29 (7.7%) minors. Of the participants, 202 were males (53.7%) and 174 were females (46.3%). Among minors, 13 were male and 16 were female. Most adults (74.4%) and minors (100%) had 3 or more family members. Of the adults, 332 (95.7%) graduated from college, while 11 (2.9%) finished their education in middle or high school. Eighteen (5.2% of adults) adults and one (3.4% of minors) minor had liver or kidney diseases; among them, more than half had a mild degree of disease severity.

Of the 347 adults, 239 were Meds; 128 doctors (53.6%), 62 nurses (25.9%), 1 dentist (0.4%), 30 paramedics (12.6%), and 18 medical students (7.5%). Among Meds respondents, 81 (33.9%) were in the surgical field, 26 (10.9%) were in pediatrics, and 23 (9.6%) were in internal medicine.

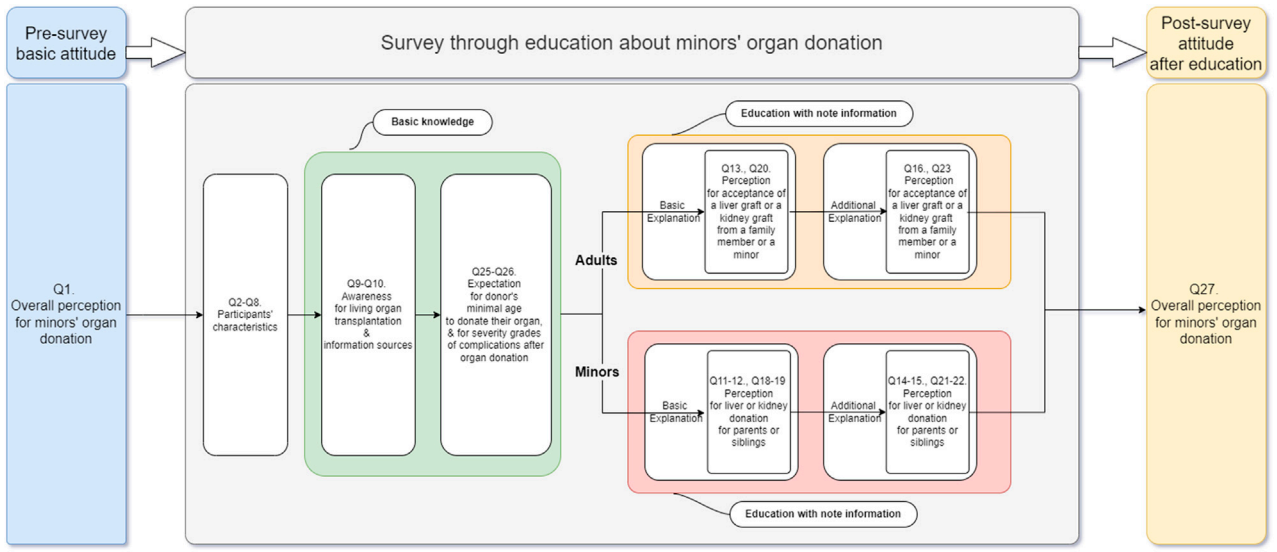


FIGURE 2 | Flowchart of the structured survey for minors' organ donation.

Awareness of Organ Transplantation

The awareness of living solid organ donation among the three groups was significantly different; 25 Minors (86.2% of Minors), 89 Non-Meds (82.0% of Non-Meds), and 236 Meds (98.7% of Meds) were aware of living donor organ transplantation ($p < 0.000$). Moreover, as shown in **Table 2**, only 12 (41.4%) Minors and 34 (32.0%) Non-Meds were aware of minors' organ donation, whereas 168 (70.3%) Meds were aware of minors' organ donation ($p < 0.001$).

Additionally, 26 minors (90%) and 95 Non-Meds (88%) gained knowledge of organ transplantation through various unstructured educational media, while 200 Meds (84%) learned through medical texts and education courses as shown in **Figure 3**.

Expected Living Donor's Age Allowed for Organ Donation by Respondents

There was no difference in respondents' expectations for the minimum age of a living donor who can donate a solid organ ($p = 0.561$); 19 Minors (65.5%), 100 Non-Meds (72.2%), and 170 Meds (71.1%) expected the minimum age to be 18 or above as shown in **Figure 4**.

Awareness of Outcomes for Recipients and Donors After Transplantation

The expected severity grades of complications for living donors after donation were not significantly different among Minors, Non-Meds, and Meds ($p = 0.707$); 16 Minors (55.3%), 61 Non-Meds (56.5%), and 138 Meds (57.7%) thought that living donors might have moderate complications indicating the possibility of death. Meds expected a higher possibility of death for recipients than Minors and Non-Meds (43.9% vs. 27.6%, 20.4%, $p < 0.0001$). Additionally, more Meds (59.0%) expected the possibility of fatal complications in recipients, including intensive care and death, than Minors (34.5%) and Non-Meds (38.9%) did ($p < 0.0001$). Even among Meds, 79.1% did not expect the possibility of living donors' deaths, although 43.9% of Meds expected the possibility of recipients' deaths. The details are shown in **Table 3**.

Under Structured Information, the Changes in the Decision to Donate Their Liver or Kidney in Minors

As shown in **Table 4**, 96.6% of Minors wanted to donate their liver to their parents after reading basic information. Even after reading additional explanations about the uncertainty of long-term outcomes of living donors, 93.1% of Minors still wanted to donate their liver to their parents ($p = 0.326$). Among Minors, 89.7% wanted to donate their liver to their siblings after receiving a basic explanation and 86.2% after receiving an additional explanation ($p = 1.000$).

Moreover, 96.6% of Minors wanted to donate their kidney to their parents after reading basic information. Even after reading additional explanations about long-term complications associated with the remaining one-sided kidney, 93.1% of Minors still wanted to donate their kidney to their parents ($p = 0.326$); 89.7% of Minors wanted to give their kidney to their siblings after a basic explanation and 86.2% after an additional explanation ($p = 0.100$) (**Table 4**).

Under Structured Information, the Changes in the Decision to Reject a Partial Liver or Kidney in Adults

Rejection Rate for a Living Liver

As shown in **Table 5**, 28.5% of all adults chose to reject a partial liver from a family member after reading basic information, and

TABLE 1 | Basic characteristics of the respondents.

		Minors		Adults			
				Non-Meds		Meds	
		N = 29	%	N = 108	%	N = 239	%
Sex	Male	13	44.8	78	72.2	111	46.6
	Female	16	55.2	30	27.8	128	53.6
Age	<19	29	100.0				
	19–29			20	18.5	26	10.9
	30–39			25	23.1	90	37.7
	40–49			54	50	78	32.6
	50–59			8	7.4	37	15.5
	60–69					8	3.3
	>70			1	0.9		
Underlying liver or kidney disease Severity	1	1	3.4				
degree of underlying disease	2			2	1.9	6	50
	3			2	1.9	1	8.3
	4			1	0.9	1	8.3
	5			1	0.9	4	33.3
Educational background		29	100.0				
middle school or High school				7	6.5	4	1.7
University, Graduate school				91	84.3	195	81.6
Post-doctor				9	8.3	37	15.5
Etc.				1	0.9	3	1.3
Family member	1			12	11.1	27	11.3
	2			12	11.1	38	15.9
	3	6	20.7	26	24.1	57	23.8
	4	19	65.5	44	40.7	88	36.8
	>-5	4	13.8	14	13	29	12.1

TABLE 2 | Awareness regarding minors' organ donation.

Questions	Minors		Adults				*p-value*
			Non-Meds		Meds		
	N = 29	%	N = 108	%	N = 239	%	
Have you ever heard about living organ transplantation?							
No	4	13.8	19	17.6	3	1.3	$p < 0.000$
Yes	25	86.2	89	82.0	236	98.7	
Do you know that minor can donate their organ?							
No	17	58.6	74	69	71	29.7	$p < 0.000$
Yes		41.4	34	32	168	70.3	

their rejection rate increased to 35.4% after reading additional explanation ($p < 0.0001$). Among all adults, 66.0% decided to reject a partial liver from a minor, although only minors may donate a liver to their family members with a basic explanation. This percentage increased to 72.0% ($p < 0.0001$) after receiving additional explanations about uncertain long-term outcomes.

Meds had lower rates to reject a partial liver from a family member than Non-Meds both after basic (27.2% vs. 31.5%) and additional explanation (33.5% vs. 39.8%). However, Meds had higher rates of rejecting a liver from a minor than Non-Meds after basic explanation (67.4% vs. 63.0%, $p < 0.0001$) and after additional explanation about uncertainty (73.6% vs. 68.5%, $p < 0.0001$). The respondents' rejection rate increased significantly both in Meds (67.4%–73.6%, $p < 0.0001$) and in Non-Meds (63.0%–68.5%, $p < 0.0014$) after additional explanation.

Rejection Rate for a Living Kidney

Among adults, 29.4% chose to reject a kidney from a family member after reading basic information, and the rate of rejection increased to 38.6% after recognizing the expected burden on the remnant kidney. Meanwhile, 72.0% of adults rejected receipt of a minor's kidney. The rejection rate increased to 79.0% after recognizing the expected burden on the remnant kidney.

Meds had higher rejection rates for accepting a kidney from a family member than Non-Meds (31.8% vs. 24.1%) after being given basic information, but Non-Meds had a higher rejection rate than Meds (42.6% vs. 36.8%) after receiving an additional explanation. The change in rejection rate was significant both in Meds ($p < 0.0001$) and in Non-Meds ($p < 0.0001$). Meds had a higher rate of rejecting a kidney from a minor than Non-Meds (73.6% vs. 68.5%, 81.6% vs. 73.1%) after receiving basic and additional explanations. The respondents' rate for rejecting a minor's kidney increased from 73.6% to 81.6% significantly in Meds ($p < 0.0001$) and from 68.5% to 73.1% in Non-Meds ($p < 0.0001$) after receiving additional explanations.

Changes in Attitude Toward Minors' Organ Donation

Among the Minors, 51.7% were willing to donate their organs, 20.7% were reluctant, and 27.6% were indecisive before the survey; and their attitude changed. However, this was not a significant change; 48.3% became willing, 20.7% reluctant, and 31.0% indecisive after providing additional educatonal explanation about long-term outcomes for living donors ($p = 0.745$). All adults had a higher rate of opposing minors' donations. Among

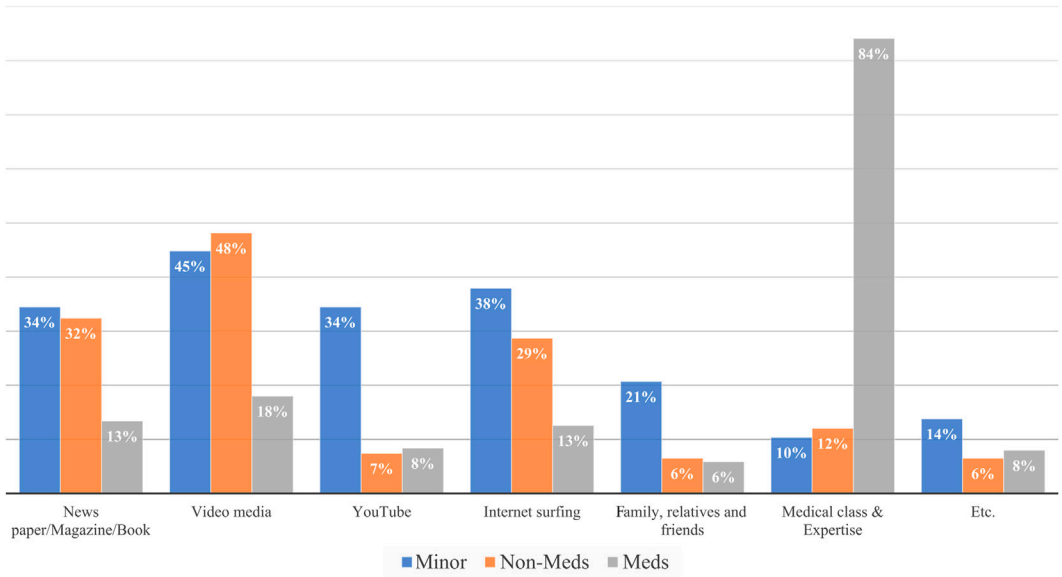


FIGURE 3 | Sources of information on organ transplantation.

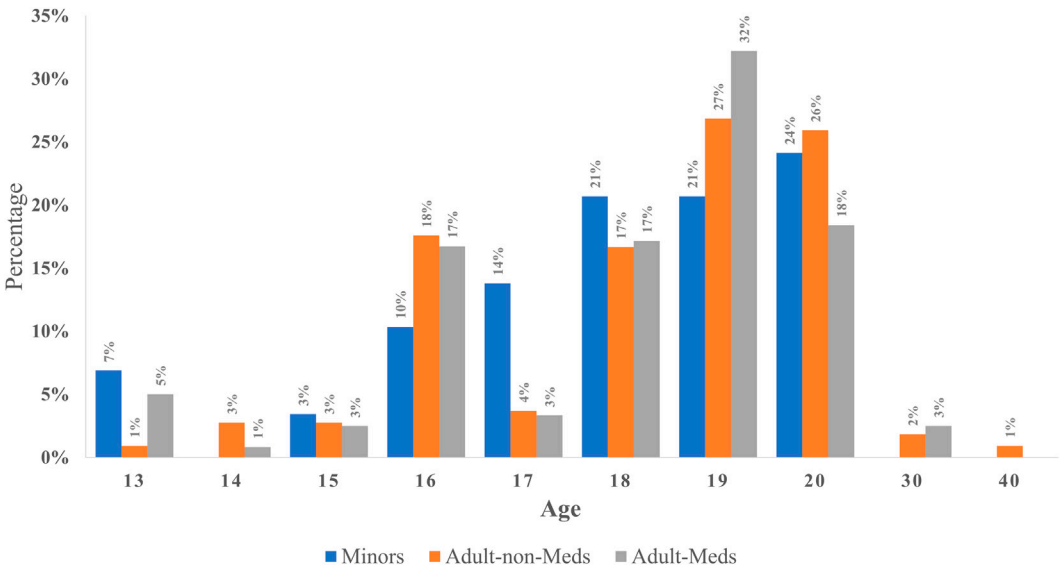


FIGURE 4 | Expected minimum age of a living donor permissible for organ donation among respondents.

all adults, 39.8% were willing to accept the donation from minors, 47.6% were reluctant, 12.7% were indecisive before the survey; and those opinions significantly changed to 34.0%, 54.2%, and 11.8% respectively with additional explanation (p = 0.013). Non-Meds had a higher rate of agreeing to accept minors' organ donation prior to the survey, but the rate of opposition significantly increased from 32.4% to 46.3% (p = 0.009) after they informed about long-term complications. In contrast, the rate of Meds who opposed minors' donation increased consistently from 54.4% to 57.7% regardless of providing additional information (p = 0.311), as shown in **Figure 5**.

DISCUSSION

Organ transplantation of both living and deceased donors is practiced worldwide. Nevertheless, supply cannot match the growing demand for organ transplantation. Therefore, to fill the shortage in supply, interest in the vast resource of minors who usually have healthy organs, promising better outcomes of transplantation and better recovery after surgery, became apparent in the field of the living donor organ transplantation (15). However, living organ transplantation using minors as a donor has not been performed in the majority of countries for

TABLE 3 | Expected severity grades of complications for living donors & recipients.

		Severity grades of expected complications						
		No complication	**Mild complication; medication**	**Moderate complication; prolonged hospital stay**	**Severe complications; intensive care**	**Possibility of death**	**Total**	***p*-value**
For Donors	Minors	2 (6.9%)	11 (37.9%)	8 (27.6%)	2 (6.9%)	6 (20.7%)	29 (100%)	$p = 0.707$
	Non-Meds	0	47 (43.5%)	33 (30.6%)	13 (12.0%)	15 (13.9%)	108 (100%)	
	Meds	5 (2.1%)	96 (40.2%)	66 (27.6%)	22 (9.2%)	50 (20.9%)	239 (100%)	
For Recipients	Minors	3 (10.3%)	8 (27.6%)	8 (27.6%)	2 (6.9%)	8 (27.6%)	29 (100%)	$p < 0.001$
	Non-Meds	1 (0.9%)	29 (26.9%)	36 (33.3%)	20 (18.5%)	22 (20.4%)	108 (100%)	
	Meds	0	28 (11.7%)	70 (23.9%)	36 (15.1%)	105 (43.9%)	239 (100%)	

TABLE 4 | Minors' decision changes regarding donating their organs.

Type of transplantation	**Group**	**To a parent**				**To a sibling**			
		After basic explanation	**After additional explanation**	**Δ**	***p*-value**	**After basic explanation**	**After additional explanation**	**Δ**	***p*-value**
Liver transplantation	Minors	28 (96.6%)	27 (93.1%)	1 (3.6%)	$p = 0.326$	26 (89.7%)	25 (86.2%)	1 (3.5%)	$p = 0.100$
Kidney transplantation	Minors	28 (96.6%)	27 (93.1%)	1 (3.6%)	$p = 0.326$	26 (89.7%)	25 (86.2%)	1 (3.5%)	$p = 0.100$

A p-value less than 0.05 is statistically significant.

TABLE 5 | Adults' decision changes regarding rejecting living organs.

Type of transplantation	**Group**	**Rejection rate a live graft from a family member**				**Rejection rate a live graft from a minor**			
		After basic explanation	**After additional explanation**	**Δ**	***p*-value**	**After basic explanation**	**After additional explanation**	**Δ**	***p*-value**
Liver transplantation	All adults	99 (28.5%)	123 (35.4%)	24 (6.9%)	$p < 0.0001$	229 (66.0%)	250 (72.0%)	21 (6.0%)	$p < 0.0001$
	Non-Meds	34 (31.5%)	43 (39.8%)	9 (8.3%)	$p < 0.006$	68 (63.0%)	74 (68.5%)	6 (5.5%)	$p < 0.014$
	Meds	65 (27.2%)	80 (33.5%)	15 (6.3%)	$p < 0.0001$	161 (67A%)	176 (73.6%)	15 (6.2%)	$p < 0.0001$
Kidney transplantation	All adults	102 (29.4%)	134 (38.6%)	32 (9.2%)	$p < 0.0001$	250 (72.0%)	274 (79.0%)	24 (7.0%)	$p < 0.0001$
	Non-Meds	26 (24.1%)	46 (42.6%)	20 (18.5%)	$p < 0.0001$	74 (68.5%)	79 (73.1%)	5 (4.6%)	$p < 0.0001$
	Meds	76 (31.8%)	88 (36.8%)	12 (5.0%)	$p < 0.0001$	176 (73.6%)	195 (81.6%)	19 (8.0%)	$p < 0.0001$

A p-value less than 0.05 is statistically significant.

more than a decade, regardless of the legality of such transplantation.

In Korea, minors above the age of 16 are legally permitted to donate their organs to their family (13). The Korean organ transplantation law stipulates as follows; "Organs, etc. (excluding bone marrow) of a living person who is between 16 and 18 years may not be recovered unless transplanted to a spouse, lineal ascendant, sibling, or relative within the fourth degree." Further, living minors' organ donation requires the consent of the donors' parents. This creates a conflict of interest, as the recipient is frequently the minor's parent. Korea is one of the countries where living organ transplantation is being performed in more numbers than deceased donor liver transplantation, and organ

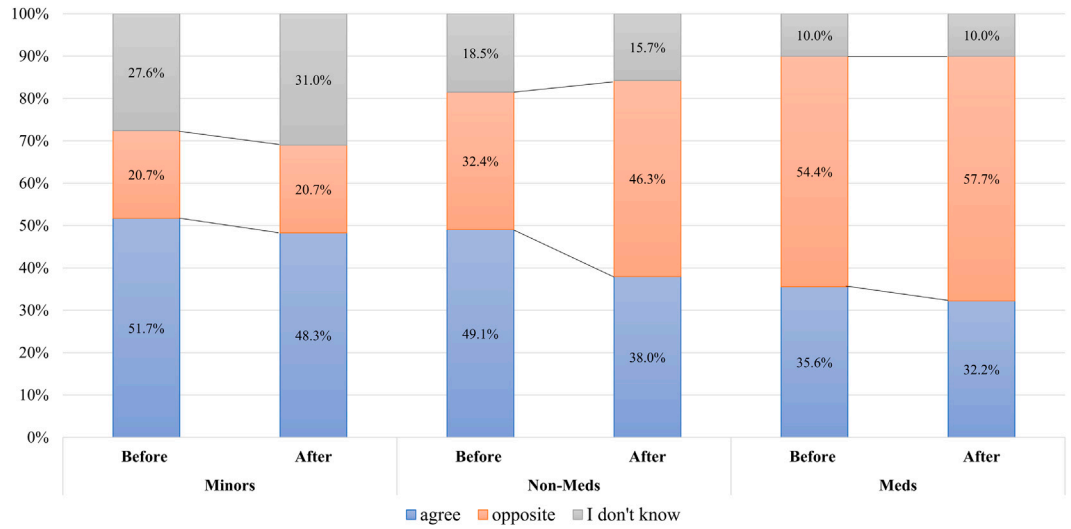


FIGURE 5 | The changes of attitude toward minors' organ donation.

transplantation using minors' organs accounts for about 3%, mainly in liver transplantation (1). This trend could be explained by the scarcity of deceased donors in Korea and the family-oriented culture. Nevertheless, this issue has to be considered socially and the law has to be revised, if needed, to prevent unwanted or ill-informed sacrifice from minors for their family, although the outcomes of minors as donors were not poor in several reports from Korea (16–18).

Minors' judgments may not be conclusive; they are often impulsive and spontaneous when making decisions that may have lasting effects, reflecting a lack of life experience (15). Therefore, it may not be easy for minors to make the right decision regarding organ donation. As can be seen from the results of this study, minors expected the severity of complications for donors and recipients to be less than adults did, which may suggest that minors were not fully aware of the risks and poor prognosis following major surgery. Further, minors' decisions did not change even after being informed of the uncertainty and poor outcomes after organ transplantation, unlike the adults. Minors are a dependent demographic group, vulnerable to family influence and coercion; they are financially and mentally dependent on their recipients (e.g., parents), which makes it difficult to determine whether their decision to donate is voluntary.

This study found that only 50% of Minors and less than one-third of Non-Meds were aware of living organ transplantation from minors. Further, most of them, 90% of Minors and 88% of Non-Meds picked up the related information from unstructured media and personal communications. This necessitates inviting public attention to the need for structured education on organ transplantation.

Geir et al. (19) reported that the risk of major complications related to living donor nephrectomy is low but represents a potential hazard to the donor. Hong et al. (13) and Choi et al. (13, 14) analyzed the long-term results of living donor liver transplantation using the big data of Korea's national health insurance and concluded that liver donors have increased long-term mortality risk compared to similar control groups without contraindications to be organ donors, the leading cause of mortality being suicide. The impact of donation on the lives of minors as donors has not been appropriately analyzed, although previous studies using big data showed that physical changes or psychological pain for minors would be significant and that minors may have more difficulty maintaining their mental and physical health (20). Nevertheless, medical personnel (79.1% of Meds) do not expect the possibility of the death of live donors and more than half of Meds (56.1%) do not expect the possibility of the death of recipients. A higher proportion of Minors and Non-Meds expect better outcomes for recipients and donors. Therefore, proper knowledge sharing and education on living donor organ transplantation of both recipients and living donors should be provided to medical experts and non-medical personnel and students. Public attention should be invited to proper education and information on living organ donation. A new living organ donation process should emerge to enable minors to make the right decisions and to protect them from social and familial pressures.

Results of the data on Meds, who received structured information and know the uncertainty of the outcomes of minors' organ donation, showed differences from those of Non-Meds and Minors. Meds showed consistently higher rates of objection to organ donation by minors than Non-Meds after receiving basic and additional explanations (54.4% vs. 32.4%, 57.7% vs. 46.3% respectively, **Figure 5**). Pediatricians (65.4%) had the highest rate of opposition among medical professionals, followed by surgeons (64.2%) and medical physicians (56.5%), even though statistically there was no difference (data not shown, $p = 0.111$). Meds tended to accept a liver graft more than a kidney

graft from a family member (the rate of rejection of liver graft = 33.5%). They might consider the poor prognosis of a patient with an end-stage liver disease without LT. However, Meds had a strong objection to accepting a liver graft from a minor from their own family (73.6%) (**Table 5**). Meds' rejection rates of donation from minors of their own family were higher than their opposition rates of minors' organ donation from the general population (57.7%).

This study has limitation. First, the small sample sizes of Minors and Non-Meds. Second, his survey was not conducted using a representative sample cohort; rather, it used a random questionnaire. Because there was no financial support for this study, the authors used a Google form and refered the link randomly to 11 National Universities, 10 medical societies, the Korean Bar Association and 3 high schools. The authors planned to collect the answers from 1000 respondants, but only 376 respondents joined the survey for the investigating period.

Nevertheless, the strength of this study is that it is the first survey to investigate the possibility of change in a respondent's decision about minors' donation when they are provided with rather unoptimistic information on the reality of LT and KT. Additionally, this survey included minors who expressed their thoughts on minors' organ donation. Structured education can change the perceptions of non-medical individuals who are in a position to consent to a minor's organ donation. Non-Meds' opposition to minors' organ donation increased after knowing the detailed, uncertain outcomes for organ transplant recipients and living donors. This does not simply indicate a passive conclusion that informed consent on organ donation by minors should include the details on the results of organ donation for minors, but rather, raises fundamental questions about the implementation of organ donation by minors. This will raise awareness toward minors' organ donation and outcomes for medical experts as well as the general public, not only in Korea but also in many other countries where living organ transplantation is performed.

In conclusion, solid organ donations, including those of minors, and their outcomes for solid organ transplant recipients were not known by non-medical adults or minors. Structured information had the potential to influence adults' attitudes toward minors' organ donation. Public attention for proper education and knowledge sharing regarding live organ transplantation and the donation should be addressed to non-medical adults and minors for protecting minors who live under the pressure of living organ donation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by under the permission of the authors and with the approval of the Seoul National University Hospital (SNUH) IRB.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the SNUH IRB. The IRB approved a request to waive the documentation of informed consent.

AUTHOR CONTRIBUTIONS

Study conception and design: YC, N-JY; survey item, data collection, analysis and interpretation of results: YC, SL, YL, MHC, KI, KCY, J-MK, SHK, HGK, N-JY; draft manuscript preparation: YC, N-JY. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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POINT OF VIEW
published: 21 March 2022
doi: 10.3389/ti.2022.10131

Donor Autonomy and Self-Sacrifice in Living Organ Donation: An Ethical Legal and Psychological Aspects of Transplantation (ELPAT) View

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Clinical teams understandably wish to minimise risks to living kidney donors undergoing surgery, but are often faced with uncertainty about the extent of risk, or donors who wish to proceed despite those risks. Here we explore how these difficult decisions may be approached and consider the conflicts between autonomy and paternalism, the place of self-sacrifice and consideration of risks and benefits. Donor autonomy should be considered as in the context of the depth and strength of feeling, understanding risk and competing influences. Discussion of risks could be improved by using absolute risk, supra-regional MDMs and including the risks to the clinical team as well as the donor. The psychological effects on the donor of poor outcomes for the untransplanted recipient should also be taken into account. There is a lack of detailed data on the risks to the donor who has significant co-morbidities.

Keywords: risk, kidney, transplantation, living donation, autonomy 2

Point of View

OPEN ACCESS

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Received: *21 October 2021*
Accepted: *02 February 2022*
Published: *21 March 2022*

Citation:
Mamode N, Van Assche K, Burnapp L, Courtney A, van Dellen D, Houthoff M, Maple H, Moorlock G, Dor FJF and Lennerling A (2022) Donor Autonomy and Self-Sacrifice in Living Organ Donation: An Ethical Legal and Psychological Aspects of Transplantation (ELPAT) View. Transpl Int 35:10131. doi: 10.3389/ti.2022.10131

INTRODUCTION

The donation of a solid organ for transplantation by a person who is alive at the time represents a unique event in healthcare, since the donor will gain no physical benefit from undergoing major surgery, which has a low but nevertheless significant rate of major complications and death (1, 2). Living donors are usually highly motivated individuals, whose appetite for risk differs substantially from that of the healthcare team (3). This may lead to conflicts between the clinical team and potential donors-some examples are given in **Figure 1**. Were the decisions of the clinical teams correct? This article explores the issues raised by these cases and others, and considers the principles

Abbreviations: ELPAT, ethical legal and psychological aspects of transplantation; MDM, multidisciplinary meeting; ESRD, end stage renal disease; LDN, living donor nephrectomy.

Case 1: A 71-year-old man wished to donate a kidney to a young boy with whom he had no emotional or genetic connection. He had the same surname as the child, and having become aware of his need for a transplant felt that this similarity was an indication to donate. His prior history of heart disease, along with his age, led the clinical team to decline him as a donor.	Case 2: A 40-year-old man wished to donate a kidney to his wife, and is found to have Type II diabetes during his work-up. On this basis he was declined as a donor. 14 months later, he re-presents, having lost 10kg and followed a recommended diet. His glycaemic control is excellent (HbA1c is 5.8%), and he is adamant, despite attempts to persuade him otherwise, that he wishes to donate as he cannot bear to see his wife suffering. His family support him, the hospital ethics committee find his decision to be freely made, and psychological evaluation finds a significant psychological benefit from donation. He is permitted to donate.
Case 3 A 75-year-old male retired Professor of Statistics, was declined in two other centres, due to an incidental 5.5cm aortic aneurysm, and wished to donate to his wife. He was adamant about donation, and calculated his absolute versus relative risk, in the context of an expectation to have a couple of good years in good health with his wife off dialysis even if their lifespan would be shortened. He proceeded to donate.	

FIGURE 1 | Examples of potentially difficult decisions regarding living donor candidates.

which might help to guide decision-making. It is an overview aimed at healthcare professionals, and is not intended to be an in-depth ethical review. Suggestions for further reading are given in **Figure 2**.

AUTONOMY VERSUS PATERNALISM

Although not universally adopted, principlism remains the dominant approach to medical ethics (4), particularly amongst the clinically-orientated. Under a principlist approach, four principles are considered in the determination of whether an intervention is ethically appropriate: autonomy, beneficence, non-maleficence, justice (5). Beauchamp and Childress suggest that each principle should be afforded equal weight, but nonetheless autonomy is often regarded as "first amongst equals" (6). In living kidney donation, beneficence is difficult to both specify and quantify accurately. There is likely to be some psychological benefit (7, 8) but there is clearly no physical benefit of donation itself. Whilst non-maleficence, or more specifically the minimisation of harm is a concomitant aim of donation surgery, some harm is unavoidable, such as the physical harm routinely associated with surgery, and sometimes unanticipated complications occur. Although teams attempt to assess the risk to the donor independently, the benefit to the recipient also plays a part (9), since without this the donation would not be justified (**Figure 3**). Some have argued for a "donor-centred" approach, where the importance of the emotional benefits to the donor is expanded when considering risks (10).

The clinical team are also agents here and ultimately responsible for decisions to offer donation as an option to an individual: an on-table death of a donor would certainly affect them profoundly, and potentially their programme and others, and hence other patients. But this could perhaps be overcome by having centralisation of high risk cases in dedicated centres or by having surgeons for "high risk" cases in centres, where everyone understood that the risks were higher and appropriate protections were in place, including transparent audit, support for staff, and avoidance of punitive actions in the event of below average outcomes.

It is quite common for clinical teams to adopt a degree of paternalism (11), whereby autonomy is infringed upon to some extent in order to serve a patient's best interests. Consider, for example, the postoperative patient who would rather not get out of bed, but is essentially cajoled into doing so. In this scenario, it might be considered that the patient's wish to stay in bed is not strongly held, and that it is heavily in their best interests to mobilise, so beneficence overrules respecting the rather weak autonomous wishes of the patient. It might then seem logical that there is a gradation of potential benefits or harms, which could be weighed against a scale of autonomous desires of increasing strength, rather than simple binary outputs for these potentially competing interests. Considering that there may be effectively different levels of autonomy, related to a degree of understanding and strength of feeling, may help here. Similarly, it might be considered that there is a scale of paternalism, ranging from "weak to strong (12)" or "soft to hard (13)." In practical terms, such an interpretation is necessarily a matter of subjective judgement, but a potentially paternalistic approach might include consideration of the following: how strongly do you feel about donating, and

Williams, NJ. On harm thresholds and living organ donation: must the living donor benefit, on balance, from his donation?', Medicine, Health Care and Philosophy 2018 21(1). 11-22.	Discusses whether it is a requirement of ethically acceptable living donation that the donor themselves should receive benefit and argues that it should not be.
Spital, A. Donor benefit is the key to justified living organ donation. Cambridge Quarterly of Healthcare Ethics 2004, *13*(1): 105-109.	Spital is someone who is notable for holding the opposite view to the above: that donors should benefit overall from donation in order for it to be permissible.
Bailey, P & Huxtable, R. When Opportunity Knocks Twice: Dual Living Kidney Donation, Autonomy and the Public Interest. Bioethics 2016 30(2):119-128.	Argues that someone should be permitted to donate both of their kidneys in some situations.
Draper, H, & Moorlock, G. "A Challenge to the Duty to 'First Do No Harm'". In: Hansen SL and Schicktanz S, editors. Ethical Challenges of Organ Transplantation: Current Debates and International Perspectives. Bielefeld: Transcript Verlag (2021) p. 151-166.	Discusses how the notions of harms and benefits have been expanded in living organ donation to include: i) The abstract moral benefit of doing something good ii) The harms of frustrating the wishes of an autonomous individual
Biller-Andorno, N, Agich, GJ, Doepkens, K and Schauenburg, H. Who shall be allowed to give? Living organ donors and the concept of autonomy. Theoretical medicine and bioethics, 2001 *22*(4): 351-368.	Explores the relationship between donor autonomy and broader contextual factors when determining suitability of a living donor.

FIGURE 2 | Suggested further reading.

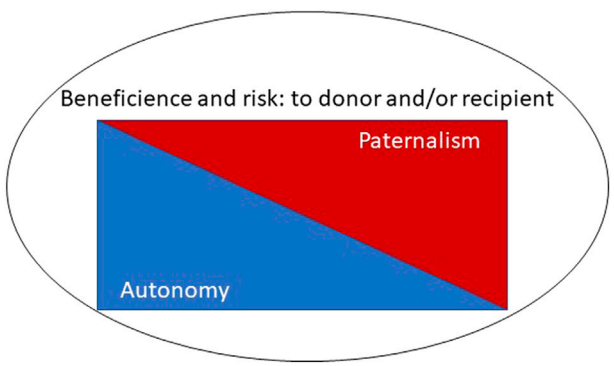

FIGURE 3 | The interplay of potentially conflicting ethical principles.

why? Do you have a reasonable understanding of the risks? How likely are you to regret this later? Despite the difficulty in answering these questions, it might be a first step in resolving the conflicts described above.

A key problem in considering the importance of autonomy in medical decision making is the difficulty in the determination of the value that should be accorded to a particular autonomous wish. That is, at what point does an apparently autonomous decision carry sufficient weight to outweigh other considerations (9). This is a key issue when considering decision making in children, who may not yet be considered independent and adults who are incompetent to make any decision, but whose wishes are nevertheless taken into account. Indeed, children not infrequently express a wish to donate to siblings, but in most jurisdictions this would be refused (14, 15). Perhaps a useful ethical approach

would be to balance the clinical team's view of the potential benefits and harms, with the depth and strength of conviction of the individual concerned. One might consider a central aspect of autonomy to be the ability to use relevant information to reason in certain ways and adopt a considered approach (5). Thus, it might be, for example, that an experienced transplant surgeon with non-insulin dependent diabetes who felt strongly that they wished to donate to their spouse could have a reasonable understanding of the risks, and should be allowed to proceed. In clinical practice, a clear understanding of the risks is often given greater validity in terms of decision making; however, it could be argued that neither depth nor strength of conviction are valid reasons for assessing the degree of autonomy. Furthermore, freedom from external pressures beyond the clinical team, for example from family members, is an important consideration in determination of the extent to which a patient's wishes are truly autonomous.

RISK BENEFIT BALANCE

The risks of donor nephrectomy are mortality 1 in 3,000 and major complications 2–5% (1, 2), while for a living liver donation the mortality rate is 1 in 200 (16). This could mean that a "high risk" kidney donor might still be exposed to less risk than a low risk liver donor. It could be argued that the difference here is the combination of lack of availability of other options and need for urgent surgery in the recipient, since a liver patient might not survive for long without a transplant, while most kidney recipients would have a dialysis option. However, in considering the risk/benefit balance for the donor, the implication must be that the difference is only a psychological one, and not physical-that is, the liver donor has the higher psychological risk of seeing a loved one die, which justifies the higher risk of donation. There can't be any other moral imperative to expose the donor to higher risks because the stakes are higher for the recipient. The logical extension of this argument suggests, however, that outcomes other than death might have a profound psychological detrimental effect on the potential donor-for example, parental donation to a child who is not thriving on dialysis, or spousal donation where the life of the donor is severely impacted by having an unwell partner (17).

One of the common errors in considering the risks of donation is to focus on relative, rather than absolute, risk. The use of absolute risk has been recommended specifically for living donors (18). A mortality rate of 1 in 1,500 is twice the normal risk but still very low, and lower than for the liver donor. Furthermore, we do not have good data on what the actual risks are in those with co-morbidities, in part because they are usually refused surgery (19). For example, previous myocardial infarction is often an exclusion criterion for kidney donors, yet if successful rehabilitation has taken place, risk factors addressed and cardiac tests are adequate, then it probably does not confer a high absolute risk (20, 21). An alternative approach might be to consider what is an acceptable upper mortality rate, and to permit donation if this threshold is not reached, even if the relative risk is doubled. Clearly challenges would remain in determining this rate, and in assessing individual donors who are below this threshold. There is certainly a need to determine more accurately and objectively the risks to both donor and recipient, in order to make the appropriate decision-just as we may not be aware of the real perioperative risk to a donor conferred by a co-morbidity, data on the risk to the recipient of not proceeding with a living donor transplant at that time is often lacking.

It is also important to consider long term as well as perioperative risk. There is even less data here. For example, the lifetime risk of ESRD after LDN in a 70-year-old man is 0.15% (95% CI 0.05, 0.28), and the relative risk for ESRD from non-insulin dependent diabetes is 3.01 (1.91, 4.74)- the absolute risk would appear to be low, but we have no data on the effect of donation on subsequent ESRD in this scenario (22).

Risk aversion may sometimes vary with specialty; surgeons and nephrologists sometimes have differing appetites for risk. Whilst the multidisciplinary meeting (MDM) or protocols and guidelines may mitigate some of these differences, an exploration of how these operate in practice, and the underlying thought processes could help in smoothing decisions. An emerging literature on cognitive biases and loss aversion, where the fear of a low probability but high loss outcome tends to outweigh potential gains, in decision making indicates an interesting start (23, 24).

Finally, risks apply not only to the potential donor, but to the operating surgeon, the clinical team, and to a national programme, since donor deaths have typically impacted on all of these. One way to mitigate this might be to take national decisions on high-risk cases, in a sense as a supra-regional MDM, which would in part shift some of the risk away for the local team in the same way that local MDM advice shares the risk beyond the operating surgeon. Equity of access is an important principle to consider, since widely differing views may pertain in different centres (18). It is also important to consider the risk to the recipient-a donor who suffers severe complications may lead to considerable distress for the recipient.

SELF-SACRIFICE AND HEROISM

We applaud self-sacrifice in many walks of life-firefighters, military, even sport, such as Formula 1, mountaineering, round the world sailing. Those who take risks to save others, or for glory or money, are often considered heroes. Why is someone who takes a risk as a donor different?

It might be argued that the difference is that they need a clinical team to facilitate their operation- but then many of the others listed above need support from teams. Arguably in these cases there is oversight of risk by another group. For example, a military unit might be ordered to retreat if the risk is too high, or the race director may stop a Grand Prix if rain makes it unsafe. It could be considered that the MDM in each unit provides a similar oversight, but given the potential risks to individual clinicians, and to programmes, of poor

Case1	Case 2
A 45-year-old man suffering from multiple sclerosis wished to end his life, due to unbearable physical suffering. He approached a clinical team asking to donate his organs as part of a procedure which would result in euthanasia. He was declined on the basis that this form of euthanasia is not permitted.	A 40-year-old woman with severe motor neurone disease, who had campaigned for euthanasia and the right to end her own life made an enquiry to NHS Blood and Transplant to request living kidney donation prior to referring herself to DIGNITAS. Her husband was supportive. She had a permanent urinary catheter (supra-pubic) and was immobile in a wheelchair, and was deemed to have full mental capacity. The case was discussed in the multidisciplinary meeting There were surgical reservations due to her immobility, anaesthetic risk, positioning on the table, risk of venous thrombosis during surgery, immediate and recovery at home More significant reservations were about her decision-making related to her perception of risk as a living donor i.e. if her plan was to end her life in any case, she would not have the usual 'stops' in her decision-making in relation to risk of death or complications from the surgery. (Equally, life-long risk would be less of a consideration for her or the team). The final decision was to not accept her self-referral for living kidney donation.
Case 3 A 45-year-old man with Huntington's disease underwent unspecified donation of a kidney. Later in life he became more unwell, and underwent euthanasia followed by retrieval of the remaining kidney as well as other organs [20]	

FIGURE 4 | Examples of living donor candidates in the context of euthanasia.

outcomes as mentioned above it might be that we are not independent enough. The wide variability in assessment criteria illustrates the difficulty here (19, 25). Nevertheless, if the local clinical team is reluctant to proceed, there is an argument for a second opinion, or for national or regional bodies to make these assessments.

EXTREME RISKS

Some potential donors might have a limited life expectancy, for example Huntington's chorea, or a reduced capacity due to illness, for example, early dementia, but still wish to donate. In these cases, it might be argued that if the organ is unaffected by the underlying medical condition, donation does not hasten death, and there is sufficient capacity to make the decision, it would be reasonable to proceed (25). However other donors might wish to take more extreme risks-for example, donating their heart and thus ending their life (26–28). Similarly, there are those who are undergoing euthanasia (28), and wish to donate as part of that process, as detailed in **Figure 4**. In this case, the acceptance of such a donor would potentially help a number of recipients to have a better quality and quantity of life. However, apart from the fact that it is not permitted, such a procedure might have very negative consequences on wider donation rates, as the perception could be that life may be ended specifically to provide organs-a concern that has been expressed in general by some who are reluctant to agree to deceased donation. The principle that individuals are entitled to decide how and when they will die has been established in some countries (Switzerland), but some may struggle with the idea that doctors should participate in organ donation which might either precipitate death or be part of the final interventions.

CONCLUSION

Decision making in the case of living donation remains difficult. There is a lack of detailed objective data regarding the risks in donors with co-morbidities, and the impact on the recipient of not proceeding. There are a number of potentially competing interests, including donor autonomy, the effect on the clinical team and wider societal effects on donation rates. One solution would be

to introduce oversight removed from the clinical centre, or to designate some centres as those for "high risk" donors. Consideration of the understanding of risk by the donor may also help guide decisions. This manuscript provides an overview of the relevant issues for a clinical audience, and does not attempt a detailed ethical analysis, which is available in the bioethical literature; we have suggested further reading in **Figure 2**.

AUTHOR CONTRIBUTIONS

NM wrote the manuscript. AL and FD coordinated the group and supervised. All other authors contributed to the discussions and writing of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

We acknowledge the support of the European Society of Transplantation for ELPAT. The ELPAT working group on Living Organ Donation greatly acknowledge Maria Valentin for her contribution to the manuscript during the time she has been involved in the writing process.

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POINT OF VIEW
published: 06 October 2023
doi: 10.3389/ti.2023.11529

Should Physicians Be Permitted to Refuse Follow-Up Care to Patients Who Have Received an Organ Transplant Through Organ Trafficking?

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In 2018, the Istanbul Declaration stated that organ transplantation via organ trafficking is a crime. Since then, the number of medical institutions in Japan who refuse follow-up care to patients who have undergone unethical organ transplantation overseas has been gradually increasing. Deterring transplant tourism involving organ trafficking is an issue that must be addressed by the government, medical institutions, and individual physicians. The refusal of medical institutions and individual physicians to provide follow-up care after organ transplantation may challenge the idea of the incompatibility thesis; moreover, it may be ethically justified in the context of conscientious objection if it is based on the belief of deterring transplant tourism instead of punitive motives or a reluctance to support a criminal activity. However, conscientious objection based on a belief in fair transplantation care is conditional; according to the compromise approach, it is limited to particular conditions, such as that the patient's medical state does not require urgent care and that the patient is reasonably able to receive follow-up care at another institution.

Keywords: transplant tourism, ethics, follow-up care, organ transplant, organ trafficking

Point of View

OPEN ACCESS

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Received: *01 May 2023*
Accepted: *25 September 2023*
Published: *06 October 2023*

Citation:
Takimoto Y (2023) Should Physicians Be Permitted to Refuse Follow-Up Care to Patients Who Have Received an Organ Transplant Through Organ Trafficking? Transpl Int 36:11529. doi: 10.3389/ti.2023.11529

INTRODUCTION

Transplant tourism is a major social and ethical issue concerning organ transplant medicine in Japan.

The Declaration of Istanbul on Organ Trafficking and Transplant Tourism states that travel for transplantation is considered transplant tourism if "it involves organ trafficking and/or transplant commercialism or if the resources (organs, professionals, and transplant centers) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population." Transplant tourism is unethical because it violates ethical principles of justice and fairness and undermines human dignity [1].

An issue closely related to transplant tourism is organ trafficking and the removal of organs from executed prisoners. Organ trafficking is defined in the 2018 edition of the Istanbul Declaration [2] as any of the following: a) removing organs from living or deceased donors without valid consent or authorization or in exchange for financial gain or comparable advantage to the donor and/or a third person; b) any transportation, manipulation, transplantation or other use of such organs; c) offering any undue advantage to, or requesting the same by a healthcare professional, public official, or employee of a private sector entity to facilitate or perform such removal or use; d) soliciting or recruiting donors or recipients, where carried out for financial gain or comparable advantage; or

e) attempting to commit, or aiding or abetting the commission of, any of these acts. The Istanbul Declaration states that organ trafficking should be criminalized [2]. The removal of organs from executed prisoners was previously legal in China, but has been prohibited since 2015. This practice can be considered unethical due to certainty of the individual's consent. In this regard, it may also constitute organ trafficking [3].

The Declaration of Istanbul states that medical professionals should help prevent transplant tourism and organ trafficking activities [4].

Owing to the unique Japanese view of life and death influenced by Shintoism and Buddhism, organ transplants from brain-dead donors is rare in Japan. Consequently, transplant tourism emerges as a means of acquiring organs through procedures that exclude living donors, including heart transplants. Recently, there has been a rise in the practice of transplant tourism, not only in cases of organ transplantation that necessitate a brain-dead donor, but also in kidney and liver transplantation, which allow for living donor transplantation. In transplant tourism, organs are obtained by placing Japanese patients at the top of waiting lists or engaging in organ trafficking. As transplant tourism most frequently occurs when potential recipients travel to countries where laws prohibiting organ trafficking are riddled with loopholes or poorly enforced, transplant tourism often exposes individuals to the risk of encountering organ trafficking [5].

To mitigate the risks of exposure to organ trafficking efforts are needed both at the individual level—for example, transplant specialists should increase patient awareness and education—and at the national level—such as excluding follow-up care from public healthcare insurance coverage and increasing transplants from brain-dead donors. Following the declaration, several hospitals in Japan announced that they would not provide follow-up care to patients suspected of participating in organ trafficking.

Apropos of this, a university hospital refused to provide follow-up care to a transplant tourism patient for similar reasons, which resulted in the patient filing for damages. The hospital had a policy of not examining or treating patients who had received kidney transplants in China involving organ trafficking (via organ brokers). Upon noting insufficient information in the patient's letter of referral regarding the course of treatment and other details, the doctor refused to treat the patient [6]. The court found the purpose and objective of the rule legitimate and the reasons satisfactory for the doctor's decision. The court stated, "It is effective and reasonable to try to curb organ trafficking and transplant tourism indirectly by means such as denying treatment to patients who have undergone such organ transplantation." However, the court did not justify the refusal of medical treatment based solely on the existence of the rule; rather, it made a judgment after a comprehensive consideration of the patient's urgent need for medical treatment, the possibility of the case being handled at another medical institution, the purpose of refusing the medical treatment, and the justifiability of the refusal. Furthermore, the director of a non-profit organization was arrested in February 2023 on suspicion of mediating unauthorized organ transplants overseas. Consequently, the Ministry of Health, Labour and Welfare indicated its plan to conduct a survey in 2023 with patients who visited medical institutions in Japan after their transplants. Thus, in Japan, medical institutions' attempt to prevent organ trafficking by refusing follow-up medical care to patients suspected of illegal organ transplant is becoming popular; however, these actions are causing social problems due to insufficient discussion.

The practical issue of how to confirm transplant tourism involving organ trafficking cannot be ignored. The Declaration of the Istanbul Custodian Group recommends that to specifically identify patients who have undergone transplants via organ trafficking, physicians should be provided with guidance and training so that they can identify the circumstances consistent with organ trafficking [6]. Examples of such circumstances include a transplant patient who received a transplant abroad without having been referred to do so by their treating physician or team, absent or incomplete information on the relationship between the recipient and the donor, absent or incomplete information on the patient's clinical course, absence of detailed medical records from both the donor and recipient, and immediately seeking care at a hospital or emergency room [7].

Furthermore, assuming that these practical issues are cleared, there is still an ethical debate as to whether it is acceptable to refuse follow-up care to a patient who is certain to have undergone a travel transplant involving organ trafficking.

AIMS

This viewpoint examines whether the refusal of follow-up care for transplant tourism patients who received a transplant via organ trafficking is ethically acceptable, using two prevailing rationales—deterrent effect and conscientious objection.

An Ethical Analysis of the Reasons for Physicians' Reluctance to Provide Follow-Up Care to Transplant Patients Involving Organ Trafficking

Some physicians are reluctant to treat patients who have received unethical and illegal organ transplants abroad [8]. Some of the reasons for this are described next.

Breach of Trust in the Physician–Patient Relationship

The first reason for this could be the difficulty in providing follow-up care owing to the breach of trust in the physician–patient relationship [9]; the patient may have participated in transplant tourism against the physician's recommendations. When the physician-patient trust is lost, it becomes difficult to provide effective treatment. Consequently, the physician would be ethically exempted from providing treatment to the patient because they would not be able to fulfill the duty of beneficence. However, if a patient undergoes an organ transplant via organ trafficking, the physician-patient relationship may rarely be so broken that the physician cannot provide effective follow-up medical care because of the physician's distrust toward the patient and *vice versa*.

Reluctance to Provide Medical Care to Criminals

The second possible reason is psychological resistance to providing treatment to individuals who have committed the criminal act of transplantation via organ trafficking. There may be feelings of discrimination against these individuals, which underlie physicians' concerns about the ethics of providing medical care to criminals [10]. However, the appropriateness of medical care must be judged purely based on medical indications, rather than the patient's attributes. A physician is expected to provide uniform medical care to all patients with the same condition, thus fulfilling the principle of fairness. As stated in the Hippocratic oath, the fairness of providing medical care regardless of individual attributes has been a professional ethic for physicians since ancient times [11]. Therefore, denying follow-up care to a patient who has received an illegal organ transplant simply because they are a criminal is unsupportable.

Reluctance to Be Involved in Criminal Activity

The third reason may relate to personal beliefs: follow-up care is ethically unacceptable because it supports organ transplantation via organ trafficking, which is a criminal act; therefore, a physician's medical practice would indirectly contribute to criminal activity. However, this belief is ethically denied owing to the principle of the double effect that postulates that the provision of follow-up care is not complicit in organ trafficking, rather that it is intended to provide physical management of the immediate post-transplant patient [12].

Realization of Fair Organ Transplantation

The fourth reason may be related to professional obligation: doctors have a duty to serve public interest, and to realize fair organ transplantation, it would be better for them to refuse to provide medical care after an illegal organ transplant. Would the fourth reason for deterring unethical transplant tourism ethically justify the refusal of follow-up care? The principle of fairness encourages the fair allocation of medical resources. Organ trafficking and transplant tourism are exploitative, as they obtain organs from citizens of poor countries and provide them to those in rich countries. This creates an ethical concern about fairness because patients in need of organ transplants in poor countries are denied the treatment opportunity. Moreover, efforts to prevent organ trade and transplant tourism appear to be an ethical obligation for physicians and medical institutions in accordance with the principle of fairness.

Conflict Between Principle for Justice and Beneficence

However, the principle of beneficence conflicts with the principle of fairness concerning follow-up care. The principle of beneficence calls on physicians to not only avoid harm but also benefit patients and promote their welfare [13]. Physicians are obligated to provide medically beneficial follow-up care. The refusal to provide such care results in the patient losing the treatment opportunity, especially in the absence of other medical facilities in the vicinity [14]. The probability of this situation is high because, unlike abortion and other procedures, only few medical institutions can provide follow-up care after a transplant. Refusal to provide follow-up care can result in serious medical and social risks for the patient. If proper follow-up care is lacking, there is a risk of loss of function in the transplanted organ. For example, if the patient is a post-kidney transplant patient, they may develop end-stage renal failure. There is also the risk of a shorter life expectancy. Lack of proper follow-up can result in, for example, post-kidney transplant patients requiring dialysis, intensive care due to infection, or re-inclusion on the transplant waiting list. This imposes a burden on the society because it requires medical expenses and resources that could otherwise be spared.

Certainty of Deterrence

Additionally, there is an issue regarding certainty in terms of deterrence, which is supported by the principle of fairness. It is unclear how effective refusal would be as a deterrent, and there is no certainty that the duty of fairness would be fulfilled. Thus, regarding certainty, the duty of beneficence (providing follow-up care to the patient) is more important for balancing the conflict between the two duties. This argument about certainty in sacrificing individual interests for the good of the community is also recognized as an important ethical concern in bedside rationing, where there is no assurance that the resources saved by not providing medical care to a certain patient will be utilized more efficiently for the benefit of other patients [15]. If the emphasis is on the consequence of achieving a fair allocation of medical resources (fair organ transplantation) as required by the principles of fairness, it would be difficult to ethically justify the denial of follow-up care based on the same principle. This is because the achievement of fair organ transplantation remains uncertain even after denying follow-up care.

Ethical Analysis of Conscientious Refusal to Provide Follow-Up Care to Transplant Patients Involving Organ Trafficking

This raises the question of whether it is always unacceptable for a physician to place the duty of fairness above that of beneficence. The above discussion focuses on the consequences of whether or not fair organ transplantation will be achieved. Conversely, it is also possible to focus on the intention of physicians to realize fair organ transplantation.

Conscientious Objection to Medical Treatment

The obligation to provide medical care can be divided into legal and ethical obligations. In terms of legal obligations, a physician is not considered obligated to provide medical care to a patient unless it is an emergency situation. In terms of ethical obligation, known as the principle of beneficence, a physician is considered obligated to provide medical care if doing so would contribute to the medical benefit of the patient. A physician's refusal to provide ethical obligatory medical care can be understood based on the concept of conscientious objection, which means refusing a duty based on one's religious, ethical, or political beliefs [16]. In

medicine, conscientious objection is sometimes recognized as "the right to refuse performing of a medical procedure for one's own beliefs, even if one is obligated to do so" [17]. A representative example is the inclusion of a conscientious objection clause in almost all abortion legislations worldwide. This clause grants medical providers with certain religious beliefs, such as Christian beliefs, the right to refuse to perform an abortion (if they consider it a sin). This is interpreted as follows: just as a woman has the right to self-determination regarding abortion, a medical professional has the right to do what they believe is ethically correct.

Conscientious Objection to Follow-Up Medical Care After Organ Transplantation

Follow-up care after organ transplantation is a legitimate medical practice and no physician would object to its importance. The difference between this specific type of follow-up care and common medical practices is that the former is subject to conscientious objection for physicians for two reasons.

Conscientious Objection to Being Involved in Criminal Activity

First, underlying the conscientious objection of physicians to provide follow-up care after transplantation of trafficked organs, may be the belief that they should not be complicit in criminal medical care. Physicians may not be resistant to the concept of follow-up care itself, but to their involuntary participation in a criminal procedure. In this case, even if it is legal to provide follow-up care, the physician could experience an ethical resistance, which is considered conscientious objection. However, this belief is ethically challenged by the principle of double effect [12]. The act of providing follow-up care is neutral in value. The physician's intention is to ensure the ongoing medical health of the patient following an organ transplant, and not to knowingly participate in any criminal activity related to transplantation via organ trafficking. Providing follow-up care has positive medical outcomes for the patient, regardless of whether it leads to complicity in criminal activity.

Conscientious Objection to Deter Transplant Tourism

The most common and prevailing conscientious objection of follow-up care in this case may be the belief that to deter organ transplantation, no follow-up care should be provided for those involved in the criminal act of organ trafficking.

Certainty of Effectiveness. The first problem with this belief is uncertainty about if refusing will promote fairness in organ transplants. However, for conscientious objection, the motivation behind beliefs is more important than the consequences. Therefore, the validity of the belief is more important than the uncertainty about the deterrent effect of refusing follow-up care in case of unfair organ transplantation.

Which Fairness Should Be Prioritized?. The second problem is the conflict within the principle of fairness–between the ethical imperatives to provide the same treatment to patients with the same condition and to create fair medical resources by conscientious objection to follow-up care [18]. To justify a physician's belief that their duty of fairness to society takes precedence over their duty of fairness to the patient, it would be necessary for that patient to have reasonable access to follow-up care from another physician, as is required in the "compromise approach" of conscientious objection [18].

Incompatibility Thesis. The third problem pertains to the "incompatibility thesis," which states, "the duties of a healthcare professional are incompatible with the demands of conscientious objection" [19]. From the standpoint of the "incompatibility thesis," healthcare professionals should always provide legitimate, safe, and (from the patient's perspective) beneficial treatment, regardless of the moral and personal values of the individual. Wicclair [16] suggests that for a conscientious objection to be recognized, the core ethical value on which the objection is based should be consistent with one or more core values in medicine. From this perspective, conscientious objection to follow-up care differs from the conscientious objection to abortion or assisted suicide based on the physician's personal values because it is based on the core medical ethical value of fairness [20]. In some cases, it may be considered acceptable to challenge the "incompatibility thesis" and give precedence to the fairness of healthcare over the wellbeing of the patient.

Impact on Patients From Disadvantaged Backgrounds. Another problem with conscientious objection is that it can be particularly harmful to individuals from disadvantaged backgrounds, including those with lower socioeconomic status, rural or remote residents, and individuals with poor health literacy. However, considering the enormous cost of transplantation tourism, overlooking the problem could lead to greater socioeconomic disparities both nationally and internationally.

Acceptable Ethical Conditions for Conscientious Objection to Follow-Up for the Purpose of Deterring Transplant Tourism Involving Organ Trafficking

Accordingly, refusing follow-up care based on the belief that it will deter organ trafficking can be recognized as a conscientious objection, which overcomes several problems. However, the objection is conditional. First, for the duty of fairness to take precedence over the duty of beneficence, the demand of beneficence should not be strong. If the patient's condition requires urgent follow-up care, the call for beneficence is considerably strong, and the conscientious objection to providing follow-up care is not ethically justified [21]. Second, when conscientious objection takes precedence over the duty of beneficence, the "compromise approach" should be followed, as conscientious objection is not an unconditionally recognized physician right [22]. In the "compromise approach," the conscientious objection to providing legitimate goods and services within the practitioner's capacity is considered compatible with the professional's duty if it does not unduly interfere with the patient's timely or convenient use of the goods

and services [18]. According to this approach, a conscientious objection to follow-up care must be based on a situation in which follow-up care is relatively easy to obtain from other medical facilities. In cases requiring advanced medical care, with few alternative medical institutions or unavailability of follow-up care at nearby medical institutions, conscientious objection is not acceptable.

Specific Acceptable Conditions for Conscientious Objection to Follow-Up for the Purpose of Deterring Transplant Tourism Involving Organ Trafficking

Thus, for a conscientious objection to be ethically acceptable, it must be based on a professional obligation to achieve fairness in organ transplantation care, not merely on a personal belief, or the fact that the patient's condition is not urgent and follow-up care from other medical facilities is available. Specifically, conscientious objection to deter organ trafficking for realizing fair organ transplantation may be acceptable if the following conditions are met:

(i) It is clear (or strongly suspected) that the person was involved in illegal organ trafficking.
(ii) The situation is not medically urgent.
(iii) It is possible for the patient to receive follow-up medical treatment at another medical institution.
(iv) If medical treatment has already started, follow-up treatment should be provided until the case is referred to another physician.
(v) The possibility of refusing follow-up care must be presented in advance.

The Canadian Society of Nephrology [23] states that while it does not intend to promote refusal to provide follow-up care to patients, individual physicians may choose to delegate follow-up care to another professional in non-urgent situations.

The Declaration of the Istanbul Custodian Group has recommended that with regard to the follow-up of travel transplant patients, the primary duty of healthcare professionals in any circumstance is to ensure the provision of care, and that it is not the responsibility of the healthcare professional to sanction patients suspected of criminal activity [7]. Therefore, it states that post-transplant tourism patients should be promptly referred for evaluation at a transplant center to ensure proper screening and care, particularly in managing infectious diseases. It also recommends applying this principle to patients who have received transplants through organ trafficking. Moreover, it emphasizes that medical institutions and public insurance should not cover the cost of organ trafficking-related transplants, but follow-up care after a transplant via organ trafficking should be paid for in the same manner as other transplant patients, provided that relevant information is recorded in an official transplant registry. While advocating these actions, the report acknowledges that in non-emergent situations, individual physicians may choose to defer the follow-up care of these patients to another physician.

Stating the policy in advance is considered important for ensuring procedural justice amidst the controversy surrounding conscientious objection [24]. Additionally, when making a conscientious objection, it is necessary to provide reasons for the refusal rather than merely stating the refusal [25]. Thus, if a physician refuses follow-up care based on their conscience regarding fair organ transplantation care, it is necessary to explain this to the patient in advance. Furthermore, practically, it would be useful for medical institutions to present their policy beforehand to avoid problems with patients, ensuring smooth access to medical care so that patients can avoid institutions that may refuse follow-up care.

However, certain practical difficulties remain, such as the definition of "another medical institution," criteria for determining "urgency," and how the involvement in "organ trafficking" can be confirmed. If no medical institution is available for follow-up care within the patient's residential prefecture or the likelihood of a life-threatening condition is high, follow-up care should be provided.

CONCLUSION

The principles of transparency and continuity of care that apply to patients who receive an organ domestically should also apply to transplant tourism patients who received a transplant via organ trafficking. According to the concept of conscientious objection, in non-emergent situations, individual physicians may elect to defer the care of these patients to another physician. However, there are numerous requirements to satisfy this condition, such as determining the illegitimacy of transplant tourism due to its involvement in organ trafficking and assuring proper follow-up at another medical institution.

Thus, concerning refusal to provide follow-up care to a patient who underwent an unethical organ transplant, the appropriate attitude for a physician is "when in doubt, do what is in the patient's best interest."

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

CONFLICT OF INTEREST

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW AND META-ANALYSIS
published: 03 April 2024
doi: 10.3389/ti.2024.12483

Public Opinions on Removing Disincentives and Introducing Incentives for Organ Donation: Proposing a European Research Agenda

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The shortage of organs for transplantations is increasing in Europe as well as globally. Many initiatives to the organ shortage, such as opt-out systems for deceased donation and expanding living donation, have been insufficient to meet the rising demand for organs. In recurrent discussions on how to reduce organ shortage, financial incentives and removal of disincentives, have been proposed to stimulate living organ donation and increase the pool of available donor organs. It is important to understand not only the ethical acceptability of (dis)incentives for organ donation, but also its societal acceptance. In this review, we propose a research agenda to help guide future empirical studies on public preferences in Europe towards the removal of disincentives and introduction of incentives for organ donation. We first present a systematic literature review on public opinions concerning (financial) (dis)incentives for organ donation in European countries. Next, we describe the results of a randomized survey experiment conducted in the United States. This experiment is crucial because it suggests that societal support for incentivizing organ donation depends on the specific features and institutional design of the proposed incentive scheme. We conclude by proposing this experiment's framework as a blueprint for European research on this topic.

Keywords: ethics in transplantation, payments, organ donation, incentives, disincentives

OPEN ACCESS

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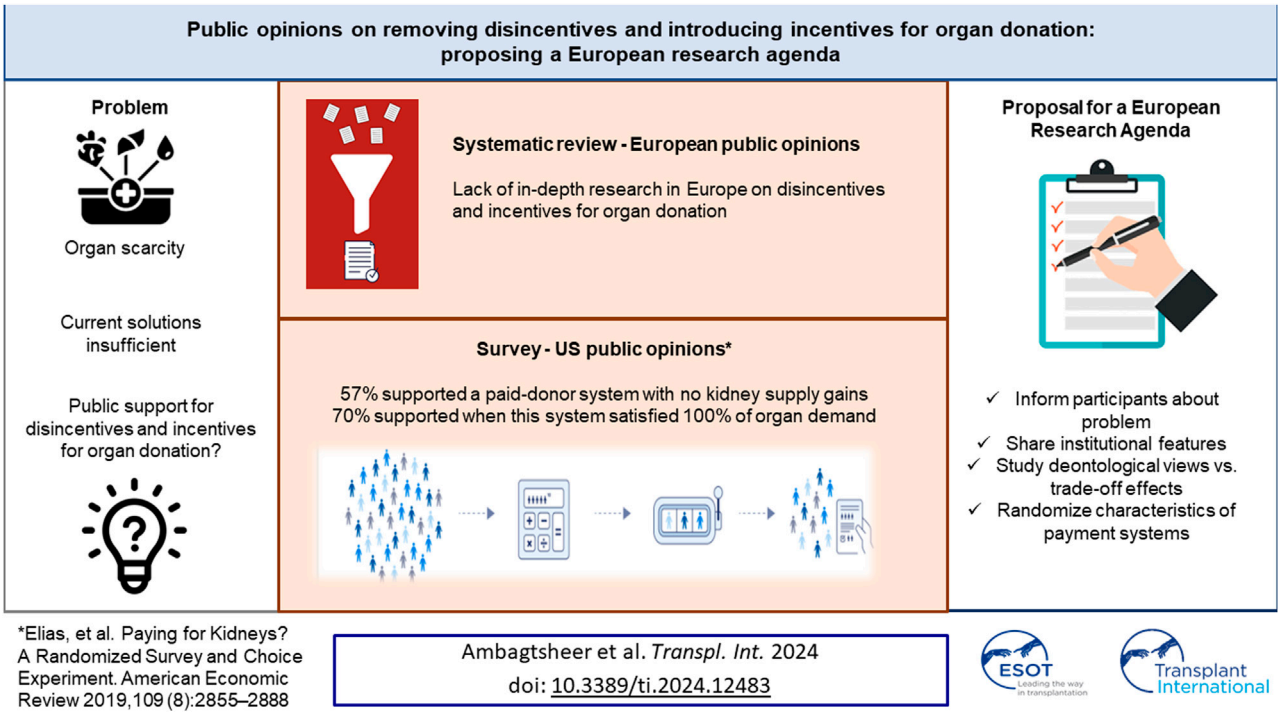
Received: *19 December 2023*
Accepted: *04 March 2024*
Published: *03 April 2024*

Citation:
Ambagtsheer F, Bunnik E, Pengel LHM, Reinders MEJ, Elias JJ, Lacetera N and Macis M (2024) Public Opinions on Removing Disincentives and Introducing Incentives for Organ Donation: Proposing a European Research Agenda. Transpl Int 37:12483. doi: 10.3389/ti.2024.12483

INTRODUCTION

The shortage of organs for transplantations is longstanding and increasing in Europe as well as in the rest of the world. The policies that many European countries enacted, such as opt-out systems for deceased organ donation [1], have not been effective in filling the gap between the need and availability of organs [2]. Furthermore, significant disparities remain in deceased and living organ donation rates across Europe [3]. In 2022, there were still over 52,000 patients registered on wait lists



GRAPHICAL ABSTRACT

in the European Union, of whom 42,000 needed a kidney transplant [4]. Roughly 100 million Europeans suffer from chronic kidney disease [5]. In 2022, in Europe, on average, 19 patients died every day while waiting for an organ transplant, and every hour, five new patients are added to transplant waitlists [6].

In recurrent discussions on how to address the plight of patients on waiting lists, monetary or non-monetary incentives have been suggested to stimulate organ donation and thus increase the pool of available donor organs. However, payments for organs are illegal in most countries. The ethical principle that "the human body and its parts shall not, as such, give rise to financial gain" [7] is broadly shared by governments, international organizations, and transplant societies [8, 9]. The prevailing position is that organ donation should be based on altruistic motivations and should be seen as a "gift" [10]. Although offering financial *incentives* to organ donors is prohibited, providing financial *compensation* is not [8]. Compensation, or reimbursement of the costs incurred by donors, including medical expenses, travel costs, and loss of income is intended to help to remove disincentives to living organ donation, but may not always suffice [11]. To encourage more people to donate, the use of monetary or non-monetary incentives might help.

The distinction between offering incentives and removing disincentives is unclear, however. The Nuffield Council on Bioethics describes a "(dis)incentive continuum" that ranges from "recompense" to "purchase," or from reimbursement for incurred losses to direct payment in exchange for organs [12]. The American Society of Transplantation and the American Society of Transplant Surgeons similarly identify a spectrum of policy options, which they describe as an "arc of change" that should begin with removing disincentives that obstruct the organ donation process [13]. In-between compensating and paying, there are various possible forms of non-financial and indirect financial rewards [14], including granting donors priority positions on waiting lists and waiving donor health insurance premiums for certain amounts of time [15]. Some of these rewards may be compatible with the ethical principle that living organ donation should be "financially neutral to the donor" [16].

Throughout the years, various policy proposals suggesting different reward systems for deceased and living organ donation have been proposed [15, 17–22]. In Netherlands in 2007, for example, the Centre for Ethics and Health, a partnership of the Dutch Health Council and the Council for Public Health and Society, recommended the introduction of financial incentives for deceased and living organ donations to the Dutch government [15]. There have been similar proposals in the United States of America (United States), China, and Singapore [23–26]. Iran is currently the only country that allows payments for living kidney donation [27]. In most proposals for reward systems for living kidney donation, a national regulatory body would regulate the process, the healthcare system (not the recipient) would make the payments, and allocation would be based on medical need [15, 28]. Although the consequences of such a model will need to be monitored, its features may allay many ethical objections towards paying donors [15, 29]. Yet, there remains considerable opposition to the implementation of these proposals [30–32].

In the context of regularly resurfacing discussions on the legalization of incentives for organ donors, it is important to understand not only its ethical acceptability, but also its societal acceptance. In liberal democracies, public policies should ideally align with citizens' moral perspectives and be upheld by stakeholders. On the one hand, given the widespread ethos that donation should be a gift, one might expect limited societal acceptance of (financial) incentives. On the other hand, markets that are assumed to be controversial or that a—in some countries—illegal, do not always elicit public repugnance [33]. It is thus crucial to approach this topic with nuance, as the debate surrounding payments for organs is often framed in black-or-white terms [34–36]. For instance, proposals for the introduction of incentives are often unduly equated with proposals for a free market for human body parts. Because, there are potentially numerous policy options for paid donation [20–22, 37], a more balanced consideration of public perspectives, ethical concerns and possible outcomes is warranted [38].

In this paper, we propose a research agenda to help guide future empirical studies on public preferences in Europe towards the removal of disincentives and introduction of incentives for organ donation. While our focus is on Europe, our considerations are also suitable for other regions. We include both deceased and living organ donation, but concentrate particularly on living kidney donation, consistent with most studies and policy proposals [15, 17–20]. In support of our objective, we present a systematic literature review on public opinions concerning (financial) (dis)incentives for organ donation in European countries. We do not only present the outcomes of these studies, but also critically discuss the nature and socio-demographic characteristics of the samples in these studies, the methodology used, and what questions these studies can and cannot answer. Next, we describe the results of a randomized survey experiment conducted in the United States in 2019 by Elias et al. [39]. This experiment is crucial because it suggests that societal support for incentivizing organ donation depends on the specific features and institutional design of the proposed incentive scheme. We conclude by proposing this experiment's framework as a blueprint for European research on this topic.

(DIS)INCENTIVES FOR ORGAN DONATION IN EUROPE: RESULTS OF A SYSTEMATIC LITERATURE SEARCH

Hoeyer et al. were the first to systematically synthesize studies on public attitudes towards financial incentives for organ donation [40]. Although their objective was to identify global trends in public opinions on financial incentives, they underscored the methodological challenges in comparing and aggregating studies due to variations in methods, contexts, and respondent selection. They also emphasized the marked differences in public opinions across these studies [40]. In their analysis of 23 studies from various countries across the globe, they observed, amongst others, a greater acceptance of financial incentives for organ donation in the United States and in the United Kingdom (UK), compared to other countries. In Central European countries (i.e., Germany, Austria, Switzerland, Netherlands) they observed minimal support for direct payments but a moderate acceptance of indirect benefits [40].

For our review, which focused exclusively on studies in European countries, we identified studies that focused on public opinions in Europe published after Hoeyer et al.'s research.

METHODS

Inclusion and Exclusion Criteria

We included studies presenting empirical data on opinions regarding financial (dis)incentives from the European general public, including subgroup such as students, medical professionals, patients and donors. Financial disincentives included reimbursement of healthcare expenses, and financial incentives included free healthcare insurance for living donors and cash rewards for families of deceased donors. Studies presenting international opinions were included as long as results from European samples could be extracted. We excluded congress abstracts and studies published in languages other than English.

Bibliographic Search

We conducted a systematic literature search to identify studies that reported European public opinions on financial (dis)incentives for living or deceased donor organ donation. An information specialist helped develop detailed bibliographic searches consisting of a combination of Medical Subject Heading (MeSH) terms and keywords for Medline, Embase and Psychinfo to identify studies that were published since the published literature review by Hoeyer et al. [40] i.e., from January 1, 2012 until April 20, 2023 (Appendix 1).

Study Selection, Data Extraction and Analysis

We merged the search results from the three bibliographic databases into a single EndNote database. Two reviewers (EMB and LHMP) independently screened the abstracts and titles, which was followed by full text review of potentially eligible studies. We resolved discrepancies between reviewers at any stage of this process by discussion and consultation with a third reviewer (FA). **Figure 1** displays a flow diagram of the selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [41]. One reviewer (FA) extracted the following data from the studies: year of publication, country, study design, sampling method, number of participants, participant demographics, overall objective of the study, questions on financial incentives and summary of findings. A second reviewer (LHMP) verified these data. Corresponding authors of the studies were

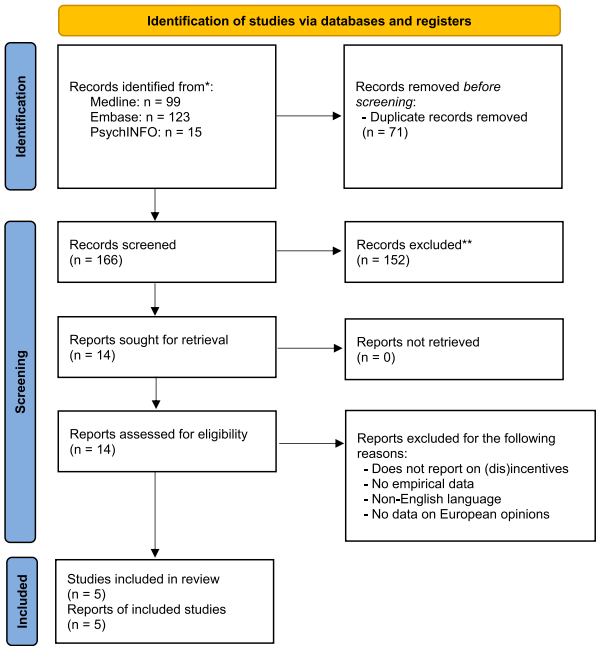


FIGURE 1 | PRISMA flow diagram showing the identification, selection and inclusion of studies.

contacted in case of missing data. We then summarized the studies in the form of a narrative review.

RESULTS

Characteristics of Included Studies

Our bibliographic search identified 166 unique references of which five studies met our criteria for inclusion (**Figure 1**) [42–46]. There were four survey studies and one study reporting semi-structured interviews. Only Ghahramani et al. exclusively addressed financial incentives for organ donation as the main focus of their study [46]. The other four studies asked only few (between one and four) questions on financial incentives, which formed part of a larger survey or interview-study that addressed opinions on organ donation and transplantation more generally. For example, in their survey exploring public attitudes towards organ donation in Denmark, Nordfalk et al. only included two questions/statements, asking respondents whether *"[I]t would be fair if donors or relatives received compensation for any potential expenses in relation to the donation"* [44].

Public opinions included opinions from the general population, students, nephrologists and patients with end-stage kidney diseases (ESKD) who had publicly solicited a living kidney donor. Studies were conducted in Romania, Germany, Denmark and Netherlands. Ghahramani et al. [46] reported opinions of Eastern and Western European transplant nephrologists but did not specify the countries. One study reported on living donation [45], three studies reported on living and deceased donation [43, 44, 46] and one study did not specify whether the question related to living or deceased donation [42]. The corresponding author of the latter study [42] was contacted with the request to provide the question on financial compensation but no reply was received.

Summary of Findings

The data in the studies were heterogeneous in terms of the characteristics of the study population, the country, and the framing of the questions regarding financial incentives (**Table 1**). Below we provide a narrative summary of the data, separately between living and deceased kidney donation.

Living Kidney Donation

Four studies surveyed public opinions regarding financial (dis) incentives for living kidney donation [43–46]. Overall, more participants tended to agree than disagree with reimbursing the costs incurred by the donation and/or allowing more indirect rewards, such as a free life-long health insurance or cheaper or free follow-up treatments [43–45]. Only a very small percentage would agree with direct financial rewards, such as cash payments [43–45].

Participants in the study by Pronk et al. also highlighted perceived risks for recipients of being transplanted with a traded kidney and an unease among recipients with benefiting from other people's poverty [45]. Most participants who had experience with public solicitation of living donors had received offers of kidneys in return for money or payment in kind, for example, employment or residency. Payments in kind were considered unacceptable to the participants and were turned down. Respondents considered public solicitation as a first step in finding a kidney donor before exploring paid donation, which they would consider if they had the means to pay a donor or if their medical condition became more urgent [45].

Ghahramani et al. [41] compared opinions of Eastern and Western European nephrologists with opinions of nephrologists from non-European countries (i.e., Canada and the United States). Eastern European nephrologists were more likely to agree with providing free life-long health insurance for living donors compared to nephrologists from non-European countries. Western European nephrologists were less likely to favor direct financial payments or rewards compared to nephrologists from non-European countries, whilst no differences were found between nephrologists from non-European countries and Eastern Europe.

Deceased Kidney Donation

Three studies reported opinions regarding financial incentives for deceased donation [43, 44, 46]. Financial models for deceased organ donation based on incentives were rejected by most participants [43, 44]. Ghahramani et al. reported that nephrologists from Western Europe were less likely to agree with providing financial rewards to families of deceased donors compared to nephrologists from Eastern Europe and other geographic reasons [46].

TABLE 1 | Characteristics of the included studies.

Author (year), country, living/ deceased donation	Methodology, sampling method	Background (n), age, gender and ethnicity	Education, socio-occupational status, religion	Questions on financial incentives	Summary of findings
Bacuşcă (2022), Romania Unclear whether living or deceased donation	Survey A 3-stage probability sampling technique to choose a representative sample of city residents	440 city residents *Age* mean 43.5 y *Gender (M:F)* 50%: 50% *Ethnicity* NR	*Education* 33% higher education, 42% high school, 16% vocational, 7% elementary *Socio-occupational status* 44% employed, 21% retired, 17% students, 16% freelancers, 7% housekeepers, 5% unemployed *Religion* Christian (98%)	Unclear how the question on financial compensation was framed	44.5% of respondents supported financial compensation, while 38.9% rejected financial compensation
Ghahramani (2013), Eastern and Western Europe Living and deceased donation	Survey A database of email addresses was created by an online search method which was supplemented by lists from national and regional nephrology societies	230 Eastern and Western European transplant nephrologists. They were part of a larger sample of a total of 1,280 international nephrologists *Age* 60% ≤ 50 years; 40% > 50 years (all 1,280 respondents) *Gender (M:F)* 72%: 28% (all 1,280 respondents) *Ethnicity* NR	*Education* NR *Socio-occupational status* Transplant nephrologists *Religion* NR	Four questions explored opinions around the following topics Q1) Free lifelong health insurance for living donors Q2) Some form of (direct) financial compensation for living donors Q3) Financial rewards for living related and unrelated donors Q4) Financial rewards for families of deceased donors	Q1) Nephrologists from Eastern Europe were more likely to agree with health insurance for donors compared to nephrologists from Canada/ United States but there was no difference between nephrologists from Canada/United States and Western Europe Q2) Nephrologists from Western Europe were less likely to favor direct financial compensation for living donation compared to nephrologists from Canada/ United States but there was no difference between nephrologists from Canada/ United States and Eastern Europe Q3) Nephrologists from Western Europe were less likely to agree with financial rewards to living-related or living-unrelated donors compared with nephrologists from Canada/United States but there was no difference between nephrologists from Canada/United States and Eastern Europe Q4) Nephrologists from Western Europe were less likely to agree with providing financial rewards to families of deceased donors compared with nephrologists from Canada/ United States but there was no difference between nephrologists from Canada/ United States and Eastern Europe

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of the included studies.

Author (year), country, living/ deceased donation	Methodology, sampling method	Background (n), age, gender and ethnicity	Education, socio-occupational status, religion	Questions on financial incentives	Summary of findings
Inthorn (2014), Germany Living and deceased donation	Survey Students were asked to participate after compulsory classes	755 students (466 students of medicine and 289 students of economics) *Age* 0–19years: 14% 20–24years: 63% 25–29years: 20% ≥30years: 3% *Gender (M:F)* 48%: 52% *Ethnicity* NR	*Education* University students *Socio-occupational status* University students *Religion* NR	Four questions explored opinions on commercialization and compensation for organ donation Q1) Financial incentives for living organ donors Q2) Statements on financial compensation Q3) One-off payments for living donors Q4) Economic incentives following *postmortem* donation	LOD: Only 5% of medical students and 9% of economics students were in favor of allowing to sell one's organs for money. The majority (73%) believed that a living donor should receive cheaper or free follow-up treatment, while 9% felt that a living donor should receive free life insurance from the state. Overall, students favored removing disincentives, e.g., compensation for health and surgery related costs, or models of reciprocity (living donors receive benefits when they need an organ themselves) over monetary 'incentives', such as cash rewards. Still, only 45% of students felt that living donors should be compensated for the related health expenses DOD: Although both groups of students tended to reject financial models, the number of students favoring financial incentives was higher among economics students compared to medical students in four out of six questions. The authors state that there was a relatively high number of students who were undecided but these data were not shown
Nordfalk (2016), Denmark Living and deceased donation	Survey	1,195 Danish citizens *Age* Mean 50years (range: 18–102) *Gender (M:F)* 49%: 51% *Ethnicity* NR	*Education* Secondary: 40% Post-secondary: 33% Short-cycle tertiary: 5% Bachelor: 15% Master: 7% *Socio-occupational status* NR *Religion* Christian protestantism: 21%; Muslim: 2%; Other: 4%; not religious: 73%	Respondents were asked to rate their agreement with the following statements 1) "It should be possible to motivate donors or relatives of potential donors with money, to make them donate organs" 2) It would be fair if donors or relatives received compensation for any potential expenses in relation to the donation"	Only 6% of citizens found it acceptable to use money as a motivation for donating organs and a slight majority (52.7%) agreed to compensate expenses related to the donation For both of these questions, women tended to disagree more with the statements than men ($p < 0.05$) The data showed a clear difference between attitudes to money used as incentives and as compensation

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of the included studies.

Author (year), country, living/ deceased donation	Methodology, sampling method	Background (n), age, gender and ethnicity	Education, socio-occupational status, religion	Questions on financial incentives	Summary of findings
Pronk (2018), Netherlands Living donation	Semi-structured interviews Google, Facebook and Twitter were searched to identify Dutch kidney patients and their representatives who publicly solicited a living kidney donor. Eligible patients were invited by email, telephone or social media	20 Dutch patients with end-stage renal disease who had publicly solicited a living kidney donor *Age* Mean 46years (range: 26–74) *Gender (M:F)* 60%: 40% *Ethnicity* 'Dutch'	*Education* Primary or secondary education: 35% Further education: 65% *Socio-occupational status* NR *Religion* NR	Patients were asked the following questions Q1) Do you believe that a public appeal for a kidney donor attracts people who want to get something in return for their kidney? For example, financial or social. Would you object to that? Q2) In general, do you believe that in the Netherlands, something could or should be offered to donors, some kind of compensation or financial reward? What do you think of that and what kind of compensation do you have in mind?	The majority of participants disapproved of buying a kidney, because they feared blackmailing, believed this would be unfair to patients who do not have the money to buy a kidney, or because they did not want to violate the law. They also believed it would be too risky to be transplanted with a traded kidney and did not want to benefit from someone else's poverty Some participants reported that they would buy a kidney if they would have the means to do so or if their medical situation became more urgent, implying that they perceived public solicitation as a step that can be taken prior to exploring paid donation. Almost all participants received offers of a kidney in return for money or payment in kind (such as employment, residency, or sexual favors). Participants also received offers from prisoners who wanted to do something good for another person Offers for payment (in kind) appalled participants and were ignored or turned down. They wanted a kidney to be an unconditional gift from a donor

NR, not reported; DOD, deceased organ donation; LOD, living organ donation.

PAYING FOR KIDNEYS? RESULTS OF A RANDOMIZED SURVEY AND CHOICE EXPERIMENT IN THE UNITED STATES

In 2019, Elias et al. published the findings of a randomized survey experiment concerning the preferences of American citizens for paying living kidney donors [39]. The study assessed whether attitudes toward a paid-donor system depend on its possible effects on the number of transplants (i.e., lives saved), or whether they reflect deontological views or "sacred values." Moreover, the survey investigated whether and how preferences respond to different institutional features of a hypothetical paid-donor system, the moral foundations of preferences for paid-donor systems, and the extent to which attitudes are heterogeneous in the population. The study's sample included nearly 2,700 American residents, stratified to match the United States population across various demographics.

The study's design included the random assignment of respondents to consider one hypothetical paid-donor kidney procurement and allocation system, asking them to view it as an alternative to the current system in which kidney donors do not receive payment. There were eight possible paid-donor systems, which were the combination of the following characteristics: the type of payment (direct cash or non-cash, like contributions to college or retirement funds), the payment amount ($30,000 or $100,000), and the entity responsible for payment (either the organ recipient or a public agency). Subsequently, each respondent made five decisions about

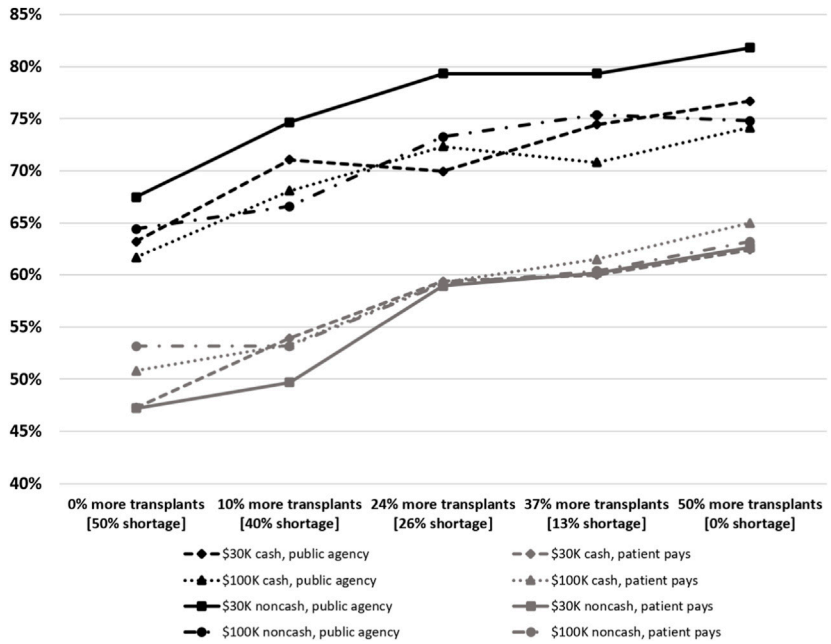


FIGURE 2 | Support for Paid-Donor Systems. Notes: The figure reports the percentage of respondents in favor of compensating kidney donors, by payer (public agency or patient), amount of compensation ($30 K or $100 K), nature of compensation (cash or noncash), and hypothesized kidney supply level. We assessed how much of the annual demand for transplants, not the waiting list, would be affected by the increase in the number of transplants. Source: [39]. (Copyright American Economic Association; reproduced with permission of the American Economic Review).

expressing support either for the proposed donor payment system or to maintain the existing, unpaid-donor system. In all five choice situations, the characteristics of the alternative system remained the same, with the only difference being the kidney supply gains, i.e., the number of additional transplants that participants were asked to assume the paid-donor system would produce in each scenario. The survey presented the five scenarios in a sequence, starting from no increase in organ donations and progressing to an increase in donations sufficient to completely eliminate the waiting list [39].

There was wide heterogeneity in preferences and strong polarization of attitudes among respondents, with large proportions of respondents either in favor of or against paying kidney donors regardless of the size of hypothesized kidney supply gains. However, the study found that support for paying donors becomes stronger when the projected increase in the number of transplants is higher. On average, 57% of respondents supported a paid-donor system with no kidney supply gains, and about 70% supported a paid-donor system when the system satisfied 100% of the demand for organs. Thus, a considerable proportion of respondents have "tradeoff-sensitive" attitudes, because their views depended on the number of additional transplants that could be obtained through a paid-donor system. When there was a sufficient increase in the availability of kidneys, these individuals were more inclined to support the legalization of a paid-donor system and had fewer ethical concerns [39].

Further, the level of support for paid-donor systems varied substantially according to the identity of the payer. Specifically, a large share of respondents opposed the private transactions where the kidney recipient would pay the donor (either directly or through their insurance). However, respondents showed much stronger support for procurement and allocation systems in which a public agency pays kidney donors and allocates organs using a mechanism similar to the current algorithm that distributes deceased donor organs based on medical urgency, blood and tissue match, time on the waiting list, etc. This finding indicates that there is a difference in opinions vis-à-vis "paying donors" and "allowing patients to purchase an organ." Opposition to the latter is very strong, whereas a large proportion of respondents supports paying organ donors when this is performed by a public agency that allocates the resulting organs fairly (i.e., not based on the patient's ability to pay). The nature and amount of payment did not have a large effect on support for paying donors. However, the paid-donor system with the highest support (more than 80% of respondents) was the one where a public agency provides donors with $30,000 noncash compensation (e.g., in the form of contribution to a retirement account) (**Figure 2**).

The study also assessed whether respondents' attitudes were based on deontological or "sacred" values toward paying living kidney donors. The authors asked participants to express their moral judgments about both the current system and the paid-donor system to which they were assigned, at each hypothesized organ supply level. The six ethical principles considered—autonomy of choice, undue influence, exploitation of the donor, fairness

TABLE 2 | A proposal for a research agenda on (dis)incentives for organ donation in Europe.

Introducing four critical features for future studies on opinions regarding paid donation schemes based on Elias et al. [39]	
1. Informing participants about the problem and about alternative solutions to the problem	Include, at a minimum, the number of waitlisted patients, waiting times, patient mortality rates, healthcare costs and alternatives (e.g., paid-donor systems)
2. Institutional characteristics	Government controlled payments; free market exchanges; organ allocation criteria; payment amount; type of monetary and non-monetary incentives; removal of disincentives
3. Deontological views vs. trade-off effects	Questions on sacred values versus expected trade-offs (e.g., higher patients' lives expectancy, shorter transplant lists), results of payment schemes; assess moral and practical views
4. Experimental methods; randomizing characteristics of payment systems	Assess how each feature impacts the acceptability of specific paid-donor systems

to the donor, fairness to the patient, and human dignity—accounted for a substantial share of the variance in support for paid donor systems. Moral judgments were especially affected by the identity of the payer and the nature of compensation. In particular, respondents viewed non-cash payments and payments by a public agency as more ethical than cash payments and payments by the organ recipient, and were most concerned about the fairness of organ allocation, which was the primary reason for their opposition to systems that involved payments made by the organ recipient [39].

CONCLUSION: A PROPOSAL FOR A RESEARCH AGENDA ON (DIS)INCENTIVES FOR ORGAN DONATION IN EUROPE

Our systematic literature review suggests that there is relatively little public support in Europe for financial incentives—especially cash payments—for organ donation, and some public support for removing disincentives. Yet, only five studies on public opinions have been conducted over the last decade in Europe. Furthermore, the majority of these studies did not focus on (dis)incentives as their main topic, but incorporated only a few questions on the issue as part of a larger investigation on public opinions on organ donation. Additionally, the questions tended to be too generic to be truly informative, as they neither specified the relevant characteristics of the proposed policies nor addressed the expected effects on organ supply. Thus, the research body in Europe on this subject is limited both in volume and methodologically, and does not allow for an in-depth and conclusive empirical assessment of the degree of public support for (dis)incentives for organ donation.

We posit that the topic of (dis)incentives for organ donation should be the central focus of in-depth studies that incorporate the various features of paid donation schemes, their implications for the donor organ supply and the nuanced moral and practical considerations that underlie them. Elias et al. demonstrate the importance of including at least four critical features when studying the delicate and complex topic of (dis) incentives for organ donation amongst the general public [39]. First, participants should be informed about the problem (e.g., number of waitlisted patients, waiting times, etc.), its implications (e.g., patient mortality, healthcare costs, etc.) and possible alternatives (e.g., paid-donor systems). Second, the various institutional characteristics that may underlie different paid-donor systems should be described. It is critical to recognize that the way a system is structured can greatly influence its public acceptance. For instance, the ethical considerations associated with a free-market exchange between prospective donors and recipients stand in stark contrast to the ethical considerations related to a government-controlled system that offers non-financial rewards for deceased donation or living kidney donation and that allocates organs based on medical need. This distinction is vital, as it underscores the necessity to meticulously define and communicate the relevant features of any proposed policy, ensuring that respondents fully grasp the implications and nuances of each system. Public opinions may also vary according to the type of incentive or disincentive that is offered. Third, studies of this topic should explore whether public opinions are influenced by the possible effects of paid donation systems on the number of transplants (i.e., gains in patients' life expectancy). It is an empirical question, and not an assumption, that the opposition to compensation and payments responds to some "sacred values" and is not amenable to the considerations of other socially relevant outcomes. Finally, adding experimental manipulation to the design of surveys is paramount for determining causality. By randomly varying the characteristics of the institutional design, researchers can directly assess how each feature impacts the acceptability of specific paid-donor systems, both from a moral and practical standpoint. This approach offers a more precise understanding of public attitudes towards the intricate balance between ethical concerns and pragmatic needs.

In light of calls for trials to experiment with payments for both living [17, 20, 21] –and deceased donation [47–49], our proposed research agenda can generate the needed evidence to evaluate the acceptability in the general population towards allowing payments for deceased and living organ donation.

In proposing a European research agenda, we call for the integration of these critical features into future empirical studies of this topic (**Table 2**). Such an approach will delve deeply into the intricate perceptions surrounding paid donor schemes. Moreover, it will clarify the specific conditions and frameworks under which general publics might deem such schemes acceptable. This information can guide law- and policymakers and other stakeholders in developing policy proposals on this topic. Erasmus MC's Transplant Institute recently received funding from the Dutch Research Council that allows us to survey public opinions across three

European countries, namely, Germany, Netherlands and Spain, while incorporating the aforementioned critical features [50, 51].

Over the last three decades, numerous moral concerns have been raised against allowing payments for organs [52–54], with many proposing various specific market designs to attenuate those concerns [17, 20, 21]. Additionally, there is an ongoing debate about the effectiveness of a compensation system in terms of its impact on the number of transplants [52, 55, 56]. The contribution of our proposed research direction lies in causally estimating how the specific design of the system and its effectiveness could influence the general population's acceptance of the system. Our aim is to provide new insights into studying the multifaceted perspectives of the European public on (dis)incentives on organ donation. Furthermore, we hope that our proposed methodology becomes a reference for other research teams. Such an approach is needed to comprehensively address and understand the complexities surrounding (dis)incentives for organ donation and to explore policy options to increase the supply of organs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving humans were approved by the Research Ethics Board at the University of Toronto (protocol 30238) and the Homewood Institutional Review Board at Johns Hopkins University (protocol 00001991). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LP, EB, FA, MM, JE, and NL wrote the manuscript; MR reviewed the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Wichor Bramer from the Erasmus MC Medical Library, Rotterdam, Netherlands, for his assistance in developing the search strategies.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12483/full#supplementary-material

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SYSTEMATIC REVIEW AND META-ANALYSIS
published: 31 October 2022
doi: 10.3389/ti.2022.10751

Early-Phase Clinical Trials of Bio-Artificial Organ Technology: A Systematic Review of Ethical Issues

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Regenerative medicine has emerged as a novel alternative solution to organ failure which circumvents the issue of organ shortage. In preclinical research settings bio-artificial organs are being developed. It is anticipated that eventually it will be possible to launch first-in-human transplantation trials to test safety and efficacy in human recipients. In early-phase transplantation trials, however, research participants could be exposed to serious risks, such as toxicity, infections and tumorigenesis. So far, there is no ethical guidance for the safe and responsible design and conduct of early-phase clinical trials of bio-artificial organs. Therefore, research ethics review committees will need to look to related adjacent fields of research, including for example cell-based therapy, for guidance. In this systematic review, we examined the literature on early-phase clinical trials in these adjacent fields and undertook a thematic analysis of relevant ethical points to consider for early-phase clinical trials of transplantable bio-artificial organs. Six themes were identified: cell source, risk-benefit assessment, patient selection, trial design, informed consent, and oversight and accountability. Further empirical research is needed to provide insight in patient perspectives, as this may serve as valuable input in determining the conditions for ethically responsible and acceptable early clinical development of bio-artificial organs.

Keywords: ethics, regenerative medicine, bioengineering, research ethics, first-in-human clinical trials, bio-artificial organs, clinical trials, early-phase clinical trials

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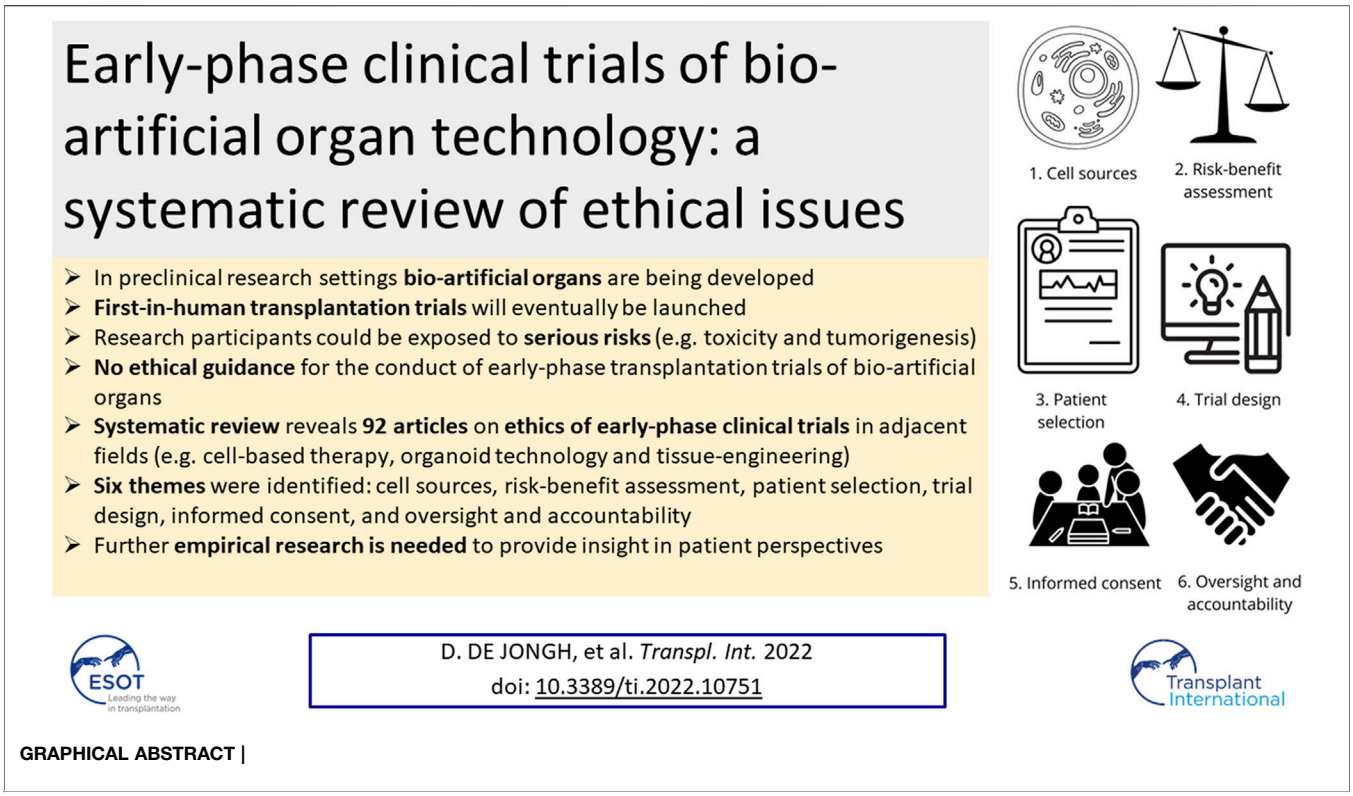
Received: *08 July 2022*
Accepted: *07 October 2022*
Published: *31 October 2022*

Citation:
de Jongh D, Massey EK, Cronin AJ, Schermer MHN, Bunnik EM and the VANGUARD Consortium (2022) Early-Phase Clinical Trials of Bio-Artificial Organ Technology: A Systematic Review of Ethical Issues. Transpl Int 35:10751. doi: 10.3389/ti.2022.10751

INTRODUCTION

For patients with end-stage organ failure, having an organ transplant is often the best and only cure. Advances in surgical techniques and immunosuppressive medication means that organ transplantation is now widely and successfully used. However, there are still important challenges to overcome, notably the shortage of donor organs and the short and long-term side effects of taking lifelong immunosuppressive medication.

In the last decade, the multi-disciplinary field of regenerative medicine has emerged. Regenerative medicine uses technologies such as tissue engineering and 3D bioprinting to (re)generate, repair or replace damaged tissues and organs. Regenerative medicine and tissue engineering are terms often used interchangeably in the scientific literature. In this article however we use the term regenerative medicine to refer to the aim of the intervention (to regenerate), and tissue engineering to refer to the



GRAPHICAL ABSTRACT |

method for creating regenerative products. Regenerative medicine could, by way of illustration, combine patient-derived cells (e.g., in the form of organoids made from induced pluripotent stem cells) with cutting-edge technologies such as tissue engineering, to develop transplantable personalized bio-artificial organs. For example, the European Commission-funded VANGUARD project aims to engineer a vascularized and immune-protected bio-artificial pancreas for transplantation into patients with Type I Diabetes. The ambition of the VANGUARD project[1] is for the transplanted bio-artificial pancreas to produce insulin and treat the underlying diabetic disease without requiring the patient to take lifelong immunosuppressive medication. Similarly, in other disease areas, first steps are being taken towards the generation of transplantable bio-artificial organs, including livers (1), bladders (2), kidneys (3), hearts (4), small intestines (5) and lungs (6, 7). These bio-artificial organs are currently still at the preclinical stage and are being tested in laboratory settings or animal studies.

It is likely that researchers will reach a point at which sufficient preclinical evidence has been collected to suggest that bio-artificial organs might be beneficial and safe for humans. At that point, early-phase clinical trials will be initiated to test the safety and efficacy of these products in humans. In early-phase clinical trials, human research participants could be exposed to serious risks, such as toxicity, infections and tumorigenesis. This is especially so in regenerative medicine trials requiring invasive and non-reversible procedures, resulting in permanent alterations of participants' bodies (8).

It is not clear to what extent existing ethics oversight and guidance for the conduct of clinical trials is applicable to or sufficient for the clinical translation of bio-artificial organs. First, drug authorities, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), were originally set up to decide on marketing authorisation of *pharmaceutical agents*, not complex cell-based products. In Europe, bio-artificial organs are likely to be classified as Advanced Therapy Medicinal Products (ATMPs) (9), just like cell-based therapies. However, this classification may not completely cover the bio-artificial organ as, unlike most pharmaceutical agents, it is not a substance that can be injected or infused, but a complex product—more like a (cell-based) device—to be used in transplantation, which involves a (innovative) surgical intervention. Second, while there are internationally recognised guidelines for the ethical conduct of research involving human subjects, issued for instance by the Council for international Organization of Medical Science (CIOMS) (10) and the World Medical Association (WMA) (11), these guidelines should be expanded in order to make them applicable to the clinical translation of bio-artificial organs. The ethics guidelines of the International Society for Stem Cell Research (ISSCR) have been developed specifically for human stem cell research and clinical translation of cell-based interventions (12), but do not discuss applications of regenerative medicine in *organ transplantation*. Without the relevant guidance,

[1]VANGUARD. New generation cell therapy: bioartificial pancreas to cure type 1 diabetes. https://vanguard-project.eu/ (Accessed 1 July 2022).

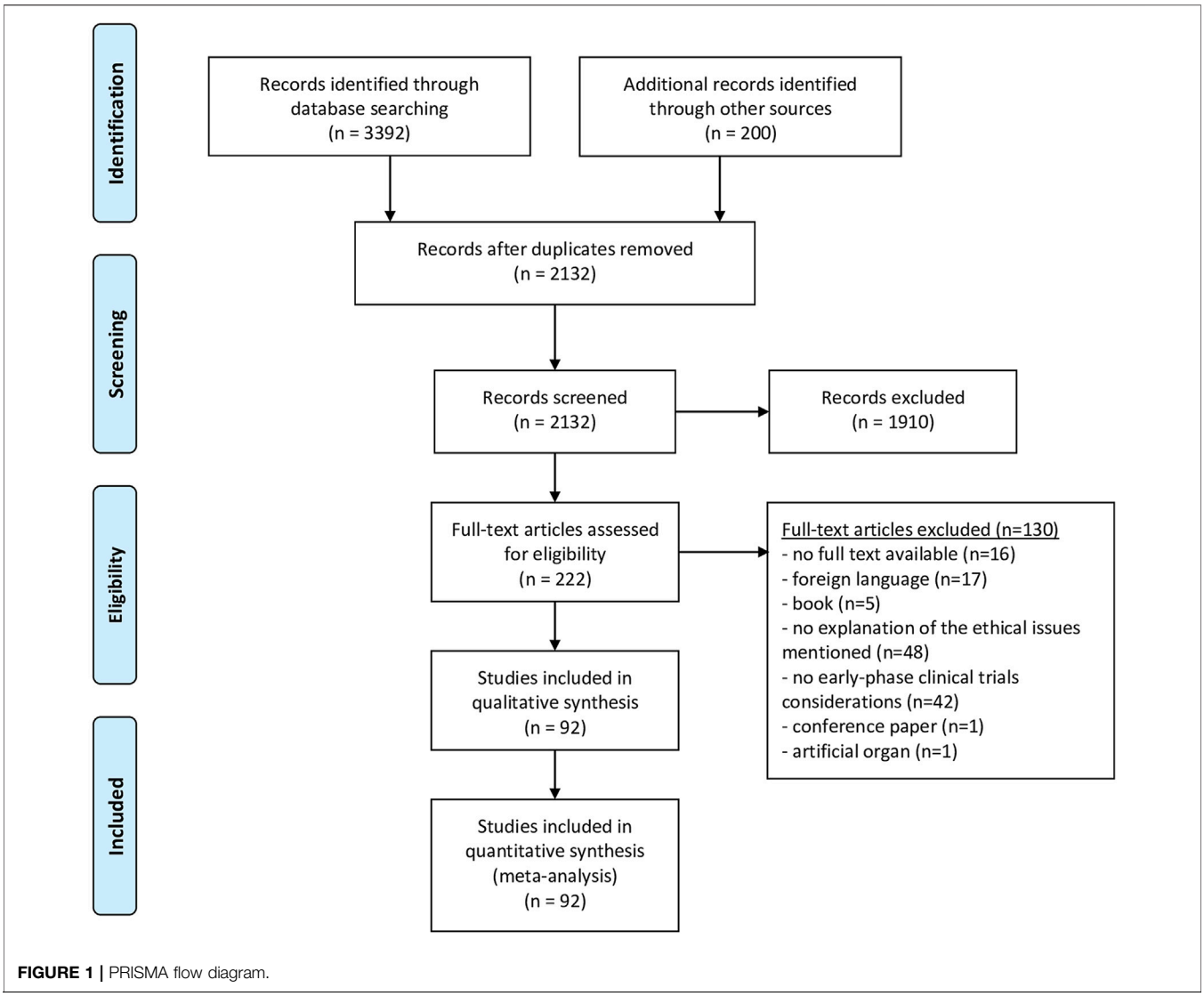


FIGURE 1 | PRISMA flow diagram.

it would be difficult for research ethics review committees (RECs) to evaluate the ethical acceptability of early-phase clinical trials of bio-artificial organs. Therefore, guidance on the safe and responsible design and conduct of early-phase clinical trials of transplantable bio-artificial organs should be developed.

In this systematic review we examined the published literature on early-phase clinical trials in the adjacent fields of regenerative medicine, including tissue-engineering, 3D bioprinting, cell-based therapy, organoid technology and synthetic biology. We undertook a thematic analysis of relevant ethical points to consider for early-phase clinical trials of transplantable bio-artificial organs. The results of our systematic review and thematic analysis will be valuable for researchers, research ethics review boards, policy makers and clinicians with an interest in regenerative medicine and involved in the translation of bio-artificial organs for clinical transplantation. However, above we hope our analysis will contribute to the preparation of robust guidelines and recommendations in this highly complex and evolving field.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Articles in the fields of regenerative medicine, tissue-engineering, 3D printing, cell-based therapy, organoid technology, synthetic biology and bio-artificial organs describing ethical points to consider (issues, questions, or challenges) for early-phase clinical trials	Letters to the editor Editorials Opinion articles Non-biological medical devices Engineering a specific tissue only for research purpose Describing ethical issues associated with pre-clinical research only

METHODS

We performed a systematic review of the literature, following the PRISMA statement, as far as applicable (see **Supplementary Materials**). The review protocol has not been published or registered. The authors (DJ, EB and EM) developed the search strategy in consultation with a university librarian. We conducted

TABLE 2 | Included articles.

Author	Title	Year	Journal	Research field
Aalto-Setälä et al.	Obtaining consent for future research with induced pluripotent cells: opportunities and challenges	2009	PLoS Biology	Cell-Based Therapy
Afshar et al.	Ethics of research on stem cells and regenerative medicine: ethical guidelines in the Islamic Republic of Iran	2020	Stem Cell Research & Therapy	Regenerative Medicine
No Author	European Medicines Agency, CAR Secretariat and US Food and Drug Administration	2011	Regenerative Medicine	Cell-Based Therapy
Apatoff et al.	Autologous stem cell therapy for inherited and acquired retinal disease	2017	Regenerative Medicine	Cell-Based Therapy
Attico et al.	Approaches for effective clinical application of stem cell transplantation	2018	Current Transplantation Reports	Cell-Based Therapy
Baker et al.	Ethical considerations in Tissue Engineering Research: case Studies in Translation	2016	Methods	Tissue Engineering
Bhangra et al.	Using Stem Cells to Grow Artificial Tissue for Peripheral Nerve Repair	2016	Stem Cells International	Cell-Based Therapy
Bliss et al.	Optimizing the Success of Cell Transplantation Therapy for stroke	2010	Neurobiology of Disease	Cell-Based Therapy
Bobba et al.	The current state of stem cell therapy for ocular disease	2018	Experimental Eye Research	Cell-Based Therapy
Bredenoord et al.	Human tissues in a dish: The research and ethical implication of organoid technology	2017	Science	Organoid Transplantation
Brignier et al.	Embryonic and adult stem cell therapy	2010	Journal of Allergy and Clinical Immunology	Cell-Based Therapy
Chan.	Current and emerging global themes in the bioethics of regenerative medicine: the tangled web of stem cell translation	2017	Regenerative Medicine	Cell-Based Therapy
Chan.	Research Translation and Emerging Health Technologies: Synthetic Biology and Beyond	2018	Health Care Anal	Synthetic Biology
Chung	Stem-cell-based Therapy in the field of urology: a review of stem cell basic science, clinical application and future directions in the treatment of various sexual and urinary conditions	2015	Expert Opinion in Biological Therapy	Cell-Based Therapy
Coombe et al.	Current approaches in regenerative medicine for the treatment of diabetes: introducing CRISPR/CAS9 technology and the case for non-embryonic stem cell therapy	2018	American Journal Stem Cells	Cell-Based Therapy
Court et al.	Bioartificial liver support devices: historical perspectives	2003	ANZ Journal of Surgery	Bioengineered Organs
Daley et al.	Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines	2016	Stem Cell Reports	Cell-Based Therapy
Davis et al.	The role of Stem Cells for Reconstructing the Lower Urinary Tracts	2018	Current Stem cell Research & Therapy	Cell-Based Therapy
Davidson.	Brave Pioneers or Clinical Cowboys?	2010	Cell Stem Cell	Cell-Based Therapy
De Vries et al.	Ethical Aspects of Tissue Engineering: A Review	2008	Tissue engineering	Tissue Engineering
De Windt et al.	Ethics in musculoskeletal regenerative medicine; guidance in choosing the appropriate comparator in clinical trials	2019	Osteoarthritis and Cartilage	Regenerative Medicine
Fears et al.	Inclusivity and diversity: Integrating international perspectives on stem cell challenges and potential	2021	Stem Cell Reports	Cell-Based Therapy
Fung et al.	Responsible Translation of Stem Cell Research: An Assessment of Clinical Trial Registration and Publications	2017	Stem Cell Reports	Cell-Based Therapy
Garg et al.	Stem Cell Therapies in Retinal Disorders	2017	Cells	Cell-Based Therapy
Genske et al.	Rethinking risk assessment for emerging technology first-in-human trials	2016	Medicine, Health Care and Philosophy	Synthetic Biology
Giancola et al.	Cell therapy: cGMP Facilities and manufacturing	2012	Muscles, Ligaments and Tendons Journal	Cell-Based Therapy
Gilbert et al.	Print Me an Organ? Ethical and Regulatory Issues Emerging from 3D Bioprinting in Medicine	2018	Science and Engineering Ethics	3D Bioprinting
Goula et al.	Advanced Therapy Medicinal Products Challenges and Perspectives in Regenerative Medicine	2020	Journal of Clinical Medicine Research	Regenerative Medicine
Haake et al.	Concise Review: Towards the Clinical Translation of Induced Pluripotent Stem Cell-Derived Blood Cells- *Ready for Take-Off*	2019	Stem Cells Translational Medicine	Cell-Based Therapy
Habets et al.	The inherent ethical challenge of first-in-human pluripotent stem cell trials	2014	Regenerative Medicine	Cell-Based Therapy
Hara et al.	New Governmental Regulatory System for Stem Cell-Based Therapies in Japan	2014	Therapeutic Innovation & Regulatory Science	Cell-Based Therapy
Hayakawa et al.	A study on ensuring the quality and safety of pharmaceuticals and medical devices derived from the processing of allogeneic human somatic stem cells	2015	Regenerative Therapy	Cell-Based Therapy
Hildebrandt	Horses for courses: an approach to the qualification of clinical trial sites and investigators in ATMPs	2020	Drug Discovery Today	Cell-Based Therapy
Hug	Understanding voluntariness of consent in first-in-human cell therapy trials	2020	Regenerative Medicine	Cell-Based Therapy
Hyun	Allowing innovative Stem Cell-Based Therapies Outside of Clinical Trials: Ethical and Policy Challenges	2010	Journal of Law, Medicine and Ethics	Cell-Based Therapy

(Continued on following page)

TABLE 2 | (*Continued*) Included articles.

Author	Title	Year	Journal	Research field
Hyun et al.	New ISSCR Guidelines Underscore Major Principles for Responsible Translational Stem Cell Research	2008	Cell Stem Cell	Cell-Based Therapy
Kim et al.	Report of the International Stem Cell Banking Initiative Workshop Activity: Current Hurdles and Progress in Seed-Stock Banking of Human Pluripotent Stem cells	2017	Stem Cells Translational Medicine	Cell-Based Therapy
King et al.	Ethical issues in stem cell research and therapy	2014	Stem Cell Research & Therapy	Cell-Based Therapy
Kleiderman et al.	Overcoming barriers to facilitate the regulation of multi-centre regenerative medicine clinical trials	2018	Stem Cell Research & Therapy	Regenerative Medicine
Knoepfler	From Bench to FDA to Bedside: US Regulatory Trends for New Stem Cell Therapies	2015	Advanced Drug Delivery Reviews	Cell-Based Therapy
Kusunose et al.	Informed consent in clinical trials using stem cells: Suggestions and points of attention from informed consent training workshops in Japan	2015	South African Journal of Bioethics and Law	Cell-Based Therapy
Lederer et al.	Neural stem cells: mechanisms of fate specification and nuclear reprogramming in regenerative medicine	2008	Biotechnology Journal	Cell-Based Therapy
Lee et al.	Conditional approvals for autologous stem cell-based interventions	2018	Perspectives in Biology and Medicine	Cell-Based Therapy
Levin et al.	Special Commentary: early Clinical Development of Cell Replacement Therapy: Considerations for the National Eye Institute Audacious Goals Initiative	2017	Ophthalmology	Cell-Based Therapy
Lim et al.	Whole Organ and Tissue Reconstruction in Thoracic Regenerative Surgery	2013	Mayo clinic Proceedings	Tissue Engineering
Liras	Future research and therapeutic applications of human stem cells: general, regulatory, and bioethical aspects	2010	Journal of translational Medicine	Cell-Based Therapy
Liu et al.	Advances in Pluripotent Stem Cells: History, Mechanisms, Technologies, And Applications§	2020	Stem Cell Reviews and Reports	Cell-Based Therapy
Lomax et al.	Return of results in translational iPS cell research: considerations for donor informed consent	2013	Stem Cell Research & Therapy	Cell-Based Therapy
Lomax et al.	Regulated, reliable and reputable: Protect patients with uniform standards for stem cell treatments	2020	Stem Cells Translational Medicine	Cell-Based Therapy
Lowenthal et al.	Specimen Collection for Induced Pluripotent Stem Cell Research: Harmonizing the Approach to Informed Consent	2012	Stem Cells Translational Medicine	Cell-Based Therapy
Lowenthal et al.	Ethics and Policy Issues for Stem Cell Research and Pulmonary Medicine	2014	Chest	Cell-Based Therapy
Lu et al.	Tissue Engineered Constructs: Perspectives on Clinical Translation	2015	Annals of Biomedical Engineering	Tissue Engineering
Madariaga et al.	Bioengineering Kidneys for Transplantation	2014	Seminars in Nephrology	Bioengineered Organs
Maekawa et al.	Development of Novel Advanced Cell and Gene Therapy and GMP-Controlled Cell Processing	2005	Japan Medical Association journal	Cell-Based Therapy
Main et al.	Managing the potential and pitfalls during clinical translation of emerging stem cell therapies	2014	Clinical and Translational Medicine	Cell-Based Therapy
Masuda et al.	New Challenges for Intervertebral Disc Treatment Using Regenerative Medicine	2010	Tissue engineering	Regenerative Medicine
Moradi et al.	Research and therapy with induced pluripotent stem cells (iPSCs): Social, legal and ethical considerations	2019	Stem Cell Research & Therapy	Cell-Based Therapy
Nagamura	The Importance of Recruiting a Diverse Population for Stem Cell Clinical Trials	2016	Current Stem Cell Reports	Cell-Based Therapy
Naghieh et al.	Biofabrication Strategies for Musculoskeletal Disorders: Evolution towards Clinical Application	2021	Bioengineering	3D Bioprinting
Nagpal et al.	PERSPECTIVES: Stroke survivors' views on the design of an early-phase cell therapy trial for patients with chronic ischaemic stroke	2019	Health Expectations	Cell-Based Therapy
Neri	Genetic Stability of Mesenchymal Stromal Cells for Regenerative Medicine Applications: A Fundamental Biosafety Aspect	2019	International Journal of Molecular Sciences	Cell-Based Therapy
Niemansburg et al.	Participant selection for preventive Regenerative Medicine trials: ethical challenges of selecting individuals at risk	2015	Journal of Medical ethics	Regenerative Medicine
Niemansburg et al.	Regenerative medicine interventions for orthopedic disorders: ethical issues in the translation into patient	2013	Regenerative Medicine	Regenerative Medicine
Niemansburg et al.	Ethical implications of regenerative medicine in orthopedics: an empirical study with surgeons and scientists in the field	2014	The spine Journal	Regenerative Medicine
O'Donnell et al.	Beyond the Present Constraints That Prevent a Wide Spread of Tissue Engineering and Regenerative Medicine Approaches	2019	Frontiers Bioengineering and Biotechnology	Regenerative Medicine
Oerlemans et al.	Regenerative Urology Clinical Trials: An Ethical Assessment of Road Blocks and Solution	2013	Tissue engineering	Tissue Engineering
Oerlemans et al.	Towards a Richer Debate on Tissue Engineering: A Consideration on the Basis of NEST-Ethics	2012	Science Engineering Ethics	Tissue Engineering

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TABLE 2 | (*Continued*) Included articles.

Author	Title	Year	Journal	Research field
O'Keefe	American Society for Bone and Mineral Research- Orthopaedic Research Society Joint Task Force Report on Cell-Based Therapies	2020	Journal of Bone and Mineral Research	Cell-Based Therapy
Otto et al.	Ethical considerations in the translation of biofabrication technologies into clinic and society	2016	Biofabrication	3D Bioprinting
Parent et al.	The ethics of testing and research of manufactured organs on brain-dead/recently deceased subjects	2019	Journal of Medical Ethics	Bioengineered Organs
Patuzzo et al.	3D bioprinting Technology: Scientific Aspects and Ethical Issues	2018	Science and Engineering Ethics	3D Bioprinting
Schneemann et al.	Ethical challenges for pediatric liver organoid transplantation	2020	Science Translational Medicine	Organoid Transplantation
Scopetti et al.	Mesenchymal stem cells in neurodegenerative diseases: Opinion review on ethical dilemmas	2020	World Journal of Stem Cells	Cell-Based Therapy
Sekar et al.	Current standards and ethical landscape of engineered issues—3D bioprinting perspective	2021	Journal of Tissue Engineering	3D Bioprinting
Seok et al.	A Personalized 3D-Printed Model for Obtaining Informed Consent Process for Thyroid Surgery: A Randomized Clinical Study Using a Deep Learning Approach with Mesh-Type 3D Modeling	2021	Journal of Personalized Medicine	3D Bioprinting
Shineha et al.	A Comparative Analysis of Attitudes on Communication Toward Stem Cell Research and Regenerative Medicine Between the Public and the Scientific Community	2018	Stem Cells Translational Medicine	Regenerative Medicine
Sievert et al.	Tissue Engineering for the Lower Urinary Tract: A Review of a State of the Art Approach	2007	European Urology	Tissue Engineering
Smith et al.	Challenging misinformation and engaging patients: characterizing a regenerative medicine consult service	2020	Regenerative Medicine	Regenerative Medicine
Sniecinski et al.	Emerging stem cell based strategies for treatment of childhood disease	2018	Transfusion and Apheresis Science	Cell-Based Therapy
Stegemann et al.	Cell therapy for bone repair: narrowing the gap between vision and practice	2014	European Cells and Materials	Cell-based therapy
Sugarman and Bredenoord	Real-time ethics engagement in biomedical research	2020	EMBO reports	Organoid transplantation
Sutherland and Mayer	Ethical and Regulatory Issues Concerning Engineered Tissues for Congenital Heart Repair	2003	Thoracic and Cardiovascular Surgery	Tissue Engineering
Takashima et al.	Lessons for reviewing clinical trials using induced pluripotent stem cells: examining the case of a first-in-human trial for age-related macular degeneration	2018	Regenerative Medicine	Cell-Based Therapy
Taylor et al.	Ethics of bioengineering organs and tissues	2014	Expert Opinion on Biological Therapy	Tissue Engineering
Trommelmans et al.	Ethical reflections on clinical trials with human tissue engineered products	2008	Journal of Medical Ethics	Tissue Engineering
Trommelmans et al.	Informing participants in clinical trials with *ex vivo* human tissue-engineered products: what to tell and how to tell it?	2008	Journal Tissue Engineering Regenerative Medicine	Tissue Engineering
Trommelmans et al.	An Exploratory Survey on the Views of European Tissue Engineers Concerning the Ethical Issues of Tissue Engineering Research	2009	Tissue Engineering	Tissue Engineering
Trommelmans et al.	Is tissue engineering a new paradigm in medicine? Consequences for the ethical evaluation of tissue engineering research	2009	Medical Health Care and Philosophy	Tissue Engineering
Tsang	Legal and ethical status of stem cells as medicinal products	2005	Advanced Drug Delivery	Cell-Based Therapy
Vijayavenkataraman et al.	3D bioprinting - An Ethical, Legal and Social Aspects (ELSA) framework	2016	Bioprinting	3D Bioprinting
Zamborsky et al.	Regenerative Medicine in Orthopaedics and Trauma: Challenges, Regulation and Ethical Issues	2018	Orthopaedics and Trauma	Cell-Based Therapy
Zocchi et al.	Regulatory, ethical, and technical considerations on regenerative technologies and adipose-derived mesenchymal stem cells	2019	European Journal of Plastic Surgery	Regenerative Medicine

[a]*Author name stated in **bold**: ethical considerations for early-phase regenerative trials are elaborately discussed in the paper.*

the literature search in September 2021, using seven scientific databases: PubMed, EMBASE, Medline, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and PsycINFO. An additional systematic search of the grey literature (i.e., relevant literature published outside of commercial or academic publishing) was conducted in Google Scholar. Search strings were constructed by keywords and their truncation, and relevant database-specific subjects headings [MeSH terms] (see **Supplementary Materials**). Due to language barriers, only articles in English or Dutch were considered for full-text analysis. We screened all titles and abstracts until September 2021 with no restriction for date of publication. Only outdated research guidelines that have subsequently been updated were not included. Based on title and abstract, articles that fulfilled the inclusion criteria were selected. Two researches independently carried out the selection (DJ and EB). Articles were discussed in case of differences between DJ and EB in the selection to come to a consensus. Full-texts were screened by DJ. The articles that did

FIGURE 2 | Summary of the content of the article.

not meet the inclusion criteria during full-text screening, were excluded. Finally, the reference lists of the articles selected for full-text screening were checked for scientific articles or other documents that may be relevant and included if inclusion criteria were fulfilled (by DJ) (see **Figure 1**).

Inclusion and Exclusion Criteria

The inclusion criteria of this systematic review were as follows: articles in the adjacent fields of regenerative medicine, tissue-engineering, 3D bioprinting, cell-based therapy, organoid technology, synthetic biology, and bio-artificial organs describing ethical points to consider (issues, questions or challenges) for early-phase clinical trials. Letters to the editor, editorials and opinion articles were included as non-research manuscripts. Articles that only discussed pre-clinical research were excluded from our sample. For reasons of feasibility, articles discussing transplantation of non-biological medical devices instead of biological materials (e.g., pacemakers, blood glucose monitors, insulin pumps, or cardioverter defibrators) and articles discussing engineering of specific tissues for purposes other than organ transplantation (e.g., engineering of brains and reproductive organs for research purposes) were excluded. Finally, conference abstracts and articles were excluded (**Table 1**).

Analyses and Syntheses

The method of qualitative content analysis was employed (13). Qualitative content analysis is an inductive (bottom-up) approach to categorize ethical considerations and to develop themes within a coding frame. One researcher (DJ) conducted the analyses. Firstly, codes were assigned to all the considerations mentioned in each publication. Secondly, themes (e.g., patient selection) were created out of these codes by DJ. Thirdly, DJ, EM and EB discussed whether the created words describing the themes were representative of the codes until agreement was reached. Finally, a coding framework was built out of the identified themes. The coding framework was used to systematically keep track of ethical considerations mentioned per article.

Qualitative Content Analysis

We did not conduct a quality appraisal procedure, as there are no suitable criteria for appraisal of the quality of the literature included. This is a well-documented limitation of systematic reviews of (bio) ethical literature (14, 15).

RESULTS

The selection procedure is presented in a PRISMA Flow diagram (**Figure 1**). The search produced 2132 hits, of which 222 were deemed eligible on the basis of title and abstract, and 92 articles were included after reference checking and full-text screening. The publication dates ranged from January 2003 to March 2021 (**Table 2**).

Themes

Six themes were identified: cell source, risk-benefit assessment, patient selection, trial design, informed consent, and oversight and accountability. The content of the article referring to the six identified ethical themes is summarized in **Figure 2**.

Research Fields

These six themes were found in seven different research fields (**Table 2**). The largest body of literature focusses on ethical considerations around early-phase trials in the field of cell-based therapy; 55 articles are published in this field, and the authoritative ISSCR guidelines are widely used (12, 16–26). There

TABLE 3 | Points to consider in relation to cell sources.

Cell source	Risks and benefits	Points to consider
Xenogeneic cells or tissue	Medical risks: Risk of zoonoses Individuals could object to use cells derived from animals on religious or socio-cultural grounds	- The use of animal cells should be minimized - Components of animal origin should be replaced with human or chemically defined components whenever possible - The use of viral transcription factor genes, retroviruses or pathogenic agents should be minimized - Quality control systems, standard operating procedures (SOPs) and Good Manufacturing Practice (GMP) should be used
Autologous cells	Medical benefits: No immunological rejection	- It may not be possible to harvest sufficient numbers of patients' cells - The production cost could be high - The timeframe for cell harvest could be insufficient for timely treatment - Extra surgical interventions for participants could be necessary - Quality control systems, SOPs and GMP should be used
Allogeneic donor cells	Medical risks: Immunological rejection and disease transmission Relational issues: Ownership and privacy issues Some donors may not want their cells to become an integral, growing part of another person.	- Adequate donor consent should be obtained in a process that includes discussion of: aim of the research, return of research results, incidental findings, possibilities for withdrawal of consent, potential future research - Additional safeguards should be adopted to protect personal data - A policy should be developed on whether and how incidental findings of donor cell (genetic) screening should be returned to the cell donors and/or their relatives - Records on medical and family history of the donor of the cells should be obtained periodically - Quality control systems, SOPs and GMP should be used
Highly manipulated and/or genetic modified cells	Medical risks: Unexpected behavior of cells or tissue (e.g., tumor formation, epigenetic or genetic instability)	- Strong pre-clinical data (of the safety and functions of the cells and or tissues) should be provided - The use of manipulated cells should be minimized - Participants should be monitored for a long time - Researchers should adhere to cell processing and manufacturing protocols - Quality control systems, SOPs and GMP should be used

is less literature on ethical aspects of early-phase clinical trials in the field of 3D bioprinting, and organoid transplantation; seven articles were published on 3D bioprinting, three articles on bio-artificial organs, and two on organoid transplantation. Six empirical studies using questionnaires and interviews to investigate patients' and professionals' views on ethical considerations in early-phase clinical trials, were included. Seven papers were published in surgical journals.

Theme 1: Cell Sources

53 out of 92 articles mention ethical considerations related to the sources of cells used to generate complex tissue-engineered products such as bio-artificial or 3D bio-printed organs for transplantation into humans (9, 12, 16–24, 26–68). There are four types of cell sources: 1) xenogeneic cells, 2) autologous, 3) allogeneic donor, and 4) highly manipulated or/and genetically modified cells in humans, each with their own sets of ethical considerations (**Table 3**).

Firstly, xenogeneic cells are associated with a risk of zoonosis (17, 20, 38, 47–49). For instance, issues related to the transmission of the infectious porcine retrovirus (PERV) from pig to human (69). Potential future patients could also reject the use of these cells to generate bio-artificial organs on religious grounds or for socio-cultural reasons (e.g., to protect animal rights/welfare) (33, 38, 48, 50, 52), even if their religious leaders take a more moderate stance (33). According to the literature, using these cells for transplantation into humans should be minimized as much as possible (12, 17, 38).

Secondly, the use of autologous cells (cells taken from the patient, who is both the donor and recipient) will make immunosuppressive therapy unnecessary (9, 16, 27–29, 33, 38–45, 68), and is perceived to carry fewer risks than the use of other cell types (33). However, challenges include the high production costs (29, 57, 70), extra surgical interventions for participants (50), the time required for their production (29, 40, 50, 57, 70), and the difficulty of standardizing manufacturing procedures (4057, 70).

Thirdly, besides the medical risks of transplanting allogeneic donor cell (cells taken from another human being), for example developing immunological problems, use of these cells also raises relational issues (20, 27, 30, 38, 41, 43, 63, 71, 72). Relational issues include questions such as: Who is the owner of the human cells once it is separated from the body (30,38,41,43)?; Can cells from the human body be subjected to laws regarding property rights (38,43)?, and; To what extent can the donor's privacy and confidentiality be ensured by adopting additional measures (e.g., pseudonymisation) (20, 27, 30, 38, 41, 43, 63, 71, 72). Removing the donor's personal information is

often not desirable, because subsequent research may necessitate ongoing access to the information about the cell donor's health status requiring personal data of the donor (e.g., their name and/or address) (20,52). Further, some donors may not want their cells to become an integral, growing part of another person (12, 20, 32, 52, 73). In addition, in the course of donor cell (genetic) screening, researchers should develop a policy on whether and how incidental findings (e.g., genetic risk) will be returned to the donors and/or their relatives (12, 20, 52, 63). Donors might consider their privacy violated if scientists know their future susceptibility to genetic disorders (52). Researchers should obtain an adequate informed consent from donors to respect their autonomy (12, 20, 22, 27, 28, 34, 38, 43, 45, 52, 57, 63, 67, 72–76), and give them some degree of insight and perhaps control over the use of donated materials by informing them about the types of incidental findings they wish to receive, future commercial applications, individualized research and therapeutic uses (12, 20, 27, 38, 43, 52, 72, 76), for instance by maintaining an ongoing dialogue with the donors (76). Moreover, to safeguard the health of the recipient over the years, it may be necessary to periodically obtain records on the medical and family history of the cell donor to monitor potential health risks, such as long-term immunological or tumorigenic reactions (12, 19, 20, 22, 27, 28, 32, 34, 35, 39, 41, 49, 51–53).

Lastly, the use of highly manipulated cells (i.e., cells of which the biological nature or structural function has been altered during the manufacturing process) and/or genetically modified cells raises safety concerns, and requires more quality controls to avoid undesired events (9, 12, 18, 20–23, 27, 28, 33, 35, 40, 50, 61, 63). For instance, these cells could have an increased risk of being tumorigenic, genetically unstable or toxic (12, 18, 35). Therefore, some authors recommend avoiding the use of manipulated cells whenever possible (e.g., tumor formation, epigenetic or genetic instability) (9, 12, 18, 20, 22). However, cell manipulation and/or genetic modification might be useful and even necessary for the generation of a bio-artificial organ (e.g., to repair disease-causing mutations) (20). Cells used in tissue-engineered products are often differentiated *in vitro* prior to being combined with a scaffolding material, for example collagen, to form artificial tissue, therefore tissue-engineered products are mostly classified as more than minimally manipulated (18).

Theme 2: Risk-Benefit Assessment

One of the conditions for ethically responsible clinical research is a favorable risk-benefit ratio (**Table 4**). This means that the risks and burdens of trial participation must be outweighed by the expected scientific or social value and the (potential) benefits

TABLE 4 | Points to consider in relation to risk-benefit assessment.

Points to consider in relation to risk-benefit assessment
- Researchers should provide robust pre-clinical data (i.e. safety and efficacy of the product should be rigorously demonstrated in laboratory tests and animal models)
- Personalization of the bio-artificial organ makes the product variable; therefore, the quality control and safety requirements of mass manufacturing do not apply
- Researchers should monitor and follow up participants for a long time after the study
- Efforts should be made not only to minimize the risks, but also to maximize the scientific and social value of a trial, in order to improve the risk-benefit ratio
- Clinical teams who conduct clinical trials of bioartificial organs should have experience with regenerative medicine technologies and with post-trial follow-up care

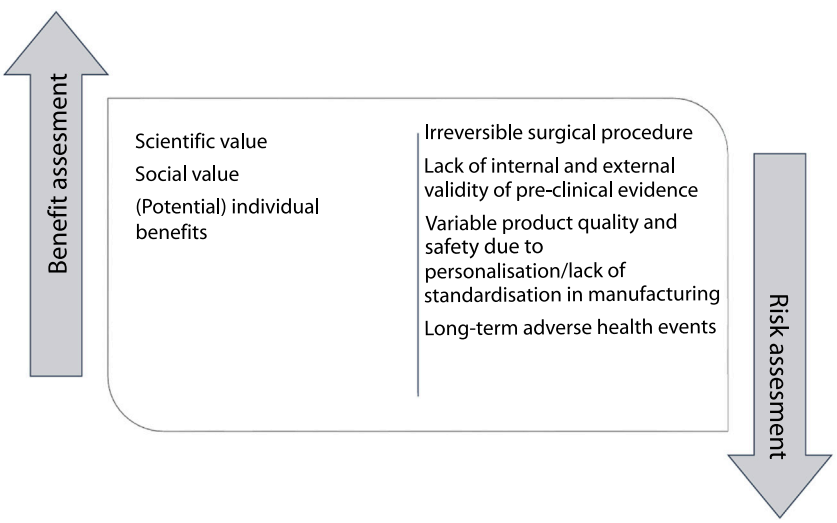

FIGURE 3 | Risk-benefit assessment.

for individual participants (12, 16, 21, 23, 24, 28, 29, 32, 34, 37, 45, 50, 53, 57, 64, 66–69, 77, 78) (**Figure 3**). The requirement of a favorable risk-benefit is difficult to meet in early-phase research, because the potential direct benefits to individual research participants in these trials are limited and uncertain (69). In the absence of direct medical benefit, justification of exposing individual research participants to potential harms in early-phase clinical trials is sought in expected scientific and/or social value (24, 30, 50, 66, 79). These include the benefits gained for science and society: generalizable knowledge and health gains for future patients (50). Knowledge of the working mechanism and the interaction of a regenerative medicine technology with the body, gathered in early-phase clinical trials, is necessary to move these technologies to the next clinical phase of clinical development (24, 30, 50, 66, 69). The anticipated social value of bio-artificial organs is potentially high, as they are intended as cures for patients with end-stage organ failure and might be more cost-effective than existing organ replacement therapies (66). At this stage, however, the social value is highly uncertain.

Transplanting regenerative medicine into human recipients requires an irreversible (innovative) surgical procedure, which is associated with risks of harms and complications. Once the regenerative product is implanted in the body, it may not be possible to completely remove it (50). For instance, surgical removal of the product will be impractical or associated with greater risks [i.e., infections or complications of anesthesia (33)], and there will be some irreversible changes, such as scarring (50, 70). In addition, unlike non-biological medical devices, the regenerative product will most likely interact and integrate with the rest of the body, which may have uncertain, possibly unforeseeable long-term adverse health events for the recipient (16, 18, 21, 23, 24, 27, 28, 31–34, 37–40, 48, 50, 58, 62, 66–70, 72, 73, 77, 79–86).

When researchers are dealing with uncertain but potentially high risks, they are advised, before undertaking an early-phase clinical trial, to provide preclinical evidence of high internal validity (e.g., through replication) and external validity (e.g. through careful study design) (12, 16, 23, 27–29, 31, 34–37, 43, 46, 49–51, 53, 57, 59, 61, 62, 64–69, 77, 79–81, 84, 85, 87–90). Some argue that large animals should be used, because these animals can better imitate the human anatomy and/or pathology than small animals (1281). Others recommend to involve unbiased third parties to repeat some of the research (69). Even if robust preclinical evidence is available using these strategies, some unexpected risk will inevitably remain, such as unforeseeable long-term adverse health events for the recipient. Researchers should be aware that preclinical evidence from animal models may not correctly predict the duration, function and interaction that occur in a human body (16, 24, 27, 31, 34, 37, 39, 50, 65, 68, 79–82). In addition, the personalization of regenerative medicine makes the product variable, therefore, the quality control and safety requirements of mass manufacturing for external validity do not apply (32, 34, 35, 48). A major benefit of personalization, however, is that it may take away or reduce the need for the use of life-long immunosuppressive therapy for recipients, and avoid well-known side effects such as infections and nephropathy (45, 69).

To detect health risks associated with potential long-term adverse events, such as genetic instability, undirected or uncontrolled cell growth, research participants must be carefully monitored (16, 19, 21, 23, 24, 28, 29, 32, 34, 42, 46, 50, 58, 64, 67–70, 81–83, 85), with long-term follow-up (12, 19, 21, 23, 27–29, 32, 34, 35, 37, 38, 40, 46, 50, 51, 53, 62, 66–70, 73, 79, 81, 85, 87, 91, 92). On the one hand, intensive monitoring may be perceived as reassuring or beneficial by research participants (50, 83, 93). On the other hand, possible life-long follow-up could also be burdensome for participants (50). Given the complexity of tissue-engineered products, clinical teams conducting these studies should have experience with other regenerative medicine therapies (e.g., cell-based therapy) and with post-trial follow-up care (81).

Theme 3: Patient Selection

In the patient selection procedure, a new kind of trade-off has to be made: against enormous benefits stand potentially large risks (e.g., tumour formation). Selection of patients in early-phase clinical trials is a major ethical theme in the literature (12, 27, 31–34, 37, 42, 43, 45, 48, 50, 66, 67, 69, 70, 77, 81, 82, 94). Potential target groups can be divided into 5 categories: healthy individuals, individuals at risk, children, patient with early-stage disease and patients with end-stage disease (**Table 5**). First, it is considered unacceptable to ask 1) healthy individuals for clinical studies of regenerative medicine applications, especially of tissue-engineered products which are designed to function in the body of the recipient, given the high risks (34) and lack of benefit (32,34). Also, when regenerative applications are personalized (i.e., composed, in part, of patient-derived material), the only eligible recipient will likely be the patient themselves (48). Second, the scholarly literature contains arguments in favour of the selection of 2) individuals at risks, with 3) early-stage disease (31, 37, 48, 50, 69, 77, 81, 94), and 4) children (37, 38, 48, 78). These individuals are relatively healthy, if a regenerative medicine application is used into one of these groups, it may help 1) to achieve more health benefit, and 2) to prevent (long-term) severe complications (31, 37, 48, 50, 69, 77, 81, 94). On the other hand, it is uncertain whether these individuals, who may not have developed or will develop symptoms at all, will indeed come to suffer from end-stage organ failure at all and be in need for a transplant. At the same time, as the procedure is novel, risky and invasive, their current physical condition could worsen significantly (50). Lastly, based on the literature, the most eligible patients for early-phase clinical trials are patients who have reached the 5) end-stage of their disease (12, 27, 31, 33, 34, 42, 43, 45, 48, 66, 69, 70, 81, 82, 94). These patients no (or no longer) have effective or suitable treatment options at the time of enrolment and may be facing limited life expectancy (12, 27, 31, 33, 34, 42, 43, 45, 48, 66, 69, 70, 81, 82, 94). When serious complications occur, they may have less to lose than healthy individuals or patients with stable disease (, 12, 32–34, 48, 50, 66, 67, 77, 94). Also, for patients who have reached the end-stage of their disease, a bio-artificial organ could potentially be associated with greater medical benefits.

TABLE 5 | Points to consider in relation to patient selection.

Suggested research participants for early-phase clinical trials	Reasons for and against selection
Healthy individuals	For - Healthy individuals are most resilient to physical harms (thus, harms are minimized) Against - No clinical value for the participant - Risks are too high
Individuals at risk - No symptoms - Risk factors for disease	For - Less damage to the body from disease or disease-related complications, which could lead to better health outcomes compared to more advanced disease stages - Disease can be prevented Against - Risks could be too high - Unnecessary treatment (participants may not develop the disease)
Early-stage patients - Mild to moderate disease - Medically controlled disease	For - Less damage to the body from disease or disease-related complications, which could lead to better health outcomes compared to more advanced disease stages Against - Risks are too high - Alternative treatment options may be available - Treatment could worsen the disease
Children Diagnosed with the disease	For - Less damage to the body - Serious complications can be prevented - Benefit can be enjoyed the longest Against - Risks may be too high - Alternative treatment options may be available - The disease may not proceed to advanced stages - Long-term follow-up may be burdensome for the participants - Children are unable to provide informed consent
Advanced-stage/end-stage patients - Severe disease - Unstable disease - No or no longer a suitable treatment option available	For - There is an unmet medical need, as effective treatment options are not or no longer available - Potential for medical benefit from participation in the trial - Less to lose when serious complications occur Against - The body is already damaged; this damage might be irreparable - Treatment could worsen the disease

Theme 4: Trial Design

Intervention

Six articles in our sample argued that the traditional model for clinical translation—phases I to phases II, III and IV, in which toxicity and/or efficacy of new drugs are tested—may not be suitable for clinical trials of transplantable applications of regenerative medicine in humans (17, 24, 37, 38, 62, 81). Schneemann et al. proposed that early-phase transplantation trials should combine safety and efficacy outcomes in their trial design to maximise participants' chances at obtaining medical benefit (37). Schneemann et al. suggested participants should be given a "dose" (in the context of bio-artificial organs: a certain quantity of engineered tissue) that is expected to be therapeutic, and efficacy should be added as an outcome measure (37). Combined safety and efficacy trials are associated with lower risks and costs than traditional studies, which could have positive effects on the likelihood of successful clinical development and help prevent promising interventions from failing (17, 81).

Outcomes

In the literature, relevant outcome measures for regenerative medicine clinical trials are discussed in 18 papers (12, 16, 19, 21, 24, 32, 34, 37, 43, 50, 61, 64, 69, 77, 80, 81, 87, 94). Both clinical outcome measures (e.g., survival rate or functional status) and patient-reported outcome measures (PROMs) (e.g., quality of life or experienced symptoms) are considered important (12, 21, 34, 43, 69, 77, 81, 87, 94). In later stages of clinical development and implementation, registries should be set up so that real-world outcome data can be collected to facilitate fair evaluation of the benefits of this technology. In addition, in later stages researchers should not only measure clinical outcome measures, but also PROMs, in order to ensure that new technologies not only affect biological parameters favourably, but also improve patients' lives (37, 69, 94). By giving potential participants the opportunity to define outcome measures, they become active stakeholders in the trial design (37, 69, 78, 94). Further, asking patients to define outcomes could help increase the enrolment of participants in the trial (21, 37, 69, 94).

TABLE 6 | points to consider in relation to trial design.

Trial design	Points to consider
Intervention	- Researchers should set up combined efficacy and safety trials
Outcomes 1. Patient-reported (e.g., quality of life, treatment satisfaction and experienced symptoms) 2. Professional defined (survival rate, functional status and biological parameters)	- Patients should be actively involved in research design as stakeholders - PROMs should be developed for later-phase clinical trials and adopted in trial design
Skills and materials	- Learning curves of surgeons should be corrected for - The effects of the risks associated with surgical procedures on the outcomes of trials should be corrected

Skills and Materials

Authors also suggest to involve surgeons early on in the trial design, since they know what surgical skills and materials are needed to perform surgical trials safely (43, 37, 35, 12, 87). Clinical translation of bio-artificial organs in transplantation may require surgeons to learn new techniques and develop new instruments, therefore minimizing the number of surgeons involved is suggested (**Table 6**). Additionally, different surgeons may learn and refine surgical techniques in different ways, which may (temporarily) affect the outcomes of trials (34, 68, 95). Therefore, it is advised to account for a learning curve and for variability in experience between surgeons (32, 68, 66, 77, 96).

Theme 5: Informed Consent

The ethical requirements of clear informed consent is mentioned frequently in the literature (12, 16, 17, 20–25, 27, 29, 31–34, 37, 38, 43, 45, 50–52, 59, 60, 64–69, 75–77, 79, 81, 83, 85, 89, 90, 92, 93, 97, 98). Valid informed consent requires that participants must be adequately informed about relevant aspects of research participation, including the aim of the procedure, duration of the study, their right to withdraw, and the risks and benefits implications of the trial (**Table 7**). Less often mentioned as an essential component in informed consent is information on the specific composition of the regenerative medicine application, although some authors find it important (33, 81, 83). One survey showed that participants want to be especially informed about issues that could directly affect their health status, such as foreseeable risks, impact on quality of life and safety measures (83). Participants are worried about the risks associated with genetic manipulation of transplantable tissue and about commercialization of cells (33, 83).

Given the lack of evidence on the risks, however, it could be difficult for researchers to provide full disclosure. Rather, participants should be made aware of the uncertainties surrounding the risks and benefits of investigational regenerative medicine technologies (20, 21, 23, 24, 32–34, 65, 72, 81, 98). Participants should be given the opportunity to consult an independent expert (33, 98), and can be offered psychological support (81), or consult a patient advocates (81), to assist them in the decision-making process (33, 60, 81, 83, 84, 98). To minimize "the therapeutic misconception," the (sometimes) mistaken belief among research participants that they will benefit from trial participation, measures should be taken to ensure that research participants are aware of the fact that research is conducted not with the goal of providing them medical treatment, but of obtaining generalizable information (12, 16, 17, 21, 24, 25, 29, 31, 33, 37, 50, 57, 60, 64, 67, 69, 81, 93, 97, 98). Researchers should avoid presenting the potential of the product in an overly optimistic light, overestimating the possible benefits, or giving unrealistic timelines for it to reach the clinic (30). Also, to strengthen comprehension, researchers are advised to present information about the trial not only in writing but also visually (33, 60, 68, 79), encourage patients to ask questions, and avoid scientific jargon by using only simple words or easily understood terminology during the informed consent process (20–22, 29, 31, 57, 69, 93, 98). Researchers may use the teach-back method (98) or even an "exam" or questionnaire (33) to ensure that participants understand the information and make an informed choice (33, 34, 81, 98, 99). Participants must also be aware that

TABLE 7 | points to consider in relation to informed consent.

Procedural	Substantial
- Informed consent from participants with decisional capacity or their legally authorized representative should be obtained - Relevant information about the trial, should also be presented visually - Patients should be encouraged to ask questions - Scientific jargon should be avoided by using only simple words or easily understood terminology - The teach-back method, exams or questionnaires could be used to ensure that participants understand the relevant information - Participants should be encouraged to ask independent experts/patient advocates for advice or assistance in the decision-making process - Participants need to be informed that the intervention is not likely to provide direct medical benefits	- Potential risks, benefits and uncertainties - Composition of the product - The irreversible nature of the intervention - How adverse events will be dealt with - The right and practical difficulty to withdraw - How life-long follow up will be organized - The possibility to consent for partial or complete autopsy in the event of death

participating in a trial might diminish their chances of getting access to future treatment opportunities (21,48,50).

A widely endorsed norm in research ethics is that participants should always have the right to withdraw their consent without negative consequences for the health care they receive. However, for participants in early-phase clinical trials of regenerative medicine technologies, withdrawal may be complicated (34). While it may be possible to withdraw from follow-up, removal of bio-artificial organs (in their entirety) may not be possible. For this reason, the opportunities for withdrawal or lack thereof, and the implications of trial participation for the future health and safety of participants must be discussed beforehand, as part of the informed consent process (34). In particular, research participants should be aware of the need for a long-term follow-up and the possibility of (long-term) adverse events (32, 34, 81). Lastly, some authors suggest informing and asking participants to provide consent for a partial or complete autopsy after their death. Obtaining this information will improve the scientific value of the study and contribute to the safety of future research participants (12).

Theme 6: Oversight and Accountability

The literature suggests that researchers should be especially careful when communicating with patients, physicians, other stakeholders, and the general public about regenerative medicine applications, as overly optimistic expectations might easily arise (17, 21, 22, 25, 29, 46, 52, 57, 62, 64, 67, 69, 78, 80, 81, 86, 90, 93, 94, 100) (**Table 8**). The ways in which research is represented in the media affects societal perspectives and frames policy debates (17, 67, 86, 100). In frontier science, of which research on bio-artificial organ transplantation is an example, researchers might wish or feel compelled to attract media attention to obtain financial support (17). However, they should refrain from inaccurate or incomplete representation of research, as this could ultimately have negative consequences for the advancement of the field and the integrity. For instance, researchers should avoid sharing findings with the press before peer review (17, 62) or could follow the ISSCR guidelines with regard to the conduct, public engagement and accountability of clinical trials (12, 16). In addition, researchers should be open to (international) collaboration between scientists, ethicists and clinicians (18, 22, 23, 25, 28, 35, 36, 38, 39, 41, 45, 50, 54, 57, 63–65, 73, 77, 81, 84–86, 89, 96, 100–102) and the conduct of interdisciplinary dialogues, involving scientists, such as engineers and biologists, but also patients, clinicians, policy makers, industry partners, ethicists, and the general public (17, 24, 29, 35, 37, 38, 46, 55, 64, 73, 80, 81, 84, 86, 90, 93) to encourage responsible innovation, and build and maintain long-term trust in research and the development of regenerative medicine applications. Adopting a similar strategy around bio-artificial organ technologies is highly desirable.

All research involving clinical applications of regenerative medicine must be subjected to independent RECs for approval. The main task of these oversight bodies is to ensure ethical conduct of clinical research and to protect human research participants. However, it is uncertain whether existing RECs have sufficient specific technical and clinical expertise in the fields of both organ transplantation and regenerative medicine to be able to evaluate the risks associated with bio-artificial organ transplantation trials. Multiple authors have proposed to set up specialized RECs or advisory boards with experts from various backgrounds for the evaluation of clinical trials of regenerative medicine technologies (9, 16, 19, 20, 22, 24, 28, 29, 32, 45, 46, 62–65, 67, 69, 77, 78, 80, 85, 92). These experts could assist RECs in assessing the scientific underpinnings of the clinical trial protocols and the risks of abnormal product function and proliferation (16). According to some, such specialized RECs should ideally also include lay people (21, 80). Moreover, authors recommend providing education opportunities for surgeons, researchers, nurses and ethicist in training, on the ethical aspects related to ATMPs (9, 20–22, 29, 36, 40, 45, 64, 65, 69, 70, 73, 77, 87, 92, 93).

Researchers should pre-register clinical trials and publish understandable and complete data on each step along the research pathway regardless of whether the data is positive, negative or inconclusive (12, 16, 24, 28, 29, 69, 80, 81). Being transparent about data could also inspire other researchers to go into new research directions (69).

TABLE 8 | points to consider in relation to oversight and accountability.

Oversight and accountability	Points to consider
Public awareness and patient engagement	- The information should be publicly available - Interdisciplinary dialogues between scientists, ethicists, patients, policy-makers, clinicians, industry partners, and the general public should be stimulated - Dissemination of non-peer-reviewed research results should be avoided - Participants should be referred to patient advocacy groups - Participants should have an active role in research (e.g., as active stakeholders)
Strengthening of RECs	- RECs should be expanded with experts in regenerative medicine/organ transplantation or set up advisory boards or specialized working groups to support RECs - Patient representatives should be invited to participate in RECs - Educational activities should be organized for RECs
Stimulate (data) transparency, minimize publication bias and diminish selective reporting to create long-term trust in research	- Preclinical researchers should publish negative, positive and inconclusive results - Researchers should pre-register clinical trials - Data monitoring plans should be put in place - Researchers, clinicians and regulators should be stimulated to collaborate - Guidance should be periodically revised

DISCUSSION

In the rapidly evolving field of regenerative medicine, it is important that early-phase clinical trials are performed in a responsible and ethically acceptable way. Such trials can lead to unforeseeable serious harm for research participants, as, for instance, has occurred during early-phase clinical trials of gene therapies in the 1990s, in which research participants have died (103). Yet clinical translation of bio-artificial organ technologies has the potential to make available life-saving therapeutic products to patients suffering from end-stage organ failure and to remove the need of (life-long) immunosuppressive therapy, which has hitherto been a serious disadvantage of organ transplantation.

To our knowledge, this is the first systematic review of the literature on early-phase clinical trials in regenerative medicine, tissue engineering, cell-based therapy, bio-engineered organs, organoid transplantation, synthetic biology, and 3D bioprinting, which summarizes relevant ethical points to consider in early-phase research on transplantable bio-artificial organs. Our review reveals that a significant body of literature exists on ethical considerations around early-phase trials in the field of cell-based therapy. However, there is strikingly little literature on ethical aspects of early-phase clinical trials in the field of 3D bioprinting, and organoid transplantation. There is also little attention for ethical aspects of early-phase regenerative medicine trials in surgery; only seven papers were published in surgical journals. A further noticeable finding in this review was the paucity of empirical ethics research in the scientific fields that were included in the review: only six empirical studies were found (21, 77, 83, 93, 94, 98), three of which focussed on the perceived ethical challenges of regenerative medicine among professionals in the field (21, 77, 83), and three of which focussed on patients' perspectives (93, 94, 98) on ethical considerations for early-phase clinical regenerative trials. Yet insight in patients' perspectives is essential to assessing the social value of new technologies and to determining the conditions under which it should be offered to patients.

In total, six themes were identified in the literature: cell source, risk-benefit assessment, patient selection, trial design, informed consent, and oversight and accountability. We found that ethical considerations around cell sources were mentioned most often, which is consistent with an earlier review of the ethical aspects of tissue engineering by de Vries et al (38). For each of the six themes, we have distilled and discussed ethical points to consider, which can be valuable for research groups and RECs who will be setting up or evaluating early-phase clinical transplantation trials of bio-artificial organs in the future, and for health care professionals working in the field of organ transplantation with an interest in innovative technologies. Below, we would like to reflect on important points made on two themes: trial design and informed consent. These themes are underrepresented in the literature, and need specific attention before early-phase bio-artificial organ transplantation trials can be initiated, and evaluated by RECs.

First, when designing clinical trials, researchers should not focus exclusively on gathering data on clinical outcomes, but also on understanding research participants' perspectives. Qualitative studies of patients' perspectives can help elucidate their needs and preferences with regard to the set-up and conduct of clinical trials, the use of outcome measures, the design and performance characteristics of the product that is being developed, the type of follow-up care that will be offered, etc., so that the process of clinical development and the resulting bio-artificial organ technologies are optimally aligned with patients' perspectives, to improve their quality of life. Also, trials should be designed such that data on long-term clinical outcomes of transplantable bioartificial organ technologies can be gathered. An exploratory survey among European tissue-engineers by Trommelmans et al. found that the majority of respondents insisted on long-term follow-up (83). Given the irreversibility of transplantation of bio-artificial organs and its potential for adverse events emerging only after a long time, long-term follow-up procedures may be essential in trials of bio-artificial organs. This requires long-term—possibly even lifelong—commitment of participants (34), and long-term trust relationships between researchers and patients. Barriers to long-term follow-up studies frequently reported include outdated contact information, lack of financial reimbursement for follow-up services, and direct and indirect costs charged to participants (104,105). Researchers in regenerative medicine could learn from prior experiences in overcoming these barriers. One such strategy is to discuss the long-term follow-up planning with participants during the informed consent procedure (106). Additional research is needed to identify barriers specific to long-term follow-up of bio-artificial organ transplantation trials, and to develop strategies for overcoming them.

Second, during the informed procedure, researchers should communicate reasonably foreseeable risks and benefits associated with participation in clinical trials. However, little guidance exists on how researchers should communicate such risk and benefits in cutting edge early-phase research (107, 108), in which there is a high degree of uncertainty surrounding these risks and benefits due to limited knowledge. There are concerns that researchers might overestimate and exaggerate the benefits in early-phase clinical trials, which is a potential source of "therapeutic misconception" (109, 110). For instance, Kimmelman et al. (110) analysed patient information and informed consent documents on risky, novel, experimental early-phase gene-transfer trials for seriously ill patients, and concluded that these were often inappropriately optimistic about the direct benefits for individual participants. The results of this study are relevant, because early-phase bio-artificial organs will also be risky and experimental. To prevent therapeutic misconception, researchers should provide realistic information to participants about the individual medical benefits and uncertainties of participation in early-phase clinical trials.

We consider it remarkable that it is often recommended, in various research fields, to use questionnaires, or extraordinarily written or oral exams, to check whether research participants have understood relevant information about clinical trial participation (16, 21, 33, 108, 110–112). It is believed that the exam approach will leave more time for the researcher, during a subsequent informed consent discussion, to focus on the aspects about which the participant's knowledge is not yet sufficient, and tailor the process to the participant's individual informational needs (113). However, it is unclear whether this focus on formally "testing" participants' knowledge of (the science underlying) the trial will lead to better informed, more autonomous decisions about research

participation. It may also place more responsibility or liability on research participants when—deciding about—participating in novel, possibly risky trials. Further research will be needed to understand and improve communication about risks and benefits of participation in early-phase clinical trials of bio-artificial organs.

We did not limit this review to one specific bio-artificial organ type. Instead, we developed a general list of ethical points to consider for all bio-artificial organ technologies. However, these points to consider may play out differently in specific bio-artificial organ technologies, and may vary with organ type; for instance, to a greater extent than for hearts, lungs, and livers, there are alternative (organ replacement) therapies available for pancreases or kidneys. This difference may affect risk-benefit assessment and patient selection of a clinical trial, which needs to be taken into account.

In conclusion, there is no specific ethical guidance for the safe and responsible design and conduct of early-phase clinical trials of transplantable bio-artificial organs. However, we have shown that ethical considerations from adjacent research fields may be useful for early-phase transplantable bio-artificial organs trials. In particular, the irreversibility, uncertainty of outcomes, the ethical considerations around the cell sources used to generate the product (e.g., donor cells), and the need for life-long follow-up studies makes clinical translation of bio-artificial organ technologies ethically contentious. Ethical themes that researchers and RECs should consider when designing or evaluating studies include cell source, risk-benefit assessment, patient selection, trial design, informed consent, and oversight and accountability. Patient engagement and empirical studies of patients' perspectives on (organ-) specific bio-artificial organ technologies will be essential to realizing the social value of research and clinical translation of bio-artificial organs, and to ensuring adequate informed consent for research participation.

VANGUARD CONSORTIUM PARTNERS

Members of the VANGUARD consortium are as follows: Ekaterine Berishvili, Laura Mar Fonseca, Fanny Lebreton, Kevin Bellofatto, Juliette Bignard (Department of Surgery, University of Geneva, Geneva, Switzerland); Jochen Seissler, Leila Wolf-van Buerck, Mohsen Honarpisheh, Yichen Zhang, Yutian Lei, Monika Pehl (Diabetes Centre—Campus Innenstadt, Medizinische Klinik und Poliklinik IV, Klinikum der Ludwig-Maximilians-Universität München, Germany); Antonia Follenzi, Christina Olgasi, Alessia Cucci, Chiara Borsotti, Simone Assanelli (Department of Health Sciences, University of Piemonte Orientale, Novara, Italy); Lorenzo Piemonti, Antonio Citro, Silvia Pellegrini, Cataldo Pignatelli, Francesco Campo (IRCCS Ospedale San Raffaele, Diabetes Research Institute, Milano, Italy); Olivier Thaunat (Dept. Transplantation, Nephrology and Clinical Immunology, Lyon Claude Bernard University, Lyon, France); Devi Mey, Chiara Parisotto, Giovanna Rossi (European Society for Organ Transplantation, Padova, Italy); Patrick Kugelmeier, Petra Wolint, Markus Mühlemann, Karolina Pal-Kutas (Kugelmeiers AG, Erlenbach, Switzerland); Marco Cavallaro, Julia Götz, Jeanette Müller (Accelopment Switzerland Ltd.).

AUTHOR CONTRIBUTIONS

DdJ, EM, AC, MS, and EB contributed to conception and design of the manuscript. DdJ wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

FUNDING

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no. 874700.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors would like to thank S.T.G. Meertens-Gunput from the Erasmus MC Medical Library for her assistance in developing and updating the systematic literature search.

SUPPLEMENTARY MATERIAL

The Supplementary Materials for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10751/full#supplementary-material

Supplementary Data Sheet S1 | PRISMA checklist.

Supplementary Data Sheet S2 | Capsule sentence summary.

Supplementary Data Sheet S3 | Search term.

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ESOT | Transplant International

ORIGINAL RESEARCH
published: 16 August 2022
doi: 10.3389/ti.2022.10506

Gender and Racial Disparity Among Liver Transplantation Professionals: Report of a Global Survey

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Equality, diversity, and inclusion (EDI) are fundamental principles. Little is known about the pattern of practice and perceptions of EDI among liver transplant (LT) providers. International Liver Transplant Society (ILTS) EDI Committee survey around topics related to discrimination, mentorship, and gender. Answers were collected and analyzed anonymously. Worldwide female leadership was also queried via publicly available data. The survey was e-mailed to 1312 ILTS members, 199 responses (40.7% female) were collected from 38 countries (15.2% response rate). Almost half were surgeons (45.7%), 27.6% hepatologists and 26.6% anesthetists. Among 856 LT programs worldwide, 8.2% of leadership positions were held by females, and 22% of division chiefs were female across all specialties. Sixty-eight of respondents (34.7%) reported some form of discrimination during training or at their current position, presumably related to gender/sexual orientation (20.6%), race/country of origin (25.2%) and others (7.1%). Less than half (43.7%) received mentorship when discrimination occurred. An association between female responses and discrimination, differences in compensation, and job promotion was observed. This survey reveals alarmingly high rate of experience with racial and gender disparity, lack of mentorship, and very low rates of female leadership in the LT field and calls to action to equity and inclusion.

Keywords: liver transplantation, gender equality, leadership, women physicians, racial disparity

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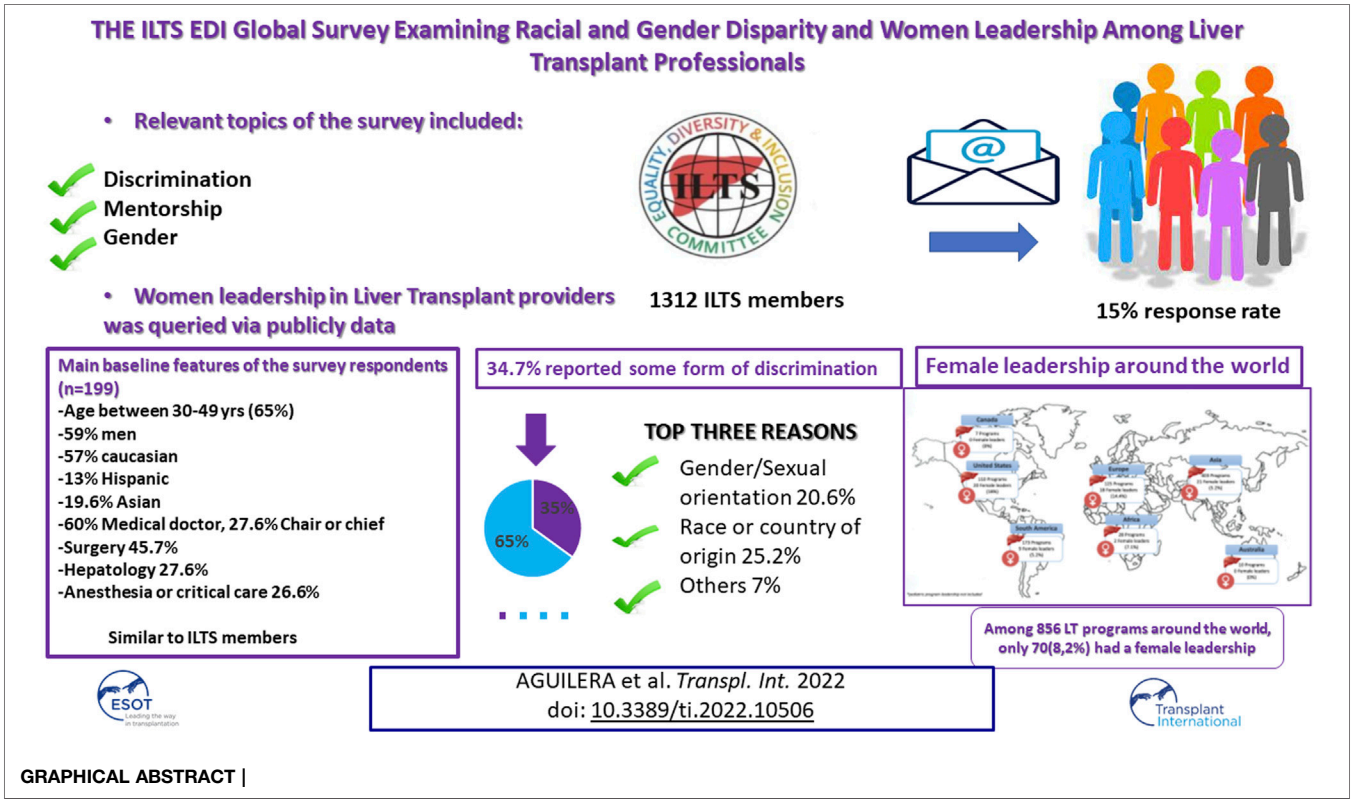
Received: *13 March 2022*
Accepted: *07 July 2022*
Published: *16 August 2022*

Citation:
Aguilera V, Andacoglu O, Francoz C, Berlakovich G, Pai S-L, Adelmann D, Ghosh S, Lunsford KE, Montenovo M, Mrzljak A, Scalera I, Xie Q, Becchetti C, Berenguer M and Selzner N (2022) Gender and Racial Disparity Among Liver Transplantation Professionals: Report of a Global Survey. Transpl Int 35:10506. doi: 10.3389/ti.2022.10506

Abbreviations: ASTS, American society of transplant surgeons; AST, American society of transplantation; EDI, equality, diversity and inclusion; ILTS, The International liver transplant society; LT, liver transplantation; ILO, International labor office.



GRAPHICAL ABSTRACT |

INTRODUCTION

Recent years have seen an exponential growth of women and minority populations among medical trainees, and the increasing workforce diversity is gradually translating to medical and surgical subspecialties (1). Further workforce diversification occurs through immigration, allowing diverse groups to travel and build career paths beyond their countries of origin. As a result, medical professional environments are becoming increasingly multicultural, international, and diverse in terms of its specialists. However, according to most recent American Medical Association report, female physicians represent 36% of all physicians as of 2019 in the United States (2). Similarly, minority groups remain underrepresented both in training and leadership positions (1, 3–7).

Many transplant professionals face challenges related to gender or racial discrimination in their work environment or face inequalities such as access to leadership positions, professional promotion, and compensation. According to the recent report from Women in Transplantation Committee, a subcommittee of The Transplantation Society of Australia and New Zealand, women comprise more than half of the Australian medical doctoral graduates and early career researchers, however less than 20% of all academic medical professorial staff are women. The report also highlighted an even more striking gender disparity in composition of the professional workforce within the field of transplantation (5). Currently, there are no female heads of unit in any of the Australian or New Zealand transplanting centers. Similarly, the report on Spanish women hepatologists demonstrated that despite a slight predominance of women (n = 239, 56.3% vs. n = 184 men, 43.7%) in the workforce, only 15 (21.4%) high-ranking positions were held by women (6). Lack of diversity among transplant center leadership is of global concern.

The International Liver Transplant Society (ILTS) Equality, Diversity, and Inclusion (EDI) Committee is committed to promoting a supportive environment for all our members, irrespective of race, ethnicity, gender or sexual orientation. The key goal of the committee is to facilitate educational and professional development and to promote an inclusive working environment for all ILTS members. As a first step toward this mission, we sought to survey the ILTS members' subjective experience with disparities or disadvantage related to gender, country of origin, and ethnicity. Respondents were asked to report their experiences with respect to leadership positions, promotion, mentorship opportunities and visibility at meetings within ILTS.

METHODS

The survey was designed and discussed with contribution by all EDI members to target the entire active ILTS membership. The primary objective of this survey was to delineate subjective opinions regarding disparities in professional training and

TABLE 1 | Baseline characteristics of the participants (only ILTS members) in the survey.

	N = 199
Age of respondents	
-<30 years	2 (1%)
-Between 30–39 years	51 (25.6%)
-Between 40–49 years	79 (39.7%)
-Between 50–59 years	45 (22.6%)
-Between 60–69 years	20 (10.1%)
->70 years	2 (1%)
Gender	
-Women	81 (40.7%)
-Men	118 (59.3%)
-Other	0 (0%)
Ethnicity	
-African or African American	4 (2%)
-Asian	39 (19.6%)
-Caucasian	114 (57.3%)
-Hispanic or Latino	26 (13.1%)
-Eastern	23 (11.5%)
-Other	2 (1%)
-Prefer no to answer	1 (0.5%)
Type of working place	
-Academic	148 (74.4%)
-Private	17 (8.5%)
-Government	29 (14.6%)
-Others	5 (2.5%)
Job Position	
-Chief or Chair	-55 (27.6%)
-Medical Doctor	120 (60.3%)
-Medical Doctor in Training	8 (4%)
-Researcher	7 (3.5%)
-Others	9 (4.5%)
Specialty[a]	
-Surgery	91 (45.7%)
-Hepatology	55 (27.6%)
-Anesthesia or Medical care	53 (26.6%)
-Pediatric Medicine	6 (3%)
-Others	19 (9.5%)
Gender of leadership position of the LT program	
In total	
-Men	155 (77.9%)
-Woman	44 (22.1%)
Surgery (*n* = 90)	
-Men	78 (85.7%)
-Women	13 (14.2%)
Hepatology (*n* = 54)	
-Men	44 (80%)
-Women	11 (20%)
Anesthesia (*n* = 53)	
-Men	36 (67.9%)
-Women	17 (32.1%)
Number of LT done in 1 year at each institution	
<50 LT	46 (23.1%)
-Between 50–100 LT	56 (28.1%)
-Between 100 and 200 LT	82 (41.2%)
->200 LT	15 (8.5%)

[a]*Some reported more than one specialty.*

practice. The second objective was to discern potential target areas for improvement in any of the possible discriminative issues. The survey included 19 questions related to age, gender identity, ethnicity, job position, and sex of the program leader. Further questions were related to perceived discrimination, disadvantage in mentorship opportunities, or parameters (**Supplementary S1**). The survey was distributed by ILTS to all members twice in November 2020 and September 2021. The responders were only able to complete the survey once and the questions were designed so only one answer were expected. All answers were collected anonymously. We collected demographic data of ILTS members including sex and age as well as location of practice and specialty as comparison group for the survey responders to determine whether the responders were representative of ILTS members.

We simultaneous conducted a search within the ILTS-EDI committee members' networks of publicly available information using the GODT website (www.transplant-observatory.org). Specifically, each member collected data

TABLE 2 | Discriminant issues among LT providers.

	N = 199
Any discrimination during your training or current position	
-Yes	69 (34.7%)
-No	130 (65.3%)
Type of discrimination[a]	
-Gender or sexual orientation	41 (20.6%)
-Race	27 (13.6%)
-Country of origin	23 (11.6%)
-Others	18 (9%)
-Prefer not to state	2 (1%)
-Religion	5 (2.5%)
Mentor Support in the event of discrimination[a]	
-Always	21 (10.6%)
-Usually	32 (16.1%)
-Sometimes	24 (12.1%)
-Rarely	34 (17.1%)
-Never	87 (43.7%)
Discrimination for job promotion	
-Yes	62 (31.1%)
-No	137 (68.8%)
Institutional support for maternity leave	
-Yes	81 (40.7%)
-No	29 (15.8%)
-Neither supportive or unsupportive	73 (39.9%)
Differences in compensations between men and women	
-Yes	34 (17.1%)
-No	165 (83%)
Disadvantages for participating in ILTS for country or language skills	
-Yes	37 (18.6%)
-No	162 (81.4%)

[a]*Some reported more than one type of discrimination.*

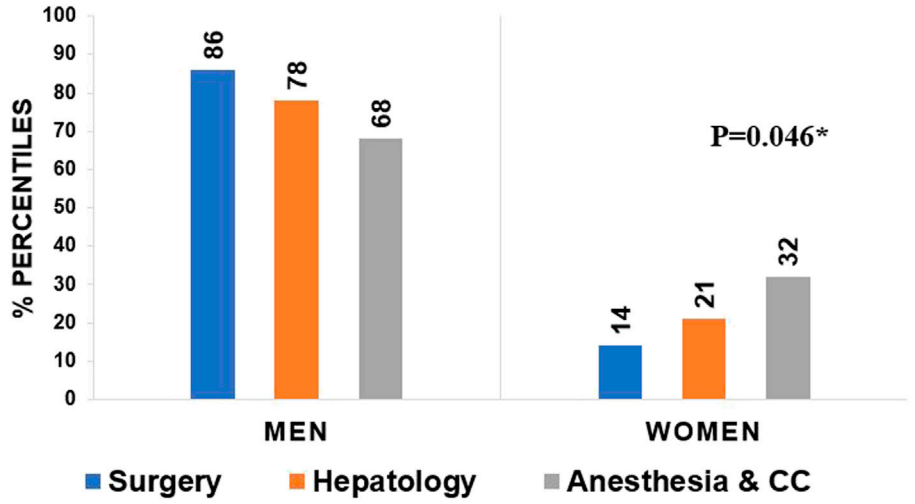


FIGURE 1 | Leadership gender among specialties; there is a significant difference between men and women leadership position between different specialties (p = 0.046, Chi 2).

TABLE 3 | Responses based on gender and discrimination issues.

	No (%)	Yes (%)	P value
Suffer any type of discrimination			**<0.0001**
-Male (n = 118)	93	25 (21%)	
-Female (n = 81)	37	44 (54%)	
Differences in compensation			**0.002**
-Male (n = 118)	106	12 (10.1%)	
-Female (n = 81)	59	22 (27.1%)	
Discrimination in job promotion			**0.006**
-Male (n = 118)	90	28 (23.8%)	
-Female (n = 81)	47	34 (42%)	
Mentor support for discrimination			0.299
-Male (n = 118)	75	42 (36%)	
-Female (n = 81)	46	35 (43.2%)	
Participation in ILTS			0.445
-Male (n = 118)	94	24 (20.3%)	
-Female (n = 81)	68	13 (16%)	

Bold is for significant p *values that is* p < *0.05.*

regarding leadership composition of centers within their countries in order expand the data on female leadership positions in transplant-related fields: Questions included: 1-Total number of liver transplant (LT) programs in the country; 2-Total number of females with the following titles: 1) LT medical director, 2) LT surgical director, and 3) LT program director/chief positions.

A descriptive analysis of variables was carried out. Categorical variables were reported as absolute frequencies. To explore the association with discrimination issues and gender, a Chi2 score was performed. A p-value below or equal to 0.05 was considered statistically significant. The study was exempted for REB University of Valencia (**Supplementary S2**).

RESULTS

The survey link was e-mailed to 1312 ILTS members and 199 responses were returned from members in 38 countries (15.2% response rate). Respondents were LT providers from Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Croatia, Egypt, France, Germany, India, Italy, Iran, Ireland, Japan, Mexico, Nepal, Netherlands, Nigeria, Norway, Pakistan, Philippines, Poland, Portugal, Puerto Rico, Russia, Spain, Singapore, Switzerland, Turkey, United Kingdom (UK), United Arab Emirates (UAE), United States of America (US), Ukraine, and Uruguay, which was similar to the ILTS membership geographic distribution (44% members from North America, 21% Europe 24% Asia and 11% others in ILTS members vs. 42%, 36%, 14% and 8.5%, respectively in survey respondents). Noticeably profile was similar between respondents and ILTS members, majority being younger than 50 years age in both groups (**Tables 1**, **2**). Forty-one percent reported themselves as women and 59% as men. Regarding ethnicity distribution, most of the respondents were Caucasian (57.3%) followed by Asian (19.6%). Most respondents (n = 148, 74.4%) reported working in an academic hospital, 76.9% (n = 153) worked in large (≥50 LT per year) programs and 174 (87.4%) were in practice for 10 years or more. Almost one-third of the respondents (n = 55, 27.6%) were either chief of their division or occupied a chair position; while, only 14% of all ILTS members reported occupying a leadership role (see **Table 1**). Our respondent profile therefore included a relatively higher percentage of leaders compared to ILTS member profile. Surgeons were the most frequent respondents (n = 91, 45.7%), followed by hepatologist (n = 55, 27.6%), and the remaining were specialists of anesthesia/critical care (n = 53, 26.9%), pediatric medicine (n = 6, 3%) and other transplant-related specialties (pathology, education and

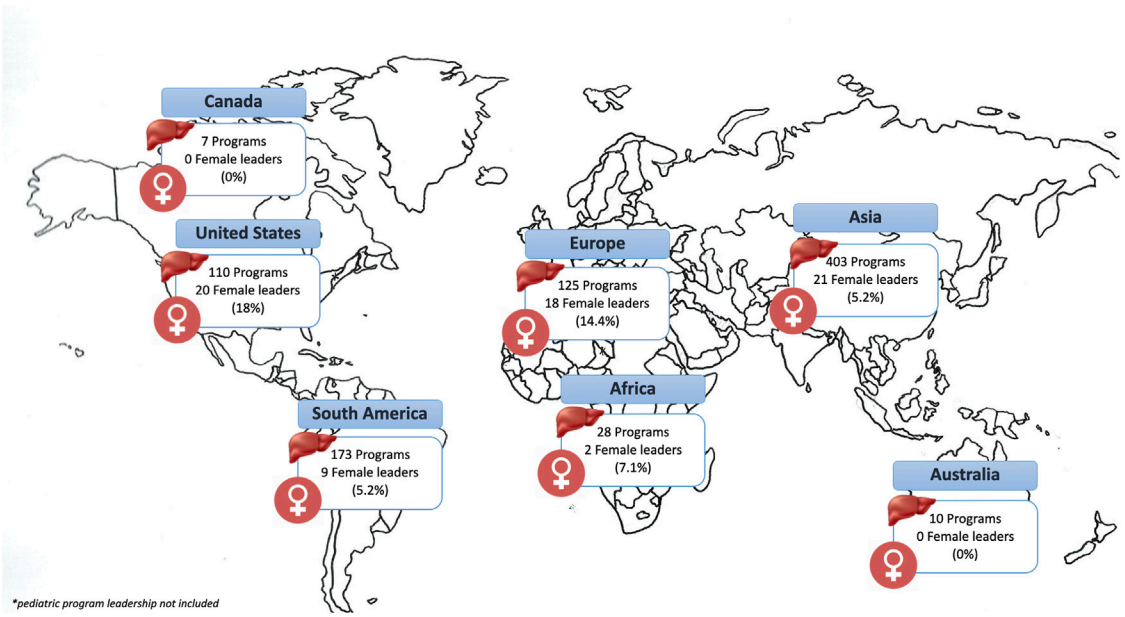


FIGURE 2 | Global map of leadership composition in liver transplant. Data source: GODT website (www.transplant-observatory.org).

research, organ allocation) (n = 19, 9.5%). This, again, is similar to ILTS membership with 46% surgeons, 28% anesthesia and 15% hepatologist 15%. However, our survey respondents had more hepatologists with more LT providers from Europe (See **Supplementary Table**).

Only 22.1% (n = 44) respondents identified a woman department/division chief when all specialties were included. When we looked at the 3 largest subspecialties, there were only 13 (14.2%) female chiefs in transplant surgery, 11 in hepatology (20%) and 17 in anesthesia/critical care (32.1%). The incidence of female leadership was significantly different between specialties and the proportion of women was lower in surgery compared to hepatology or anesthesia/critical care (p = 0.046) (**Figure 1**).

Sixty-nine (34.7%) of respondents indicated some form of discrimination or disadvantages during training or current practice (**Table 2**). Top 3 reasons of presumed basis or discrimination were gender/sexual orientation (n = 41, 20.6%), race or country of origin (n = 50, 25.2%) and other (n = 14, 7.1%), which was described as "age, political view and pregnancy". Eighty-seven professionals (n = 87, 43.7%) reported they never had a possibility to work with or receive support from a mentor during their training or career when a potential discrimination issue appeared. Sixty-two (31%) responded that they felt at disadvantage for a job promotion due to one of the above discriminations. Thirty-seven (18.6%) reported perceived disadvantage in relation to the country of origin or language skills in terms of participation at ILTS meetings or in leading collaborative projects. Although some forms of discrimination are not completely equal, we decided to combine gender and sexual orientation and race and country of origin due to the small number of respondents.

Less than half (40.7%) of survey respondents reported that they perceived their institution to be supportive of pregnancy. Thirty-four (17.1%) reported differences in compensations (salary, bonus, incentive payments, research stipends, honoraria, and distribution of profits to employees) between women and men within their workplace (**Table 2**).

We also compared answers between genders and 1) any type of discrimination, 2) discrimination in job promotion, 3) differences in compensation, 4) access to support for discrimination and 5) participation in ILTS. Women reported higher overall discrimination rates ($p < 0.001$), differences in compensation (p = 0.002), and discrimination in job promotion (p = 0.006) compared to men (**Table 3**).

In addition, based on the individual network search, a global map of leadership composition in LT units was created (**Figure 2**). The search identified any female leaders in LT: medical or surgical directors, program director, or chief of LT program. The total number of total female leaders in each country was then divided by the total number of programs in the country. Female leadership positions composition was: North America, United States: 110 active LT programs with 20 (18.1%) female leadership, Canada: 7 LT programs with zero female leadership, South America: 173 LT programs, with 9 (5.2%) female leadership, Europe: 125 LT programs, with 18 (14.4%) female leadership, Asia: 403 LT programs, with 21 (5.2%) female leadership, Africa: 28 LT programs, with 2 (7.1%) female leadership, Australia: 10 LT programs, with zero female leadership positions. Out of 856 LT programs around the world, we were able to identify only 70 (8.2%) females in leadership positions.

DISCUSSION

ILTS represents a diverse society of liver transplant professionals including , surgeons, anesthesiologists, and research scientist, as well as other transplant professionals from around the globe. As such, ILTS is an ideal group for the study of discrimination and inequality differences prevalent in different medical specialties. Our current survey, although small in scale, represents the global distribution of ILTS members and reveals important findings that merit attention. First, even though 40% of the respondents identified as female between 40 and 59 years of age, only 22.1% of the group occupied a leadership position. Moreover, gender differences in leadership roles were most prominent amongst surgeons compared with hepatologist or anesthesia/critical care (14.2% vs. 20% vs. 32.1% respectively, $p = 0.046$). Unequal distribution of female professionals in leadership position has been previously reported across various fields in medicine (1, 3–7), and we now confirm a similar gender bias in liver transplantation. According to a recent report from United States, the female transplant workforce has increased from 3.7% in 1980 to 18.4% in 2010, however only 13.1% of practicing US transplant surgeons in that survey were female (8). It is highly likely that even fewer were practicing in the liver transplant area. It is difficult to ascertain with our results whether low women in LT is due to progression failure (i.e., women are not promoted to leadership roles after they are in practice) or if it is because there are too few women liver transplant surgeons. Historically women are minority among surgical specialties. Bingmer et al. reported women represents 32% of all surgical specialties according to the United States Census, Bureau of Labor Statistics and Association of American Colleges data between 2004–2018 (9). This imbalance appears compounded amongst liver transplant surgeons, and male representation remains disproportionately higher at advanced stages of the medical career (4, 7–8). Many actions need to be taken at the hospital/university level and within medical societies to encourage female participation as well as minorities to ensure adequate academic and clinical support in order to promote advancing in leadership positions in academic LT career paths. The first step is undoubtfully to gather granular data to fully understand the scope of the problem, as we have attempted to do with our survey. We will continue to create and work on various aspects of lower representation in LT field leadership.

These gender differences in leadership position among transplant centers are also highlighted by the world map representation (**Figure 1**). Out of 856 LT programs worldwide, only 8.2% of leadership positions were held by women. Most notable were the geographic differences in female leadership, with rates varying between 0–18% by continent. In addition, in the previous report by the EDI committee, lack of female leadership was similarly highlighted (Forthcoming: Accepted awaiting publication) (**Figure 2**).

Second or more strikingly, 34.7% of LT providers reported some form of discrimination, related to gender, sexual orientation, race, and country of origin. Again, female LT providers perceived higher discrimination rates ($p < 0.0001$). Although perceived discrimination is not an objective data, it is the legal term for discrimination and refers to individual's perception of negative attitude, judgement, or unfair treatment due to their specific characteristics such as gender, race, ethnicity, and social status. We acknowledge the subjective nature of self-reported discrimination; however we believe this is something we cannot change and yet as society and ILTS-EDI committee, we feel we need to investigate discrimination and all kind of disparities no matter how subjective it is. In addition, 43.7% reported they never had opportunity to work with or receive support from a mentor during training or current career, in relation to the discrimination issues. While great strides in gender equality have been made in the past 2 decades, further understanding of unintentional bias and micro aggressions are clearly necessary. Furthermore, career mentorship is one of the most important determinants of success in academic medicine and research. There is suggestion that successful mentoring programs should have intent, structure, process, resources and be evaluated (10). The ideal conductive system is not well defined, and some authors advocate for a more flexible or organic mentorship based on their objectives rather than over predefined or assigned mentor for success. Improved mentorship access, especially from those with similar racial, ethnic, or gender backgrounds, is critical in overcoming such disparities. While transplant societies are practicing mentor-mentee match programs in various fields, we propose every institution should initiate and foster mentor-mentee matches not only for trainees but also for staff or faculty. Along the same line, ILTS plans to promote mentorship among its members to rectify these situations, not only in terms of academic promotion, but also to identify and address any type of discrimination.

Another interesting information from the survey was that the support for maternity leave was only acknowledged by 44.2% of responders. The International Labor Office (ILO) highlights the importance to guarantee maternity leave as an essential means for preventing maternity from becoming a source of discrimination. According to 2017 report, the ILO's estimates of the numbers covered reveal that 41% of employed women have a statutory right to maternity leave, and 34% of the totals are legally entitled to cash benefits during maternity leave[1]. Indeed, in medicine, some studies have reported higher wellbeing in residents with longer maternity leaves (11). Unfortunately, a recent study showed that perception about parental leave among surgical residents, including lack of knowledge regarding policies and lack of support from peers/faculty have an impact on considering surgery as a career (12). Our responses might reflect a complex mix of societal norms, cultural values, and government regulations. While we are aware there could be government or country specific regulations, we propose every center should review existing parental leave policies

[1]https://www.ilo.org/global/topics/care-economy/WCMS_838653/lang–en/index.htm

and should make the best possible effort to reform these into financially and structurally supportive policies.

Another remarkable issue is differences in promotion and compensation, such that 17.1% in our survey reported compensation differences between men and women.

Compensation differences has been reported in adjusted analyses and has potentially been linked to household responsibilities and childbearing, as well as difficulties in finding an effective mentor (13). In line with this finding, our survey showed that female responders reported higher rates of compensation differences ($p = 0.002$), in addition to higher rates of discrimination in job promotion ($p = 0.006$), compared to male respondents. Without specific job description or academic rank comparison, it is difficult to make a firm conclusion. However, transparency about salary is not universal; therefore, one could also argue that differences in compensation could be even higher than reported. We fully support equal pay for same rank same job descriptions for everyone. We propose every institution should make the best possible effort to be transparent about compensation.

To our knowledge, this is the first report of self-reported discrimination in the field of LT. Gender, race, and country of origin were amongst the highest categories that ILTS members felt the most disparity. A 34.7% reported rate of disparity amongst our members is alarming and requires immediate attention by transplant stakeholders. While we are aware that change in the culture of medicine or the field of liver transplant takes time, and that it is clearly subject to local regulatory rules, we propose the following as possible solutions followed by international societies: 1- Promote underrepresented groups and female providers in academic and clinical work, which would require institutional support; 2- Create individual mentorship programs within institutions, starting at the trainee and staff level and extending to include junior faculty 3- Advocate for actual paternity leave policies 4- Create a work environment of caring about equity, diversity and inclusion. This could start with local dedicated EDI committees within the division, initially through volunteers and eventually extending to participation of all division members. 5-Professional societies prioritize or perhaps use 50-50 quota (i.e., 50% men, 50% women and other minority groups) that is inclusive of women, underrepresented gender and professionals from various countries of origin at meetings, sessions, chair positions, presenter selection or process selections.

Limitations of our report include the following: 1) a low response rate of 15%. This could certainly cause bias, for instance, we might have received more answers from members with negative experiences. Yet, our society distribution is very similar in major characteristics such as gender, age, and specialty distribution to that which responded to the survey; 2) a relatively higher leadership representation responded in compared to that of the ILTS society. This could be interpreted different ways. On the one hand, this may mean a high number of participants who were trained in the remote past i.e., at an "era" that did not take EDI issues into consideration and, hence, a personal experience that may not be representative of today's LT world. In other words, there could be an "era effect" in our results and potential era bias. On the other hand, it may mean the contrary, a high number of participants that have eventually climb the ladder but want to express the difficulties in getting there; 3) Lastly, it is difficult to actually compare compensation responses; as, we do not have details of job description: i.e. full time job, academic rank comparison, or country specific variations.

CONCLUSION

In conclusion, we, herein, report the first international survey among liver transplant providers regarding disparity and female leadership. Our survey suggests that liver transplant providers may experience discrimination based on gender or race, lack of mentorship or support for discriminatory actions and very low rates of female representation in LT leadership positions, the lowest being in liver transplant surgery. In addition, we identified higher rates of overall discrimination, discrimination in job promotion as well as compensation differences reported by female LT providers compared to male respondents. Identifying the reality is the first step to mitigate these issues. As the ILTS EDI-committee, we propose some action items. Furthermore, we at the ILTS will continue to work towards creating various task forces and work groups to dive deep in these disparity issues.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Concept and design: VA, MB, and NS. Data collection: VA and OA. Analysis and interpretation of data: VA, OA, MB, and NS. Writing of the manuscript: VA, OA, MB, and NS. Critical editing and final approval of the manuscript: VA, OA, MB, NS, S-LP, GB, DA, SG, KL, MM, AM, IS, and QX.

FUNDING

This work was carried by Equality, Diversity and Inclusion (EDI) Committee of The International Liver Transplant Society (ILTS).

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

Authors would like to thank Jwana Riberio da Silva, International Liver Transplant Society Office, K.I.T. Group GmbH, Germany, for her assistance with data collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10506/full#supplementary-material

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Official journal of the European Society for Organ Transplantation

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