

Editorial Comments

From Helsinki to Istanbul: What can the transplant community learn from experience in clinical research?

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In June of 1964, the World Medical Association developed the 'Declaration of Helsinki' (available at www.wma.net) as a statement of ethical principles to provide guidance to investigators and physicians involved in human research. Over 40 years later the declaration remains '... a respected institution and one of the most influential documents in clinical research' [1]. Though it is not binding to any local or international law, it draws its authority from the degree to which it has been codified, or influenced, as well as from national or regional legislation and regulations. Despite criticisms, the declaration is widely accredited with improving both the ethical and scientific quality of clinical research. It should be recalled however that the Helsinki Declaration was not developed and adopted in a vacuum; it was a response to horrific abuses of human rights, in the name of scientific research and medical progress, such as those perpetrated on inmates of Nazi concentration camps.

In April of 2008, representatives of the international organ transplant community will be meeting in Istanbul to face a situation that bears comparison to that faced by clinical researchers in the 1960s. Documents—designed to codify the ethical treatment of living donors have been published by professional transplantation organizations but their impact is limited [2,3]. The use, by Chinese authorities, of organs from executed prisoners [4] certainly ranks as a crime against humanity and an abrogation of basic human rights, as does the exploitation of destitute or vulnerable organ 'donors' by traffickers in many parts of the world. All the parties in the vigorous debate that is taking place in the lay and professional press over the wisdom of commercialization of living donation abhor these abuses. The core of the debate is how best to put an end to such abuses. As we struggle to find an answer, what can we learn from the experience of the clinical researchers? Can the international transplant community produce its own declaration

that will have the authority to protect the rights of living donors while promoting healthy transplant practice?

The text of the Helsinki Declaration

The introduction to the Helsinki Declaration includes the following categorical statement taken from the International Code of Medical Ethics:

A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.

It also recalls that

It is the duty of the physician to protect the life, health, privacy, and dignity of the human subject.

For those of us engaged in living organ donation, this serves as a reminder that the organ donor is no less a patient than is the recipient of his or her organs. As such, the living organ donor is entitled to the same degree of advocacy that is presumed for the recipient. A favourable outcome to a living donor transplant requires that both the donor and recipient do well, both in the short-term and the long-term, and both from a strictly medical and psychosocial standpoint.

There is an ongoing need for new pharmaceutical agents to treat life-threatening illness, just as there is a shortage of organ donors for recipients with advanced organ failure. Yet, the introduction to the Declaration of Helsinki includes the following statement:

... considerations related to the well-being of the human subject should take precedence over the interests of science and society.

With this point, the Declaration is reminding us that the welfare of the research subject should be more important than the success of the project in which he or she is engaged. Similarly, the welfare of the living donor must not be sacrificed because of the needs of recipients: the ends must not be used to justify the means. A long waiting list for kidney transplants is not an adequate reason to loosen concern for the welfare of donors: in contrast, it is a cause for even greater vigilance, lest the threat to the long-suffering

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recipients become an alibi to lower the standards for donor protection.

Further, the Helsinki Declaration is cognizant of the fact that research subjects may come from populations who are vulnerable, either because of illness or because of social status:

The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required . . . for those who may be subject to giving consent under duress.

The same concerns certainly apply to living organ donors in the event that they come from economically or otherwise disadvantaged populations.

In the debate over the commercialization or incentivization of kidney donation, it sometimes appears as if wide cultural, political and religious differences between countries will make it difficult to come up with a common set of guiding values. Similar challenges face clinical researchers all over the world, yet the Helsinki Declaration declares that

No national, ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this declaration.

The living organ donor, just like the human research subject, ought to have basic rights and protections that are universal. Human subjects in any part of the world should be protected by an irreducible set of ethical standards [5], so should living organ donors.

The Helsinki Declaration reminds us that

The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

The mere fact that an individual agrees to be subjected to a research protocol cannot be used as justification for its application. Consent is not a free license; research subject autonomy does not trump medical advocacy. Translated to the world of organ transplantation this reminds us that a living donor consent does not free the physicians from responsibility for his or her welfare, defined in the broadest sense.

The Declaration goes on to state that

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed.

Translated to the realm of living organ donation, consent to undergo a nephrectomy requires a nuanced understanding, by both the medical team and the donor, of the potential short- and long-term implications of the procedure. Potential living donors who may be educationally, socially or economically vulnerable to a degree that does not allow them to adequately assess risk and benefit should not be permitted to donate in any system, whether commercialized or altruistic.

Further,

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

Available evidence suggests that altruistic living organ donors, in spite of, or perhaps because of, the absence of financial gain, do indeed benefit from donation in terms of self-esteem, psychologic well-being, and social status [6]. Such benefits do not appear to accrue to commercialized donors, many of whom appear to be dissatisfied with their outcome [7] or even to suffer significant psychosocial injury [8,9].

Financial compensation for research subjects and living donors

The Helsinki Declaration is silent on the issue of financial compensation for research subjects. In the United States, Federal regulations, based on the Belmont Report—Ethical Principles for the Protection of Human Subjects of Research (available at <http://ohsr.od.nih.gov/guidelines/belmont.html>)—require that local Institutional Review Boards (IRBs) ensure that the possibility of coercion or undue influence of prospective research subjects be minimized. Payment for research is not considered a benefit of participation, but instead a compensation for time and inconvenience. Clinical investigators must identify the amount and schedule of all payments. The IRB serves to ensure that the amount, method and timing of the reimbursement are not coercive or unduly influential. Recruitment materials for clinical research subjects should not emphasize payment or characterize it as a benefit.

But how does one estimate the dollar value of compensation? Much of the ongoing debate over the incentivization or commercialization of organ transplant donation echoes the debate that has taken place over the years over payment of research subjects. Dickert and Grady [10] have described the persistent ethical challenge that exists because of the tension between the need to recruit subjects for clinical research studies and the obligation to offer them certain types of protection. They describe advantages and disadvantages of three models of reimbursement and their application: the market model, the wage-payment model and the reimbursement model.

The market model, based on a 'supply and demand' philosophy that would permit the payment of large sums of money to potential research subjects, is similar in many respects to that proposed by proponents of commercialized kidney transplant donation. Not only do the authors regard this model to be ethically problematic, they make the following critical point: ' . . . large total payments and completion bonuses may provide an incentive for the subject not to explore carefully the risks and benefits of the research or to conceal important health information in order to become or remain eligible for the study and thus receive payment'. Evidence suggests that the higher the payment level the greater is the propensity to conceal [11]. Parallel concerns have been addressed regarding the impact of payment of large sums of money to potential living kidney donors [12]: the propensity to conceal relevant information in these circumstances may account for the high incidence of infectious complications in recipients

of vended kidneys [13]. The provision of employment to otherwise unemployed potential living kidney donors would also be subject to the same ethical and practical limitations.

The reimbursement model for the payment of the expenses of research subjects is non-controversial in its application to living donors and is already codified by law in the United States (available at www.optn.org) and in the ethics statements of professional transplant organizations [14]. It aims to make the procedure 'revenue neutral' by reimbursing expenses required for travel, parking, child care, meals, lodging, phone calls and time away from work. In this respect, federal law in the United States currently permits paid leave for 1 month for government employees (*Public Law* 1999; 24: 106–56) and many private employers have similar programs (list available at www.a-s-t.org). The reimbursement model is intended to preclude financial profit for the research subject and the living donor. Though currently not typically included, the provision of health insurance for living donation-related medical problems, short-term life insurance and expenses for supporting family members is also consistent with the reimbursement model [15]. It should be noted that the reimbursement model takes no account of the effort or discomfort involved either in research or organ donation.

The wage-payment model operates on the principle that participation in a research project requires little skill on the part of the research subject but may require time, effort and endurance of undesirable or uncomfortable procedures. Subjects are paid on a scale that is commensurate with other unskilled but essential jobs [10]. This model can be used to assess the financial value of the time lost from work in the reimbursement model so as to avoid wide variation among subjects with different earning potential. Application of some combination of the reimbursement model and the wage-payment model has been recommended and has typically led to the payment to research subjects of small amounts of money, by Western standards [16]. Application of the wage-payment model to living donors for a finite period until they return to work might be consistent with the principles of the Helsinki Declaration in countries where employment rates are high and social disparity is limited. Such payments could be individualized up to a fixed ceiling and reviewed by a standing committee to ensure probity. In countries with high unemployment rates and wide social disparities, even the relatively small amount of money resulting from the application of the wage-payment model could lead to the exploitation of vulnerable populations in a manner inconsistent with the intent of the Declaration. The vulnerable, in countries both rich and poor, with high and low unemployment rates, and developed and undeveloped social 'safety-nets', are not appropriate candidates for living organ donation.

Next steps

How can the international transplant community replicate or advance the role of the Helsinki Declaration in protecting research subjects and raise the standard of the global

transplant endeavour? How can a new declaration succeed when other well-meaning efforts have not? The Helsinki Declaration has succeeded, despite not being established in international law, because of the recognition that the whole field of clinical research and its critical benefits for mankind were gravely threatened by egregious abuse. National supervisory bodies and IRBs will not approve clinical research protocols unless they ascribe to the Helsinki Declaration; pharmaceutical companies will not permit their nascent products to be clinically tested unless the protections of the Helsinki Declaration are in place, and medical journals will not publish the results of clinical research unless it is categorically stated that the rights of the research subjects have been protected. Similarly it is appropriate to require that governmental accreditation of organ transplant programs include proof of protection for living organ donors; that insurance coverage for living donor transplant procedures be conditioned on such protection; that national and international transplant databases insist on such protection as a condition of inclusion; that membership in professional societies be restricted to those who accept such conditions; and that presentation or publication of clinical research involving living donors be similarly conditioned.

It is naïve to presume that the application by the transplant community of these and similar measures would bring to an end the criminal and unethical exploitation of living donors that casts such a long shadow. The Helsinki Declaration did not end the abuse of clinical research subjects but it has certainly improved their lot. With disciplined application of similar principles, the integrity of international transplant endeavour can be maintained and strengthened, not just for the welfare of living donors, but for the welfare of patients with end-stage organ failure all over the world: it is they who have the most to gain from healthy organ transplant practice.

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Fact or fiction of the epidemic of chronic kidney disease—let us not squabble about estimated GFR only, but also focus on albuminuria

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Introduction

In this issue of the journal, Glasscock and Winearls question the need to conclude that there is an epidemic of chronic kidney disease (CKD) [1], while Coresh *et al.* emphasize in their response that there definitely is a need to study glomerular filtration rate (GFR) estimates [2]. This is an important debate since after the publication of the KDOQI guidelines on the classification of CKD in 2002, many programs have been started to screen subjects for CKD, in an attempt towards preventing complications in the subjects involved. In this respect, it is important to note that CKD is not only associated with an enhanced risk of developing ESRD, but also with an increased risk of cardiovascular events [3].

The definition of the five stages of chronic kidney disease

The detection of subjects with CKD is facilitated by clear definitions on what we should screen for and who we should

screen. For this purpose, the KDOQI classification has a great value. This classification is based upon two manifestations of renal damage: first, the presence of either micro- and macro-albuminuria, erythrocyturia or abnormalities on renal ultrasound and second, an impaired eGFR [4]. In fact, an impaired eGFR is the only characteristic needed to define a subject as having a stage 3, 4 or 5 CKD (eGFR 30–59, 15–29 or <15 ml/min/1.73 m², respectively). The presence of other signs of renal damage is not required for the definition of stages 3–5. These are mandatory for the definition of the stage 1 and 2 CKD, while measurement of the eGFR in these earlier stages is required only to distinguish between stages 1 and 2 (increased albuminuria, erythrocyturia or abnormal ultrasound, together with the eGFR >90 or 60–89 ml/min/1.73 m², respectively).

For assessing renal damage besides an impaired eGFR, most surveys use a well-defined measure of micro-albuminuria [5–8] or dipstick-positive proteinuria [9–11]. A dipstick test is easy to apply and cheap. Many patients with dipstick positivity appear to have micro-albuminuria during confirmation. Of the subjects that were trace, 1+ or 2+ positive on a protein dipstick, 61, 71 and 41% had micro-albuminuria, whereas only 1, 7 and 50% had macro-albuminuria, thus showing that the submaximal categories of dipstick positivity are more indicative of micro- than macro-albuminuria [12]. However, these data also show that dipsticks are often false positive, limiting their applicability for screening purposes. In this respect, it seems more prudent for population screening to use a quantitative and more accurate measurement of urinary albumin by nephelometry in a laboratory or a point-of-care device [13].

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