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SPECIAL TOPIC

A Call to Accountability: Reporting Outcomes in Vascularized Composite Allotransplantation

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Summary: Because nearly all the vascularized composite allotransplants performed in the United States have been proposed and carried out as research, the ethical duty to report outcomes pertains. This duty is set forth in several international statements, including the World Health Organization's Statement on Public Disclosure of Clinical Trial Results, the 2013 Helsinki Declaration, and the Singapore Statement on Research Integrity. These international statements call for the reporting of negative and inconclusive outcomes as well as positive outcomes, and for the reporting of results from previously unreported past research. In 2014, the Organ Procurement and Transplant Network vascularized composite allotransplant committee proposed mandatory data collection and submission requirements for transplants, but only for those which took place in September 2015 or later. Reporting of data for the allotransplants which took place before September 2015 was regarded as optional, even though the pre-September 2015 transplants represent the majority of vascularized composite allotransplants in the United States and all the long-term outcome data. We encourage the American Society of Reconstructive Transplantation and the Organ Procurement and Transplant Network committee to embrace the international ethical standards and to hold all vascularized composite allotransplant programs in the United States accountable for reporting data on outcomes of pre-September 2015 transplants. *(Plast Reconstr Surg Glob Open 2019;7:e2266; doi: 10.1097/GOX.0000000000002266; Published online 14 June 2019.)*

INTRODUCTION

In 1964, as kidney transplantation using immunosuppression was just beginning, an attempt was made to transplant a hand and forearm. After this initial attempt failed due to rejection, interest in what has come to be known as vascularized composite allotransplantation (VCA) evaporated.[5] Only after the development of more advanced immunosuppression did substantial work begin with research in nonhuman primates. Several attempts were made to perform VCA on nonhuman primates in the 1980s, but all failed within 6–12 months.[6–9] The first modern VCA attempted in humans was attempted by Dr. Hoffman and his team in 1996, a knee transplant that survived for more than 1 year. The German team carried out 6 knee transplants over a 10-year period. Although all were lost within 56 months, graft survival of one significantly exceeded the graft survival of the first French transplant.10.[10] In 1999, an American team in Louisville, Kentucky carried out what turned out to be the first upper extremity transplant with a long-term survival.[11,12]

Since that first attempt in the modern era, upper extremity transplantation has been performed on more than 75 patients worldwide.[13,14] In addition, more than 40 patients have received a partial or full-face transplant.[15] Others have received lower extremity, penis, larynx, abdominal wall, and uterus transplants.[16–20] Although there have been some excellent outcomes in VCA, outcomes for the field as a whole remain mixed. Significant challenges remain if the field is to become established as a widely recognized and accepted form of treatment for large numbers of patients.

One recognized challenge in the field is a lack of routine data sharing.[21–25] Although the Organ Procurement and Transplant Network (OPTN) VCA Committee provided a partial remedy to this problem with its requirement for data collection and submission for transplants

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from September 2015 forward, this remedy falls far short of international ethical standards for reporting the outcomes of research and deprives those in the field, potential patients, and the public of critical information. In the absence of this information, it is difficult to argue convincingly that the knowledge base, skills, and systems are in place to consistently produce good to excellent outcomes and that the field thus deserves the trust of patients and third-party payers.

INTERNATIONAL RESEARCH REPORTING STANDARDS

Concern over the failure to report outcome data of research has led to the creation of several statements by various international groups and funders of clinical research. Among these, the 2013 Helsinki Declaration, the 2017 statement of the World Health Organization (WHO), and the 2010 Singapore Statement of the World Conference on Research Integrity are the most prominent. In each of these, the ethical duty to report outcome data is emphasized.

The World Conferences on Research Integrity began in 2007 as an attempt to prevent misconduct and promote integrity across a wide range of research fields. The initial meeting was in Lisbon, Portugal, followed by meetings in Singapore (2010), Montreal (2013), Rio de Janeiro (2015), and Amsterdam (2017).[26] It is noteworthy that an insistence on the importance of data reporting was a major feature of their very first group statement, the Singapore Statement on Research Integrity. Specifically, the statement calls on researchers to "report findings and interpretations fully and objectively . . . as soon as they have had the opportunity to establish priority and ownership claims."[3]

The World Medical Association, founded in 1947, has come to include thousands of physicians from over 100 countries. The Association's focus is on medical ethics, human rights, and public health.[27] In 1964, the Association published a statement on the ethics of human experimentation which was called the Declaration of Helsinki.[28] Revisions of the Declaration have taken place periodically since, with the most recent in 2013. In the 2013 revision, a section titled "Research Registration and Publication and Dissemination of Results" was added. In that section, it is claimed:

> Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports … Negative and inconclusive as well as positive results must be published or otherwise made publicly available.[28]

Inspired in part by the 2013 Helsinki Declaration, the WHO published its own "Statement on Public Disclosure of Clinical Trial Results" in 2017. In addition to the duties set forth in the Helsinki Declaration, the WHO Statement insists, "There is an ethical imperative to report the results of all clinical trials, including those of unreported trials conducted in the past." Furthermore, the statement recommends that the failure to report results should be taken into account when funding future research is considered.[1]

THE ETHICAL FOUNDATION FOR REPORTING RESEARCH OUTCOMES

Underlying the various formal statements are several substantive ethical arguments. Some of these arguments appear in the texts of the statements themselves, although only briefly. More substantive discussion of the ethical reasoning involved appears elsewhere. The ethical "rationale" for the WHO Statement is set out in an essay by Moorthy et al.[29] From a primarily consequentialist perspective, they argue that not reporting results can create inefficiency, increase cost, and impede good decision-making. Similar consequentialist arguments appear in articles by De Hert and Samama,[30] Shah and Batzer,[31] and Bauchner et al.[32]

Others offer ethical arguments for reporting outcomes grounded more in rights and duties than in consequences. Hassoun[33] focuses on the right to truly informed consent and the fundamental human right to reasonable protection from harm. She argues that when adverse results are not reported, the right of others to reasonable protection from harm is violated.[33] Nicholls et al[34] set forth an argument based on the principles of fairness and reciprocity. They also assert a duty to society, grounded in "the 'social license' of research."[34] Bauchner et al,[32] while leading with a consequentialist justification, also speak of a duty to research subjects who have put themselves at risk at least in part to generate knowledge that will benefit others.

Perhaps, the most thorough and readable argument for an ethical responsibility to report the outcome data of research comes from Iain Brassington. Brassington[35] offers 4 reasons for why nonpublication of outcome data matters. First, he argues that it violates "the 'ethos' of scientific research." According to Brassington,[35] inasmuch as progress in science depends on "replication and falsifiability," and these are "undermined when some outcomes remain unpublished," the failure to share outcome data "corrodes the nature of the scientific endeavor."

Second, Brassington[35] argues that nonpublication can lead to clinicians and patients making decisions "based on skewed information". Clinicians might cause unintended and avoidable harm to patients, and patients are deprived of the ability to exercise genuine autonomy.[35] Third, Brassington notes failure to share outcomes can lead to the waste of resources, as others pursue research that has already taken place. It can also waste resources that are used to provide treatments which have been shown (by the research data that was not shared) to be ineffective or even harmful.[35] The fourth reason Brassington offers for an ethical obligation to share outcome data of research is similar to that offered by Bauchner et al[32] and focuses on respect for research participants and their special contributions to the development of knowledge in the field of research. Participants in research may expect to contribute to knowledge acquisition which could be of benefit to others. Indeed, for some, this expectation may tip the balance in favor of participation in the research. When outcome data are not shared, the trust of research participants is betrayed and they are denied the opportunity to contribute to the common good.[35]

RAISING THE STANDARDS FOR REPORTING VCA OUTCOMES

The international standards for reporting the outcome data of research on human subjects, including unreported research from the past, are quite robust. So, too, are the ethical arguments in support of such standards. Nonetheless, the current standard of the OPTN/United Network for Organ Sharing (UNOS) VCA Committee is less stringent and the actual practice of reporting data has not met the less stringent standard.[24] Especially, concerning is the lack of access to outcome data for the VCA transplants in the United States before September 2015, considering that more than two-thirds of all upper extremity transplants and almost half of all face transplants in the United States took place before that date. Furthermore, without a full account of outcome data for the earlier transplants, the field is deprived of critical information on long-term outcomes that are necessary for a true calculation of the risk/benefit ratio.

Because of the great value of this data to practitioners, current patients, prospective patients, and potential third-party payers, the OPTN/UNOS VCA Committee and the American Society for Reconstructive Transplantation should align themselves with the WHO, the World Medical Association, and the World Conferences on Research Integrity by requiring all VCA teams in the United States to submit outcome data for transplants that took place between 1999 and September 2015 and continue to report on the condition of patients and grafts as these evolve. The requirement we have in mind is not a legal one, as neither the OPTN/UNOS VCA Committee nor the American Society for Reconstructive Transplantation (ASRT) is able to make laws. Rather, the requirement we have in mind is scientifically and medically ethical and can be expressed as organizational policy, with stated consequences. Programs that fail to comply with this requirement within a reasonable time frame should be publicly identified and perhaps otherwise sanctioned.

It is widely recognized that trust and transparency are critical to the success of the transplantation system in the United States.[36–38] OPTN/UNOS has earned trust with regard to traditional life-saving organ transplantation through efforts to be equitable, transparent, and inclusive.[39] An important step toward earning trust with regard to VCA will be for OPTN/UNOS to promote transparency by insisting that programs which wish to continue performing VCAs report their data from all past VCAs. The ASRTs stated goal of promoting "high standards in clinical care, science and … ethical practice"[40] implies support for strengthening the standard for outcome data reporting. The field of VCA was recently described in a leading journal as "maturing."[41] While progress is being made, the field cannot be described as "mature" from an ethical perspective until it holds programs and practitioners more accountable and to a higher standard.

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