REVIEW

# Vascularized composite allotransplantation – a Council of Europe position paper

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## SUMMARY

After more than 120 hand-upper extremity and 37 face transplant procedures performed worldwide, vascularized composite allotransplantation (VCA) now falls under the scope of organ transplant legislation in Europe and the United States. While in the USA, VCA has been considered as standard care since 2014, VCA in Europe is still performed through clinical research trials, except in United Kingdom. However, after two decades of favourable experience with upper extremity transplantation (UET), professionals in Europe are proposing hand allotransplantation as "controlled standard" care, as opposed to face transplantation (FT), which is still a challenging activity. The European Committee on Organ Transplantation (CD-P-TO) has elaborated a position paper to provide recommendations concerning regulatory aspects for UET and FT. It is aimed at Health Authorities in charge of the oversight – and coordination – of organ donation and transplantation, and at professional groups to help them manage such complex and costly programs dedicated to properly selected patients.

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## Introduction

Hand/upper extremity and face transplantation has rapidly evolved over the last few years, with the current need of standardizing and regulating the practice. The European Union Health Authorities on organ donation and transplantation have widely discussed the appropriate regulatory classification for allogeneic vascularized composite tissue, with the agreement that these grafts should fall under *Directive 2010/53/EU of the European Parliament and of the Council on quality and safety standards of human organs intended for transplantation* [1].


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**Table 1.** US regulatory definition - OPTN Final rule 42 CFR 121.2 – definitions [2].

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| 1. Vascularized and requires blood flow by surgical connection of blood vessels to function after transplantation; |
| 2. Containing multiple tissue types; |
| 3. Recovered from a human donor as an anatomical/structural unit; |
| 4. Transplanted into a human recipient as an anatomical/structural unit; |
| 5. Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement); |
| 6. For homologous use (the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor); |
| 7. Not combined with another article such as a device; |
| 8. Susceptible to ischaemia and, therefore, only stored temporarily and not cryopreserved; |
| 9. Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient. |

A new terminology was adopted and the term "composite tissue allograft" was replaced by the term "vascularized composite allograft" to avoid confusion with tissues and tissue bank regulations. In the United States, the Department of Health and Human Services also announced in 2011 that VCA should fall under the scope of the organ legislation. A regulatory definition based on nine criteria (Table 1) was adopted and VCA was considered to be a "standard procedure of care" covered by the federal regulations (the Organ Procurement and Transplantation Network [OPTN] Final Rule) and legislation (the National Organ Transplant Act), in effect since 3 July 2014 [2].

At a plenary meeting of the Council of Europe Committee on Organ Transplantation[1] (CD-P-TO) on October 2013, a working group was set and given the mandate of drafting a position paper on VCA. The aim of this position paper was to provide member states with guidance on regulatory and organizational aspects of VCA, as well as on technical and ethical considerations for Health Authorities and professionals involved or ready to develop a VCA program. The scope of the paper was deliberately limited to the most common types of VCA, namely upper extremity transplantation (UET) and face transplantation (FT). As a result of deliberations within the *ad hoc* working group and the CD-P-TO, the position paper was officially adopted and its content is presented below.

## Activity and results of vascularized composite allotransplantation

After various historic attempts, hand and UET began with the first hand transplant in 1998 followed by the first FT in 2005, both performed in France [3,4]. The International Registry on Hand and Composite Tissue Transplantation (IRHCTT), supported by the International Society of Vascularized Composite Allotransplantation, includes 109 UETs performed in 24 centres and 30 cases of FT performed in 10 centres, worldwide. To our knowledge, the IRHCTT includes 91% of UETs and 81% of FTs performed worldwide but Chinese recipients [5].

### Hand and upper extremity transplantation

UET is usually carried out by plastic hand surgeons in a comparable fashion to replantation surgery. The principal causes of amputation are explosion, crush injury, electrocution, clean-cut lesions and sepsis [5,6]. The level of amputation is usually distal (palmar, wrist and distal forearm) but several arm transplants have also been performed [5–9]. Some countries adopted a national agreement authorizing exclusively bilateral UET, considering the possibility to overcome the handicap in cases of unilateral amputation and the potential

[1] The European Committee on Organ Transplantation (CD-P-TO) is the steering committee in charge of organ, tissue and cell donation and transplantation activities at the European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe. As of May 2018, the CD-P-TO is composed of 34 members (Austria*, Belgium*, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France*, Germany*, Greece, Hungary, Iceland, Ireland, Italy*, Latvia, Luxembourg, Malta, Montenegro, the Netherlands, Poland*, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain*, Sweden, Switzerland, Republic of Moldova, Turkey*, Ukraine, United Kingdom*) and 20 observers (Armenia, Belarus, Canada, Georgia, Holy See, Israel, Russian Federation, United States of America, Council of Europe Committee on Bioethics, DTI Foundation, European Association of Tissue Banks, European Eye Banking Association, European Society for Human Reproduction and Embryology, European Society for Organ Transplantation, European Commission, Eurotransplant, South Transplant Alliance, Scandiatransplant, The Transplantation Society, United Network for Organ Sharing, World Health Organization and the World Marrow Donor Association). (*) European countries performing UET or FT.



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negative psychological impact when the patient observed differences between the native and transplanted limbs [10,11].

Despite sustained immunosuppressive therapy, the majority of recipients (87.8%) experienced acute rejection (AR) episodes (0 to 12; median 3) during the follow-up period ranging from 6 months to 18 years. To date, 13.4% upper extremity transplanted patients have developed signs of chronic rejection or graft vasculopathy [5,12]. Under-immunosuppression seemed to be the principal cause, mainly because of poor compliance to immunosuppressive treatment [12]. However, the risk of late deterioration or graft loss may persist despite optimal immunosuppression [13]. The collected data show that hand allograft recipients developed metabolic disorders, opportunistic infections and malignancies [7,9]. More data are needed for comparison with solid organ transplant complications. The IRHCTT reports a patient survival rate of 96.7%, at 10 years. Graft survival in UET is currently 86.6% at 10 years [5]. A few attempts to reconstruct large body defects, like combined face and hand transplants or quadri-membral transplantation have not succeeded so far because of severe infection and surgical failure [14,15].

Sustained long-term physiotherapy is required before functional recovery, which is also influenced by the level of amputation and the point of follow-up. All transplanted patients reached protective sensation, 91% of them tactile sensation and 82% a certain degree of discriminative sensation. Patients regained independence in daily activities, such as dressing, shaving, driving, riding motorcycles, writing and some of them returned to work [5–16].

### Face transplantation

Candidates for FT present with severe disfiguration involving functional "aesthetic units", particularly those of the central part of the face (nose, upper and lower lips, chin and tongue). The functional deficits are correlated with the units involved: blindness, impaired or impossible swallowing, oral eating and drinking difficulty and slurred or unintelligible pronunciation. Many patients breathe through a tracheostomy and are fed via gastro- or jejuno-stomies [17]. Partial or total FT is considered when disfiguration affected more than two functional-aesthetic units of the face or scalp [18].

In the post-transplant phase, 72.7% of face transplants have experienced one to nine episodes of AR (median 3) during a follow-up period, ranging from 15 months to 10 years [5,19]. Two cases of chronic rejection have been reported after FT [5,20]. To the best of our knowledge, five deaths among the face transplants have been declared to the registry since 2004 [19]. The IRHCTT reports a patient survival rate of 83.3% at 10 years. [5].

FT is aimed at improving the patients' QoL, based on both aesthetic and functional recovery. Ninety percentage of recipients declared an improvement in their QoL, although 50% required medical treatment for complications [5]. Physical recovery is related to the need for further surgical enhancement after the transplant and to the progress of their functional status done during the recovery phase (i.e. feeding, breathing). The capacity of the patient to integrate the graft into their body image also influenced their social re-integration [14]. Functional recovery has been assessed based on the recovery of discriminative sensibility, which was obtained in 90% of recipients, and of muscular tone with consequent recovery of movements [5]. One year after transplantation, patients were able to perform the majority of basic movements and daily activities at various degrees, such as opening and closing eyelids, eating, drinking, swallowing, chewing, speaking, smiling, kissing and blowing [11].

The psychological situation is also complex as the recipient has to deal with the distress of the disfiguration before the transplantation, and then the new body image and fear of the way others will perceive him/her [19,21,22]. The psychological dimensions in FT are even more important than they are in UET. Candidates have severe facial disfigurement, with aesthetic and functional deficits, which may lead to depression, social isolation, alcohol abuse, and increased risk of suicide in the majority of cases. Indeed, disfigured patients experience many psychological and social problems, such as lowered self-confidence, negative self-image, social anxiety and marital problems [23]. The subjective patient's acceptance of the "new" face and the patient's commitment to social reintegration are determinants for final transplantation success [24]. Unfortunately, psychological outcomes and QoL improvements that determine the value of the procedure are not well-documented, and assessment protocols are needed to understand better whether the QoL improvement outweighs the actual risks of death derived from surgery and immunosuppression. Of note, FT may not only improve the patients' QoL but offers a new social identity [25,26]. At present, the international experience shows that FT is a valuable therapeutic option in properly selected candidates.

## Recipient selection and informed consent

Patients' compliance with the life-long immunosuppressive treatment and the long-lasting rehabilitation program is the key in achieving a successful functional recovery. Besides careful pretransplant medical evaluation, including specific morphological studies, immunological and surgical evaluation, a pretransplantation psychosocial assessment is of utmost importance. A past or present psychiatric history should be explored, including anxiety, phobias, insomnia, nightmares, addictions, delusions, personality traits, depression and suicidality [11]. Reactive depression because of a complex injury does not preclude FT, but other forms of depression should be carefully evaluated [27].

Establishing the patient's capacity to provide valid consent for VCA is a key element of the psychological evaluation. The patient must understand the risks of surgery, the risks of chronic immunosuppressive treatment and the demand of rehabilitation during post-transplant life. It is important to know whether the candidate has realistic expectations about the transplant. Thus, it is important to know what the patient expects to gain from the surgery, including improved function, decreased pain, recovery of body integrity and whether these expectations are realistic in the face of the associated risks.

It is the duty of the transplant team to provide the patient with comprehensive information to support their decision to proceed with an allogenic reconstruction or not. The minimal information for each VCA transplant procedure was specified in 1999 [28]. Information provided to candidates and their relatives must detail the risks of surgery and anaesthesia, together with the risks of graft loss and the possibility of re-transplantation, potential drug-related complications, malignancies, infections and long-term psychological effects. Patients may be overwhelmed by the large amount of medical information given, and they may lack awareness of the potential for the media interest in their personal experience. Discussion of the likely outcomes, as well as the process for surgery and rehabilitation should be objective, accurate and balanced and avoid hyperbole. Iterative discussions to ensure patient understanding of the implications of surgery are needed during multiple pretransplant visits. Candidates for UET should have exhausted rehabilitation treatment and prosthetic management before considering transplantation. Face transplant candidates should be thoroughly informed of all alternative surgical options for treating facial deformities or defects, as well as of psychological issues. Since there is no possibility to establish an objective risk-to-benefit ratio of allogeneic reconstruction, it is the ethical responsibility of the transplant team to provide a comprehensive informed consent documentation for the patient to aid in the decision-making process.

## Donor coordination teams

The transplant coordinator's role in the operating room is essential to manage the temporal and logistical constraints of simultaneous multi-organ procurement and management of the different teams, particularly since the limb/face reconstructive plastic surgeons are less experienced in multi-organ donations. They should be aware of the planned sequence for limb, face and organ recovery, and if required, of the need to accelerate solid organ procurement in case of haemodynamic instability. For face procurement, the coordination team should be reinforced because of the duration of surgery. As a general rule, classic multi-organ procurement should not be compromised by the limb or face recovery. No case of compromised solid organ transplantation by limb/face retrieval has been reported. To date, no standardized protocol for limbs or face procurement has been established, but some experiences have been documented [29–31]. In 78.2% and 70.8% of cases, limbs and face were retrieved prior to other solid organs, respectively [5]. Donor hemodynamic stability is the cornerstone determining the optimal timing of vascularized composite allograft procurement relative to that of solid organs. Because of this additional complexity, a coordinated and detailed algorithm for each individual case, planning each team's function, operating room arrangements and surgical intervention order is required before the day of the surgery [30,31].

In the EU, according to Directive 2010/53/EU [1], as part of the national quality programs to be established by Health Authorities, specific training programs for personnel should be developed, but to date there are no international standards or guidelines in existence in the VCA domain. The success of VCA programs mainly depends on the surgeons' willingness to regularly interact with transplant coordinators, providing didactic presentations, feedback on the activity, lists of candidates waiting for a VCA, their results (pitfalls, benefits and outcomes of VCA), and exchanging points of view and outlining difficulties to be overcome.

All donors for UET were donors after brain death (DBD), while the donors were DBD in 81.5% of face transplants and the remaining cases were donors after circulatory death (DCD) [5]. As a prerequisite,



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coordination teams involved in VCA programs should be part of DBD/DCD procurement programs. The potential donor is first assessed for solid organ and tissue donation, as limbs/face should only be obtained from valid solid organ donors. The ideal donor candidate is a multi-organ donor matched with the recipient for age, size, skin tone, ABO blood type and viral serologies, as well as HLA antibodies status. Thereafter, the surgical and aesthetic criteria are applied like height, weight, gender and race match.

The coordination team involved in a VCA program should be aware of any potential candidates, either those already registered on a VCA waiting list (WL) or those proposed in the context of a clinical research protocol. The coordinator team should also evaluate the validity of potential recipient for VCA. The information about the intended donors should be summarized in a technical sheet provided by the VCA surgical team or the protocol investigator (Table 2). This information should be available to the procurement centres in order to facilitate donor detection and selection. This document should contain information on expected donor criteria (mainly morphologic) for the best donor–recipient matching.

The initial process of obtaining next of kin consent for multi-organ procurement is the one in place for DBD/DCD donation, whether opt-in or opt-out system. In Europe, where VCA are still under clinical research trials, a specific informed consent is mandatory. In the USA, although VCA programs were recently included in standard care, once a matching donor is identified by the organ procurement organization (OPO), specific and explicit consent for VCA donation has to be obtained and documented via a process separate from that of traditional solid organ donation [32].

Requesting next of kin consent for the donation of a limb or face may be quite different from a life-saving organ as these are external and highly sensitive body parts whose removal may naturally provoke some reluctance. Transplant coordinators begin the interview and secure consent by discussing the possibility of solid organ donation before approaching the subject of other body parts. The fear, prompting refusal of vital organ donation, should be overcome if an initial and a systematic approach beginning with solid organ donation is made. Another proposed strategy could consist of requesting VCA donation only if relatives spontaneously suggest that the potential donor "wanted to donate every organ". This does not exempt coordinators from providing specific information on vascularized composite allograft procurement and transplantation. In the case of donation acceptance, transplant coordinators should be able to give appropriate information to the relatives on VCA activities (what it is and what it is for), procurement modalities and post-transplantation outcomes (overall aesthetic and functional results). Giving back the deceased body to the relatives in a state consistent with the original image is a key point of a successful VCA program in order to maintain a climate of absolute trust, as much for the sake of the next of kin as that of the medical community. *Ad integrum* body restitution, i.e. restoration of the donor's external appearance and physical integrity using cosmetic prostheses, is mandatory and this information should be provided during the interview [33,34].

The face is a strong symbol of personal identity. The likelihood of a resemblance between the donor face and the face of the recipient should be clearly dismissed, as face shape is defined by the osseous and cartilaginous substructure. Coordinators should stress that face donation will primarily allow restoration of basic functions and will incidentally provide an acceptable appearance to the recipient. The recipient will not have the features or traits of the donor face, and rather a different aspect before the disfigurement [14,35]. Coordinators should emphasize that the recipient will not look like their loved one. Cultural, religious and educational factors of donor families must be respected when approaching donor families, as limbs/face are *visible/recognizable* allografts and recipient of VCAs will likely get great attention from the mass-media. Moreover, it has been reported that 100% of all the scientific reports on the first face transplant respected the privacy of the patient, while 67% of the mass media disclosed the identity of the recipient [36]. Coordinators should inform the donor family that despite best efforts, protection of confidentiality might not be fully complied, as recipients may agree to appear in public, which might unintentionally compromise donor anonymity.

## Regulatory aspects in vascularized composite allotransplantation

As VCA falls under the organ legislation, the regulatory framework to be applied is that surrounding organ transplantation. European Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation specifies that the legal framework does not intend to cover research using human organs, for purposes other than transplantation. However, organs that are transplanted into the human body in clinical trials should comply with the

**Table 2.** Technical sheet for donor selection.

Donor selection is foreseen according the following criteria:

- Type of donor: DBD, DCD
- Usual screening of DBD, no usual contraindication to organ/tissue procurement;
- Details on past trauma, maxillo-facial surgery; face cancer is a contraindication for face transplantation;
- Age range;
- Gender;
- Height and weight range;
- Skin tone-phototype, hair pattern, tattoos;
- Blood group;
- HLA typing, cross-match (a positive cross-match should preclude a VCA, lymphatic nodes and spleen tissue, serum type according to the protocol;
- Anthropometric criteria (main matching criteria):
    - For upper extremities: photographs, level of amputation, upper extremity X-ray (anterior, posterior, lateral views) and measurements (length, circumferences), skin examination (no wounds/injuries), ultrasonography study of arteries (radial, cubital, palmar arches etc.) and veins (basilic and cephalic). Of note, radial catheter insertion has been responsible for graft thrombosis. Preparation of the cosmetic prosthesis.
    - For face: photographs, X-ray (anterior, posterior, lateral views) and measurements (specific to face segments), skin examination (no wounds/injury), computed tomography (with 3-dimensional reconstruction), angiography (to be discussed with the transplant team according to the nephrotoxicity); preparation of the facial mask.

quality and safety standards laid down in this Directive [1]. Common regulatory features linked to organ donation and transplantation activities also apply to VCA programs. Among the obligations of Health Authorities, and tasks developed in chapter II of the Directive, they should ensure that procurement and transplantation centres are authorized, controlled and audited on a regular basis to ascertain compliance with the requirements of this Directive. They should also issue appropriate guidance to health care establishments, professionals and other parties involved in all stages of the chain from donation to transplantation or disposal, and ensure that the fundamental right to protection of personal data is fully and effectively enforced in all organ transplantation activities. Each clinical research VCA program has to be approved, reviewed and monitored by the national institution in charge of biomedical research authorization, ensuring that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in such research studies.

To date, each VCA transplant centre has established its own protocols describing various procurement and transplantation processes. VCA should be performed strictly in centres already performing both organ transplantation and limb replantation/plastic reconstructive surgery. They should be able to implement long-term follow-up using a multidisciplinary approach that includes a transplant medical team, a rehabilitation team, and both psychologists and social workers. These centres, usually affiliated with a university hospital, should be authorized by the Health Authority in accordance with article 9, chapter II of the Directive, before starting any VCA program [1]. In order to obtain authorization, these facilities should meet the criteria of program feasibility, standards of training of team members, infrastructural conditions and a quality-management system to ensure the quality of the overall process. Each procurement centre should also be authorized by the national Health Authority in the same manner. Procurement organizations should comply with the rules laid down in this Directive, with specific personnel listed as key persons and this coordination team ensuring that the standards of quality and safety in organ transplantation are applied throughout the donation process until donor body restoration, in accordance with applicable national rules.

Candidates eligible for UET and FT are treated in reconstructive surgery centres and in rehabilitation centres. All amputees and facially disfigured patients are potential candidates for UET and FT, respectively, but only very few patients will be found suitable for such transplantation. A waiting list (WL) for VCA programs (local as a subset of regional, national or supranational WLs) is mandatory according to the Recommendation of the Committee of Ministers of the Council of Europe to member states on the



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management of organ transplant WLs and waiting times [37]. At present, at any given time, WLs contain few candidates who are waiting for a closely matched and compatible donor in terms of gender, age, skin aspects, HLA and blood group. The requirement for physical characteristic-matching with the recipient is specific to VCA [38]. The purpose of such a WL is to ensure that patients are medically and mentally suitable to partake in a VCA program according to a regulated process of registration based on defined criteria. When the WL is created and managed on a national (or supranational) level, there is greater opportunity to find the best-matched donor for a given recipient among a larger donor pool. For now, allocation rules rely upon a small local- national list of potential candidates awaiting compatible limbs/face donors [39]. Although simple, these rules may help facilitate the process in cases where two potential candidates match one potential donor; however, this is far from today's reality. As more transplants are performed in the future, more advanced allocation rules will be required.

Outcome results for each type of transplant should be recorded in international registers. In order to guarantee clinical results and cost-effective performance, minimal yearly activity reports should be established to track program evolution, numbers of transplantations performed and their results, candidates still on the WL and their clinical conditions [39]. The only existing register, the IRHCTT founded in 2002, collects data from around the world on a voluntary basis and provides appropriate, but not yet exhaustive, oversight of VCA activities [5]. Increasing transparency through outcome reports has contributed to the high-level advances achieved in the quality and safety of VCA and to the maintenance of public confidence.

## Conclusion

Upper extremity transplantation has produced sufficient improvement in function and QoL to be considered as "controlled standard" care for strictly selected patients managed in expert centres. Some encouraging progress has been achieved in face transplantation during this last decade. The future for all types of VCA relies upon new immunologic strategies to limit the heavy burden of current immunosuppressive regimens. VCA is considered as organ transplantation, and the European Directive 2010/53/EU guarantee of quality and safety for all organ transplantations can, and should, be applied to VCA programs, whether these activities are performed under an experimental framework or as standard care. The paucity of donors contributes to the slow development of VCA programs. As key personnel, coordination teams should be part of this activity, skilled and trained to participate in each specific VCA program, and already experienced in the DBD/DCD process. VCA team leaders are invited openly to share their activity, the only way to achieve valid risk-benefit calculation studies, as well as cost-benefit evaluations of such transplants, and to assess that the overall burden (medical, ethical and financial) does not exceed the potential benefits, while preserving the essential public trust.

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The authors have declared no conflicts of interest.

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