Face Transplantation: A Review of the Technical, Immunological, Psychological and Clinical Issues with Recommendations for Good Practice

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Three years ago, the Working Party on Facial Transplantation concluded that until there was more information available about risks any potential patient would be exposed to, it would be unwise to proceed with transplantation of the human face. Over the last three years, there has been a deepening understanding of the potential psychological problems of facial transplantation as well as a very considerable debate on the ethical aspects of the procedure. Further data on experimental work in animal models of facial transplantation as well as medium-term follow-up data from 24 hand and forearm transplants in 18 patients has now become available. Furthermore, a partial facial transplantation has been performed in France and a second one in China. In this second edition of the report, the technical, immunological, psychological, and ethical issues are discussed again in the light of this developing knowledge. In particular, there has been a major expansion of the sections on the psychological and societal issues, as well as the ethical and legal problems of facial transplantation. The working party still has considerable reservations about facial transplantation. Although it accepts that on balance the risks cannot be precisely quantified, they remain substantial. Therefore, if patients are allowed to make an informed choice to proceed, they must be very carefully selected and protected in the process, along with the families of both the donors and the recipients. To achieve this, the working party insists that 15 minimum requirements, described at the end of this report, must be fulfilled before it would be appropriate for a research ethics committee/institutional review board to approve of a proposal to undertake facial transplantation.

Keywords: Face transplantation, Reconstructive surgery, Psychology, Societal issues, Ethics, Recommendations.

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In November 2003, the Royal College of Surgeons of England produced a report from its working party on facial transplantation (*1*, *2*), which reviewed the technical, immunological, ethical, psychological, and legal aspects of facial transplantation. This initiative was taken at the time because facial transplantation was being discussed with enormous media interest in England, other centers in Europe, and in the United States as a potential clinical development in the field of composite tissue allografting.

The working party agreed at the time that the technical skills to enable facial transplantation to take place were available. However, they felt that the risks of failure and the consequences of long-term immunosuppression presented very considerable psychological and ethical problems. As a result of these deliberations, the working party concluded that until there was further research and the prospect of better control of these complications, it would be unwise to proceed with facial transplantation although fully recognizing the distress of those patients who might benefit from facial transplantation. The report was not averse to facial transplantation and saw it as a future potential treatment, but felt that there was a need for a more incremental approach to some of the problems elicited in the report.

It is close to three years since the first report and there have been a number of developments which have led to the working party being reconvened to re-examine the issues discussed in that report. The most significant is that a partial face transplant from a cadaver donor (see later for technical de-

This is the second edition of a Report on Facial Transplantation from the Working Party of the Royal College of Surgeons of England.

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tails) was carried out in November 2005 in Amiens, France with encouraging progress after six months (*3*). There has been a second partial facial transplant reported from China but only the media report is so far available (*4*). Furthermore, there is now medium-term follow-up data available for the 24 hand and forearm transplants carried out in 18 patients and this is obviously relevant to some of the problems presented by transplantation of the face (*5*). In addition, there have been a number of relevant publications in the field, especially concerning the psychosocial and ethical issues involved.

The working party met over six months and took evidence from a number of experts. This second edition is presented in the same format as the first report, but with appropriate modification of the various sections. In particular, the two sections on the psychological and societal issues and the legal and ethical problems have been expanded to take into account more recent relevant literature and discussions, but also bearing in mind that the major issues concerning facial transplantation fall into these two areas. Finally, we suggest minimum requirements to be fulfilled before a unit or institution should contemplate undertaking facial transplantation. In doing so, we are mindful of the fact that facial transplantation is an experimental procedure and any proposal to undertake this procedure will be subject to independent ethical review in accordance with the Declaration of Helsinki and national regulatory systems. We hope that the outline of minimal requirements will be of assistance to ethical review bodies who are considering applications to perform transplantation of the face. We are also anxious to avoid a repetition of the media and medical frenzy that accompanied the first heart transplants in the late 1960s. Within two years of the first heart transplant, there were just over 100 cardiac surgical units performing heart transplantation, but by 1973 there were only a handful still performing the procedure because of the disastrous results that accompanied these early attempts by inexperienced teams.

TECHNICAL ASPECTS

The Principles of Tissue Transplantation

These principles form the basis of all modern plastic and reconstructive surgery. The patient's own (autologous) tissues in the form of flaps or grafts are transferred into defects created usually by trauma, burns, or ablative cancer surgery. A skin graft is a thin piece of skin, usually known as a split skin graft, with no intrinsic blood supply, that relies on the ingrowth of vessels from the recipient bed, such as muscle. A flap has its own blood supply consisting of an arterial input and a venous output. Flaps that retain their own blood supply have been used for years to cover relatively adjacent defects, especially in the head and neck.

However, transfer of a flap may involve division of that blood supply and reconnection or reanastomosis of the vessels in another site of the body, using microsurgical techniques for the vascular connections and, if necessary, nerve reconstruction. There is considerable experience in this type of surgery and such a flap transfer is known as a free flap (Fig. 1). This is an autologous transplant but a similar flap transferred from one person to another person is an allotransplant.

FIGURE 1. A free flap of skin and subcutaneous tissue.

Facial Transplantation

It is assumed in the current discussions concerning facial transplantation that the potential recipients would be limited to those who have suffered severe burn injuries or facial trauma and have survived the initial treatment. Treatment of facial burns at present involves the use of flaps and/or grafts. The disadvantages of these methods mainly consist of an unacceptable cosmetic appearance and loss of function with tight scars and lack of facial expression. The aim of facial transplantation would be to replace unacceptable grafts and flaps with tissue that has the appearance of a normal face and allows mobility of the deeper structures.

Facial transplantation differs radically from the normal methods of facial reconstruction used at present which involve autologous tissue. The face would be taken from an unrelated deceased donor and transplantation would involve using a large amount of tissue, requiring an arterial input and venous drainage as for an autologous free flap transfer.

There have been several replants of facial tissue involving replacement of parts such as the nose, ear or scalp that have been torn or cut off (avulsed). In 1998, a patient's own face and scalp were replanted (*6*). Before November 2005, the only incidence of tissue being used for facial or scalp reconstruction from another person was a report which described using tissue from an identical twin for scalp reconstruction (*7*). There is also a considerable literature on experimental composite tissue allografts (CTA) including models of facial transplantation (*8–11*). Composite tissue grafts are made up of more than one tissue, such as skin, subcutaneous tissue, muscle, tendon, and bone.

Anatomical Considerations

Survival of the transplanted facial tissue is dependent upon adequate arterial input and venous drainage. The essential vessels are the facial artery (arising from the external carotid artery) and facial vein and the transverse facial artery (arising from the superficial temporal artery) and transverse facial vein. These vessels are relatively constant, but in the absence of a facial artery, for example, the transverse facial artery becomes dominant. The anatomy of the facial vessels has been defined in normal individuals using ultrasound (*12, 13*). These studies have essentially confirmed earlier anatomical dissections (*14, 15*). The generous anastomosis between the various arterial territories ensures the feasibility of restoring the blood supply of a transplanted face by microanastomosis of selected vessels. A microanastomosis of the facial artery and vein on each side would most probably be suffi-

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cient for facial viability, but other venous anastomoses would render the transplant safer and more likely to succeed.

Types of Facial Transplantation

At present, there are two main types of facial transplantation.

Partial facial transplantation. This is the most difficult area to construct by conventional means. It can be considered to comprise the nose and upper and lower lips with a varying amount of chin and cheek (Fig. 2). It includes muscle, mucosa, and skin and would therefore require anastomoses of sensory and motor nerves for return of function. If motor function failed to return, it would later require the use of either static or dynamic fascial slings to restore movement.

From a technical viewpoint, identification of nerves and their repair coupled with the need to repair muscle bundles, mucosa, etc., would add considerably to the length of the operation required. Neural recovery does appear possible as it has been reported that the French transplant patient has some sensory return and the start of motor recovery on one side of the face (*3*).

Failure of this type of composite tissue transplant would leave one either with the option of resorting to various complicated reconstructive options or attempting a repeat transplant.

Full facial transplantation. This includes skin and subcutaneous tissue only, not muscle (Fig. 3). Surgical teams developing this procedure have extensively investigated the arterial and venous requirements for such a transfer and the variations of those vessels, in both cadaver and living studies (as mentioned earlier).

Failure of this type of transplant would leave various other treatment options which would include: a) the application of autologous skin grafts; b) the use of an artificial skin such as Integra, a dermal substitute, and later application of skin grafts; or c) a repeat transplant, which would be more likely to reject due to prior sensitization.

In this type of full face transplant, further variations would include the possibility of using ears, the nose, or eyelids in the full face transfer (Fig. 4). This of course would depend on the individual's needs and the use of these structures would have varying failure implications as more complex reconstructions may be required.

Appearance of a Full Face Transplant

This is difficult to predict. Studies using computer modeling suggest, however, that the face looks neither like the donor nor the recipient preinjury, but would take on more of the characteristics of the skeleton of the recipient than the soft tissues of the donor (*16*). There is a reasonable expectation of mobile facial expression, which is dependent upon the depth of scarring before the operation. New mobile skin and subcutaneous tissue may indeed move better than the pretransplant grafted face.

Failure of the Facial Transplantation

As with any microsurgical procedure, there is the possibility of thrombosis of the arteries or veins that have been anastomosed. If this happened, it would be apparent within hours. If rapid diagnosis of the problem were made, the

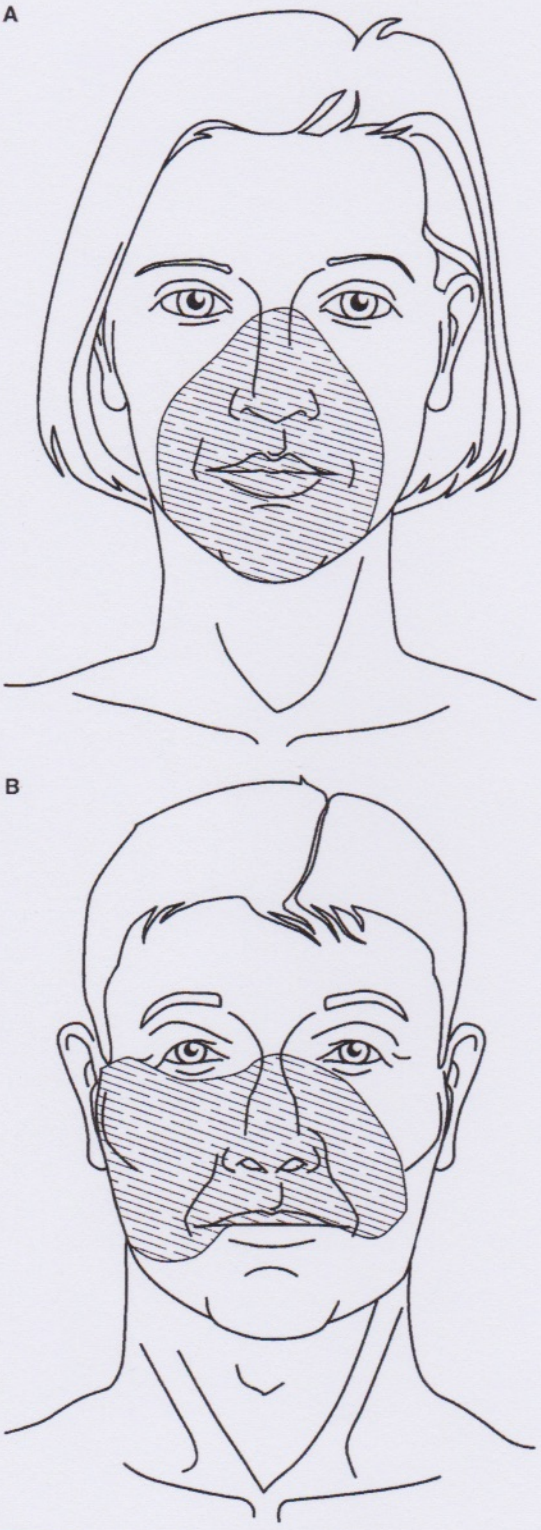

FIGURE 2. (A) Partial face transplant as performed in a patient in France. (B) Partial face transplant as performed in a patient in China.

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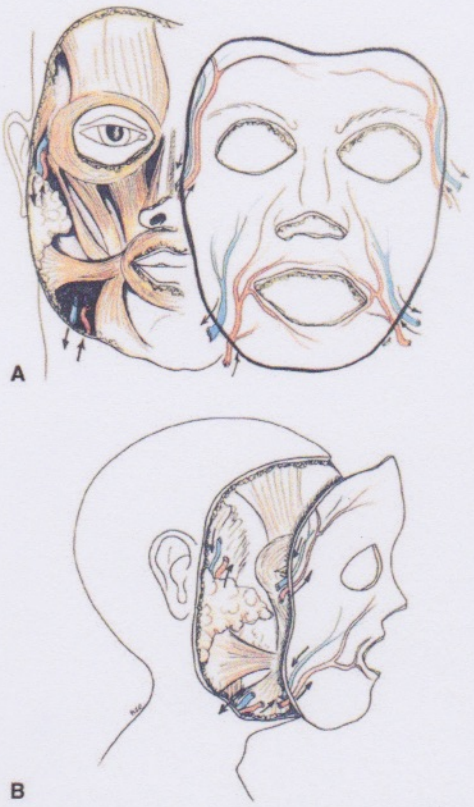

FIGURE 3. (A) Full face transplant (front view), not yet performed. (B) Full face transplant (side view), not yet performed.

anastomosis might be salvageable by reexploration and reanastomosis of the vessels. If that salvage surgery failed, the transplant would have to be removed. In conventional free flap surgery, the overall success rate is greater than 95%. Vascular thrombosis is unlikely to occur beyond the second day after the transplant. If it does happen, it is classified as a technical failure and is quite distinct from immunological acute or chronic rejection.

Acute rejection of the transplant would be apparent generally within days or weeks and, unless reversed by additional or increased immunosuppressive therapy, would lead to necrosis of the transplanted tissue.

In the event of either a technical failure or acute rejection, the transplant would have to be removed. As previous skin grafts would have been removed prior to the transplantation, the patient would have to have further skin grafts of their own tissue to cover the exposed areas on the face, assuming that there were sufficient healthy donor skin sites (a potential problem in burn patients). In this event, there is the possibility that there would be even more scarring than originally, but this is unpredictable, and indeed the bed for skin grafting might be better than it was initially due to the formation of granulation tissue. Essentially, the patient will be starting off again on the reconstructive ladder following standard techniques that have been well tested in the past. The risk of free tissue transfer failure for technical reasons in experienced

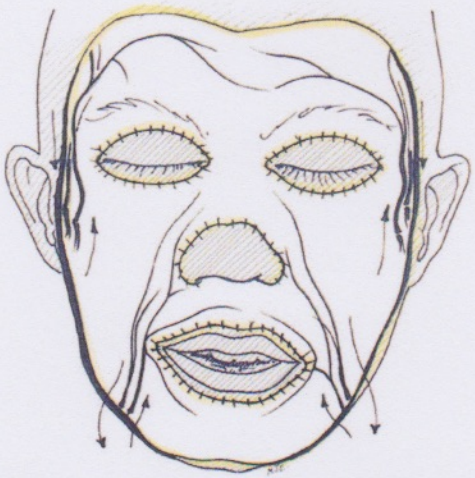

FIGURE 4. Possible appearance of a full face transplant on completion.

units is considered to be less than 5%. The risk of failure of a free tissue flap from acute rejection is as yet not possible to quantify accurately, but might be of the order of 10% based on the experience of solid organ transplantation (see Immunology section). The experience gained with hand transplants and the initial experience with the French facial transplant suggests that acute rejection can be managed by increased immunosuppression (*3*, *5*).

Bodily Integrity of the Donor

Due consideration must be given to the appearance of the donor after the facial tissues have been removed. For example, the Human Tissue Authority Code of Practice on Transplantation in the United Kingdom (www.hta.gov.uk) states that the removal of tissue from a donor after death must be undertaken by staff trained in tissue retrieval and in reconstructing the body to appear as normal as possible. In the case of face donation, reconstruction would be difficult and the use of latex or silicone prostheses may have to be considered, particularly if the family wishes to view the deceased. It is assumed that the retrieval team would be composed of members of staff from the institution that has been involved in the development of facial transplantation. However, other staff from the donor hospital may be present in theaters during the retrieval surgery and due sensitivity should be shown to their feelings and concerns in witnessing what will be an unfamiliar experimental procedure.

IMMUNOLOGICAL ASPECTS

Transplantation of any organ or tissue allograft engenders an immune response in the host directed against the donor tissues. This inflammatory reaction, which is generated by cells and antibodies, is inevitable except in the case of grafts between identical twins. The magnitude of the response varies according to the tissue or organ transplanted, and the existence of prior sensitization of the recipient against donor histocompatibility antigens. Other factors such as the degree of mismatching for major histocompatibility antigens (HLA) between donor and recipient, the age of the recipient, and as yet

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poorly understood genetic determinants in the recipient may also influence graft outcome. However, skin, the major component of a facial transplant, has been recognized for many years both experimentally and clinically as one of the most immunogenic of tissues or organs that can be transplanted (*17*, *18*).

Matching Donors and Recipients

It would be essential to ensure that the donor and recipient were compatible for the major (ABO) blood groups, and that a crossmatch between recipient and donor was negative (i.e., the recipient did not have antibodies recognizing donor HLA antigens). Whether tissue matching for HLA (the major histocompatibility complex in man), as currently performed for kidney transplantation, would confer a significant benefit on graft survival after facial transplantation is not known, but on the basis of experimental skin grafting in humans many years ago it probably would be beneficial if achievable (*19*, *20*). Interestingly, the recipient of the partial facial transplant in France, by chance presumably, received a well-matched graft with only one HLA-DR mismatch out of a possible six-antigen mismatch (*3*).

Graft Rejection

All patients who receive a transplant have to be treated with lifelong immunosuppressive agents to prevent rejection and failure of the grafted organ or tissue. In the case of a facial transplantation, the skin is likely to be the main target of rejection and as indicated earlier is one of the major obstacles to the success of human composite tissue transplantation.

Acute rejection of the skin was reported in the first patients given hand transplants (*21*, *22*) and was a common occurrence in most hand transplants performed subsequently (*5*). It was also seen in abdominal wall transplants (*23*). Rejection of the skin was easily recognized and confirmed by biopsy, allowing prompt treatment with increased immunosuppressive therapy (steroids) or, if resistant to steroids, antilymphocyte antibody therapy. However, epidermal necrosis and graft loss may occur. There is now information on 24 hand transplants performed in 18 recipients. Acute rejection occurred in the majority but in all cases it responded to additional immunosuppressive therapy (*5*). Allegedly, several of the hand transplants performed in China have failed from acute rejection but this is said to be due to poor compliance with immunosuppressive therapy. In the French face transplant, an acute rejection episode commenced around day 18 and was eventually reversed over the subsequent three weeks by a very considerable increase in immunosuppressive drug therapy (*3*). A further acute rejection occurred around six months after transplantation, requiring another increase in immunosuppressive therapy (*24*). A word of caution is advisable before extrapolating the experience of rejection in forearm and hand transplants to what might be expected in transplantation of the face. For in the former, not only is skin transplanted but also muscle, bone, and bone marrow, which might modify the subsequent immune response and improve graft survival.

The skin is also likely to be the principal target of chronic rejection. The progressive replacement of skin by fibrous tissue during chronic rejection will lead to loss of graft mobility and hence functional failure. Although currently available immunosuppressive agents have markedly reduced organ allograft loss from acute rejection, they have had little effect in preventing chronic rejection, which is the major cause of organ graft failure (*25*, *26*). Chronic rejection has now been seen in some of the hand transplants (Margreiter, personal communication). It is not possible to accurately predict the likelihood of immunological chronic rejection after facial transplantation. We know that up to 50% of organ allografts show evidence of chronic rejection after five years. It is difficult to know how to translate that in the context of facial transplantation but 30–50% might be a reasonable estimate. The effect of loss of function in a facial transplant is, as yet, impossible to predict but it may manifest itself as an inflammatory reaction and increasing lack of mobility secondary to underlying fibrosis.

Immunosuppression

Immunosuppressive therapy has well-documented side effects and may itself give rise to conditions that shorten life. The incidence and severity of such side effects are well described and this would allow an informed decision to be made as to whether these outweigh the potential benefit from facial transplantation. The risks of immunosuppression should not be underestimated. Many of the side effects are dose dependent and this will be important if patients with a face transplant require continuing heavy immunosuppression, which exceeds those used in organ transplantation. All of the currently available immunosuppressive agents commonly give rise to serious agent-specific side effects that may include hypertension, renal toxicity, diabetes, and disturbances in blood lipid levels (*27*, *28*). The majority of patients could expect to experience one or more of these agent specific side effects.

Long-term immunosuppression also increases the risk of infection and cancer. Graft recipients are particularly susceptible to viral infections such as cytomegalovirus (CMV) and fungal infections. Although these are not usually life threatening, they may cause significant morbidity. Careful monitoring and, in some cases, prophylactic antiviral agents and antibiotics are needed to reduce the risk. Immunosuppression also increases the risk of most types of cancer, for example the incidence of colorectal cancer and lung cancer is increased two- to fourfold, and there can be as much as a 50-fold increase in the incidence of cancers where a viral cause is suspected, such as non-Hodgkin's lymphoma, squamous cell cancer, Kaposi's sarcoma, and cervical cancer (*29*). Cancer of the skin, especially squamous cell cancer, is a particular problem and about half of all patients receiving an organ transplant will eventually develop a squamous cell carcinoma. These can be recognized early and usually treated effectively. By avoiding excessive exposure to direct sunlight and following appropriate screening programs, the incidence may be reduced. In some patients, however, squamous cell cancers may be quite virulent, metastasizing early. A serious condition known as posttransplant lymphoproliferative disease (PTLD) or non-Hodgkins lymphoma, which ranges in severity from a glandular fever-type syndrome to a highly malignant lymphoma, affects around 2% of organ transplant recipients (*30*, *31*). Treatment usually involves reduction of immunosuppressive therapy and chemotherapy, which may lead to graft loss from rejection.

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Adherence to Immunosuppression

Nonadherence to immunosuppressive medication is well recognized after organ transplantation and was possibly the cause of graft failure in the world's first hand transplant (*32*). An estimated 20–45% of organ transplant recipients are nonadherent at least some of the time (*33–35*). The problem is highest in the young and in those from lower socioeconomic groups. Nonadherence, if persistent, invariably leads to graft failure and is difficult to manage because this behavior is usually unpredictable and may not have a clearly identifiable cause.

Induction of Immunological Tolerance

A major goal of transplantation research for many years has been to develop clinically applicable strategies for inducing donor-specific immunological tolerance against a graft (*36, 37*). A variety of strategies are being explored experimentally and some in the clinic that would allow a recipient to accept a graft from a particular donor without the need for continual immunosuppressive drug therapy. This would leave their immune system intact to protect against infection and malignancy. Transplant tolerance can be achieved quite readily in experimental mice and rats, but attempts to achieve tolerance in larger animals have proven very difficult indeed. However, in this context, it is relevant that Siemionow and her colleagues have induced operational tolerance to both limb and facial transplants in the rat for up to one year after transplantation with several approaches (*38–40*). Interestingly, no evidence of chronic rejection was noted (Siemionow, personal communication). At present, the only clinically applicable strategies for producing transplant tolerance involve radical preoperative conditioning of the recipient accompanied by transplantation of bone marrow from the organ or tissue donor, which would be impossible to apply to the cadaver donor situation. However, there has been much recent progress in understanding the mechanisms underlying both the induction and maintenance of transplant tolerance, and so there is reasonable hope that before too long a way will be found to induce transplant tolerance in patients. Unfortunately, there is little prospect that this will be achieved within the next five years other than in a research setting. Clearly, if it did prove feasible to induce transplant tolerance clinically, this would overcome all the immunological disadvantages of facial transplantation. Indeed, many of the ethical objections to proceeding with clinical evaluation of the procedure would be eliminated.

PSYCHOLOGICAL AND SOCIETAL ISSUES

Psychological Responses to Transplantation

The growth of transplantation surgery has led to a recent increase in studies examining the psychological responses of recipients. Although many report improvements to quality of life following liver or heart transplants (*41, 42*), researchers are becoming increasingly aware that organ transplantation may give rise to a particular set of stressors, psychosocial challenges, and adaptive demands (*43*). These include:

- Fears relating to the viability of the transplanted organ;
- Fear of the aftermath of possible rejection;
- Anxiety relating to the potential side effects of immunosuppressive medication, including increased risk of infection and malignancy;
- Feelings of personal responsibility for the success or failure of the graft, linked to the need to adhere to a drug regimen, the need to alter some behavior patterns such as diet and sun exposure, the monitoring of symptoms, and regular attendance at numerous outpatient appointments;
- Integration of the transplant into an existing body image and sense of identity; and
- Emotional responses to the experience of receiving a transplanted organ, including feelings of gratitude and guilt in relation to the donor and the donor's family; these can be affected by the reason for the transplant, such as life threat as in the case of a heart transplant, versus improvements to function as in a hand transplant.

These psychological effects may be magnified in the case of facial transplantation by the factors outlined below.

Issues of Identity and Communication

The face is central to our understanding of our own identity. Faces help us understand who we are and where we come from with markers of genetic inheritance over many generations providing evidence of parentage, ancestry and racial identity (*44*). Disruption to one's facial appearance, especially the inability to recognize oneself, represents a profound disruption of body image and may constitute a major life crisis (*45*). The response to a dramatic change in facial appearance can be akin to a bereavement reaction and can result in grieving followed by a slow process of adaptation. It is thought that the early candidates for face transplants will have severe disfigurement and will have experienced the loss of aspects of their original facial appearance. However, wearing another person's face may raise complex issues of identity. The issues surrounding the integration of a donor hand into a recipient's body image have been discussed, (*46, 47*) and there has been speculation that these difficulties would be magnified considerably in facial transplantation (*48*).

Facial expressions, both conscious and unconscious, are crucial in our encounters with others. When we communicate in person, we do so through a stream of facial movements. Two thirds of our communication with others takes place through the nonverbal channels of the face. Facial expressions depend on very complex coordinations of nerves and muscles in the face and are crucial in establishing and maintaining successful relationships.

Recent research indicates that the act of forming a facial expression has an impact on how we feel. Facial muscles feed information to our brains so, for example, when the brain recognizes that we are smiling, it releases a hormonal response that accompanies a state of happiness (*49*). More research is needed before we can understand how mood is affected in those who are unable to form expressions in conventional ways. However, there are numerous reports of the difficulties experienced by those who are unable to use their faces to communicate effectively, whether through the absence of expression, or miscommunication resulting from altered expressions (*50*). Preexisting difficulties may well play a part in motivating a potential recipient to seek a facial transplantation. Yet, if the ability of the recipient to communicate

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normally following the transplant is compromised, difficulties with social interaction may persist.

Psychological Adjustment to Disfigurement

Contrary to popular opinion, a consistent finding in the research literature is that the extent of psychological distress resulting from a visible difference is not well predicted by the extent or severity of the disfiguration (*50*). Some cope well with an extensive and very visible disfigurement while others struggle to deal with a relatively minor difference (*51*). Levels of adjustment to a visible difference are not static. High levels of distress in the aftermath of disfiguring changes to appearance are common, but should not be taken as an indication that moderate to very good levels of adjustment will not be achieved in the longer term. Neither is time necessarily a great healer. Some experience debilitating distress intermittently or regularly over long periods of time (*52*).

Those who cope well have higher levels of self-esteem and derive this from factors other than their physical appearance. They enjoy high-quality social support from family and friends, have good communication skills, and do not believe a disfigurement precludes happiness and a good quality of life. Those who experience greater difficulties derive more of their self-esteem from their looks, and believe others evaluate them to a greater extent on the basis of their physical appearance (*52*). They experience higher levels of general anxiety, social anxiety, and depression; lack confidence in social situations; and do not believe that interventions other than those aimed at reducing their disfigurement will be effective in ameliorating their distress. It is generally this latter group, the more psychologically vulnerable, who are the most motivated to undergo multiple surgical procedures as part of an ongoing quest for a "normal" or unremarkable appearance (*50*). They are also more prone to unrealistic expectations of change following surgical intervention (*51*). Paradoxically, the more vulnerable will be less well equipped to deal with the aftermath of complex transplant surgery, uncertain outcomes, and ongoing treatment regimens.

Alternative Interventions

Although cosmetic and reconstructive surgery is often reported by recipients to be beneficial in the short term, it is by no means a universal panacea for appearance-related problems. In the absence of studies involving long-term follow up, the jury is still out on whether appearance-enhancing surgery produces lasting psychological benefit (*53*) or improvements in social functioning (*54*).

Cognitive-behavioral interventions (i.e., interventions focused on producing changed thoughts and behaviors) have been shown to produce significant improvements in self-esteem, anxiety, depression, and social confidence for people with a variety of visible disfigurements (*55*, *56*). Reported benefits are maintained, and in some cases enhanced at a six-month follow-up. As the most frequently experienced difficulties relate to problems with social interaction, interventions designed to enhance social interaction skills have also been developed. Results to date are promising (*57–59*). More research is needed, however, in order to identify the long-term impact and to clarify which components of these interventions are the most effective.

Psychological Support for Face Transplant Patients

All stages of the face transplantation process will present psychological challenges for recipients, their families, and donor families. Optimum psychological support will require a substantial and long-term commitment by skilled and experienced professionals working as an integral part of the transplant team. At a minimum, teams wishing to undertake face transplantation should ensure that psychological expertise is available to:

- Assess the suitability of candidates for transplantation and to support those deemed unsuitable after assessment;
- Ensure that prospective patients have understood and assimilated the risk/benefit information and can achieve valid informed consent;
- Provide therapeutic support and intervention for patients during the wait for a donor;
- Provide long-term support and intervention in the aftermath of transplantation;
- Provide support for recipient's families at all stages of the transplant process; and
- Offer support for donor families as necessary.

Assessing the Suitability of Candidates for Face Transplantation

Motivation to seek treatment and expectations of outcome. The potential psychological costs of undergoing a facial transplantation are considerable. These may include a long wait for a suitable donor, the stress of a major surgical procedure, an anxious postoperative wait to see whether the graft is successful, ongoing concerns about the possibility of chronic rejection, a demanding postoperative drug regimen with concomitant risks and side effects—some of which may affect appearance and may not be well tolerated by those especially sensitized to visible difference (e.g., the onset of hirsutism or alopecia) (*60*). In order to justify these costs, expectations of outcome are likely to be very positive (*61*). This may be especially true in the early days of this procedure, before it is possible to research long-term outcomes and actual levels of risk. The transplant team should have a clear understanding of the problems that are motivating the candidate to seek a face transplant, and the ways in which the surgery is expected to alleviate these. In relation to other plastic surgery procedures, unrealistic preoperative expectations of outcome are more likely to be associated with poor postoperative psychological adjustment (*53*). Prospective patients who focus on physical and/or functional (rather than psychological) change are likely to be the most satisfied (*62*, *63*).

Prior engagement with other potential solutions. An assessment should be made of whether the prospective patient has been offered any alternative, less risky interventions to tackle their difficulties. Which (if any) approaches worked, and why did the intervention fail to meet the patient's needs successfully? If it seems likely that psychological interventions would produce significant benefits for the candidate, these should be offered prior to selection for transplantation.

Psychological stability and adjustment. The prospective patient should be sufficiently resilient to cope with the considerable stress associated with the transplant, including the "unknowns" associated with a new procedure of this nature,

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the complex immunological and behavioral postoperative regimen, the risks of rejection, and intrusive media interest. Raised preoperative levels of anxiety and neuroticism have been associated with poorer psychosocial outcomes up to three years postoperatively in other groups of transplant patients (*41*).

Level of cognitive functioning. This should be sufficiently good to understand and assimilate complex risk/benefit information. As people filter information about risks and benefits in very individual ways, (*64*) and, because unrealistic optimism about risk and outcome in surgical patients is common (*65, 66*), understanding of the information given should be carefully checked. As candidates for face transplantation are likely to be highly motivated to undergo this procedure, the transplant team should be satisfied that candidates are capable of assessing whether possible improvements in quality of life outweigh the potential morbidity and mortality caused by long-term immunosuppression (*66*) and the stress of potential or actual rejection of the transplant.

Adherence "credentials". As adherence to a complex postoperative regimen is crucial to the successful outcome of the transplant and as some degree of nonadherence occurs in up to 46% of patients undergoing other types of transplant (*33–35, 67*), it would be advisable to assess the prospective patient's previous track record of compliance to medication or other forms of treatment (*63*). In transplant recipients, levels of adherence to drug regimens and levels of success in modifying risk behaviors have been shown to relate to a complex interaction of factors. These include personal characteristics, such as the age and educational level of the recipient, satisfaction with the outcome of the transplantation, beliefs about the consequences of nonadherence, side effects of the regimen, psychosocial status, and levels of practical and emotional support from family and friends (*68*). Because the patient will be required to change aspects of their lifestyle (e.g., diet, exposure to sun), a review of current patterns of relevant behaviors and levels of confidence in the ability to change them would be advisable (*69*).

The candidate's social support network. An assessment of the support offered by family and friends of the candidate should be made, because good-quality social support will buffer patients against stressors at all stages of the transplant process (*52*).

Support for those deemed unsuitable for face transplantation. The possibility of face transplantation may raise the hopes of many—few of whom will be suitable candidates for the procedure. The transplant team should have appropriate plans to provide support and alternative interventions for those who are assessed but not considered suitable for a face transplant.

The Preoperative Wait for a Donor

Once assessed as suitable, patients may have to endure a long and stressful wait for a suitable donor (*63*). Active monitoring and support should be offered on a regular basis. Even when it is judged that relevant risk and benefit information has been successfully assimilated by prospective patients, the transplant team should ensure that unrealistic expectations of postoperative change do not develop during this time.

Postoperative Support

Significant psychological difficulties including anxiety, depression, and stress reactions have been reported in several groups of transplant patients during the postoperative period (*70*). During the immediate postoperative period, communication difficulties (for example, lack of speech due to a tracheotomy, lack of movement in the facial graft) will make it hard for patients to articulate their feelings and needs.

Teams should be vigilant for signs of psychological rejection of the donor face, for example, lack of interest in looking at the face in a mirror or indications that the patient feels the new face is "not the real me" (*48, 63*). Interventions to facilitate the integration of the graft into the patient's self-image should be initiated in the early postoperative phase, for example, through self-care activities such as massaging surgical scars (*63*). The recipient may need assistance to resolve complex feelings about the donor (for example, curiosity about the sort of person, guilt about the donor's death, gratitude to the family).

The patient may be anxious about the real or imagined responses of others to the new face. Prior to discharge, the psychological staff and the rest of the transplant team should implement a program of gradual social exposure/management of social situations and should continue to encourage a sense of ownership of the face, promoting confidence in the appearance and function (*63*).

The Postdischarge Period

Dealing with an altered appearance. Recipients will have to deal with the reactions of family and friends, both to their changed appearance and to any changes in previous patterns of nonverbal communication. There will be initial uncertainty concerning the extent to which the new facial appearance will be accepted. There may be a mismatch between the recipient's preoperative expectations and how others actually respond. Ongoing support will be necessary to facilitate the gradual process of integration of the graft into the person's body image, and in the development of strategies for effectively dealing with encounters with others. Levels of sensation and movement in the face are likely to gradually increase during the first postoperative year, necessitating regular modifications to self perceptions and communication techniques.

In the case of strangers, the recipient will have to develop coping strategies to explain any visible signs of surgery, or any deficits in nonverbal communication that may accompany the transplant. If the transplant is so successful that others do not notice any signs of surgery, the recipient will have to decide whether to disclose the existence of the transplant. If recipients have been the subject of any publicity, they may be recognized by strangers and will have to deal with unsolicited questioning and unwanted attention. The risks to privacy may continue, and the recipient may need support in dealing with ongoing intrusions by the media.

Research suggests that a proportion of heart, liver, kidney, and hand transplant patients continue to experience psychological distress in the years following transplant (*41, 47, 67, 70*). Although more research is needed to fully understand this distress, a substantial proportion may be accounted for by ongoing fears of rejection and the side effects of immunosuppression.

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Adhering to treatment regimens. Posttransplant medical regimens are complex and some degree of nonadherence is surprisingly common (*33–35, 67*). As raised levels of distress and perceived stress are thought to contribute to nonadherence to immunological regimen in other groups of transplant patients (*67*), active ongoing efforts to promote psychological well-being and to support adherence are indicated (*71*). These should include strategies to cope with the side effects of immunosuppression (*72*).

As recipients will be at greater risk of developing infections and cancer, transplant teams should provide psychological support for recipients who must make unenviable decisions if they contract a serious condition. For those affected, there will be a trade off between maintaining immunosuppression (and minimizing the risk of rejection of the transplant) and boosting the immune system to maximize the chances of recovery (and possibly survival) by reducing or halting the immunosuppression. This latter course would lead, almost certainly, to rejection of the transplanted face and may well be unacceptable to a patient with a face transplant.

The risk of chronic rejection. As the "costs" of the failure of a face transplant are so high, patients are likely to be very vigilant for potential signs of rejection. In addition, transplant teams will encourage patients to self-monitor for early indicators of the rejection process. This vigilance may heighten levels of anxiety and fear, and strategies to actively manage this emotional response should be in place. If chronic rejection occurs, reductions in the plasticity and mobility of the face may result due to steadily increasing fibrosis of the transplant, especially around the eyes and mouth. Increases in immunosuppression may halt the process of rejection; however, these fibrotic changes in appearance and mobility would not be reversed. In extreme cases, the face may become masklike. These changes will require adjustment and adaptation, and the inability to show expression through facial movement will hamper social interaction. Fears of the total failure of the transplant will be further raised. Appropriate psychological support will be crucial at this time.

Transplant failure. Current estimates suggest a very real possibility of transplant failure with levels of risk increasing over the lifetime of the recipient. The psychological impact of the removal of the donor face and of the surgical procedures involved in any of the rescue packages will be considerable for all concerned and should not be underestimated. As a second transplant is unlikely, patients will probably undergo further conventional reconstructive procedures. The results of these may be hugely disappointing, particularly as recipients will have found the results of their pretransplant reconstruction unacceptable. Recipients may consider themselves to be in position that is worse than their pretransplant state. Particularly intensive support will be necessary at this time for the recipient, the recipient's family, and possibly for members of the transplant team.

The Recipient's Family

There has been relatively little research on the effects of transplantation on the families of recipients. The main areas of stress appear to focus on:

- The pressure of increased responsibilities related to optimizing the health of the recipient posttransplant (for example, reducing the risk of infection in the home environment; facilitating adherence to the postoperative drug regimen) (*71*) and
- Worries about the recipient's future physical and psychological well-being.

It has been reported that psychological distress occurs well above normative levels in family members during the immediate postoperative period, but levels appear to decline gradually in the longer term (*71*).

The face transplant "journey" is likely to be challenging for the recipient's family and supporters. The quality of support available to transplant recipients is widely acknowledged to contribute to their psychological adjustment by buffering the stress associated with the procedure and its aftermath. The family and supporters should be offered appropriate interventions preoperatively to enable them to:

- Assimilate relevant risk and outcome information;
- Relieve the stress of supporting the transplant candidate in the decision whether or not to undergo the procedure;
- Address their concerns for the patient's future physical and psychological health; and
- Explore any worries they may have about the impact of the transplant on the family and on individual members (for example, concerns about the effect on intimate relationships) (*63*).

Postoperatively, family members should be monitored for signs of excessive stress and anxiety. They may experience distress in relation to the immediate postoperative appearance and lack of facial functioning in the patient. Strategies may be needed to encourage acceptance of the new face. Family members should also be encouraged to help the patient to integrate the new face into his/her body image, to develop effective new ways of communicating and expressing emotion, and to prepare "scripts" for others about his/her new appearance (*63*). Supporters of the recipient will need to understand the importance of adherence to the immunological regimen and may need practical strategies to help maximize this in the recipient.

In the event of chronic rejection of the graft, and in cases of graft failure, the toll on families and supporters is likely to be considerable. The transplant team's plans for support should include the recipient's significant others.

Family members may also be the focus of media attention, and may need help in dealing with media intrusion.

The Donor Family

Transplant teams should also offer psychological support to donor families. The decision to donate a face of a close relative is likely to be made in the immediate and highly stressful aftermath of the death of a loved one. As the face is so closely aligned with recognition and identity, the motivation for donation may be more complex than in organ donation (for example, the family may believe that the donation will mean the relative will "live on" in some tangible way). Teams will need to develop a protocol concerning the level of support offered to donor families. Although there are well-established guidelines for the level of information given to

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families about the use of their relative's organs and tissues the intense media attention that will be associated with face transplants in the early years will inevitably make it possible for families to identify the recipient. Donor families should be made explicitly aware of this potentially distressing media exposure at the time of consenting to donation and their response to this should be monitored.

The process of bereavement may be affected in a number of ways by the donation. The rituals of death and burial may be disrupted by the early removal of the donor face (*73*). The donor family may also need support to deal with unwelcome media intrusion in the immediate and longer-term aftermath of their bereavement. In the event of a graft failure that receives media publicity, the donor family may experience a reawakening of their distress.

Societal Issues

There have been concerns that facial transplantation might have a negative effect on donation to conventional transplant programs. Reluctance to donate a relative's face may, for example, lead to the refusal to donate any body part. The impact of media coverage is also difficult to predict. Negative media coverage of poor early results may discourage potential donors, or extensive coverage of good results may increase overall donation rates. The impact of facial transplantation on donation rates for conventional transplant programs should be carefully monitored.

Experience gained following the introduction of other high profile appearance enhancing procedures suggests several likely scenarios:

- Recipients, their families, the donor's family and the transplant surgeons will be the subject of invasive press interest and publicity. All parties will need to deal with the considerable challenge of media intrusion.
- The existence and inevitable publicity surrounding the procedure will fuel the notion that a good quality of life cannot be achieved by people with disfiguring conditions. This is unhelpful for the large numbers of people affected now and in the future.
- The general public will develop unrealistic expectations of the postoperative benefits and risks of facial transplantation.
- The existence of the procedure will raise the expectations of many, while only being suitable for a few.
- Once a treatment exists increasing numbers of people will consider its use for purposes other than the original intention. It has been suggested that face transplantation will be suitable for people with congenital or post-tumoral disfigurements, or immediately posttrauma (*74*). In addition, the example of the aging rich seeking to look more youthful has been cited (*75*).

ETHICAL AND LEGAL ISSUES

Any form of surgery entails some level of risk of harm. Nonclinicians who use knives to inflict wounds on others may be found guilty of criminal charges. Surgeons who do so will not be so charged. This is for two reasons. They do not intend to cause such harm and any wounds they administer are done to achieve therapeutic benefit and with the informed consent of the competent patient, including consent to the known risks of the procedure (*76*, *77*).

It is therefore the patient and not the surgeon who is responsible for the decision that surgery be performed and who must accept any harm that results, provided that the surgery was properly done, the harm was unavoidable, and the patient was properly informed about the risk of it. The surgeon is responsible for carrying out the procedure in a fashion that conforms to acceptable professional standards and only doing so while believing it to be in the best interests of the patient. Ideally, therefore, the professional relationship between the patient and surgeon should be one of partnership.

Patients share in this partnership to the degree that surgeons respect their autonomy—their ability to make informed choices about proposed treatments. However, the duty to respect autonomy is not absolute. Even when surgical procedures entail a high risk, patients may still wish for them to go ahead. Organ transplantation entails the risks of both acute and chronic immunological rejection, together with the risks of other complications related to immunosuppressive drugs. Many patients accept such hazards because of the quality/duration of life they can expect without the transplant when compared with the known risks of having it. However, this risk-benefit ratio must also be professionally acceptable to surgeons. They will not be obligated to perform surgery unless they too believe that the risks to which they are subjecting their patient are proportional to the potential benefit that therapy might offer. The reason for such discretion is that surgeons have a duty to protect their patients as well as to respect them. In practice, therefore, any decisions to proceed with surgery should follow from concurrent autonomous choices of both patients and surgeons.

These choices, however, may sometimes conflict. Patients may refuse surgery that surgeons deem appropriate and demand surgery that surgeons do not believe merits the risk. Patients may refuse because they believe that potential risks are unacceptable. Equally, patients may want surgery whatever the risks, perhaps because of their otherwise low life expectancy or poor quality of life. Yet surgeons may still refuse to operate, whatever patients may wish (*78*). Refusal will occur when the surgeon believes that operating will pose an even greater risk of death or may even further compromise a patient's quality of life (*79*). In such circumstances, patients may seek a second opinion but if this produces the same result, there will be no option but to accept professional consensus. Here, the duty to protect the life and health of patients can be seen to trump the duty to respect autonomy.

This potential conflict between the professional duties to respect and to protect is of particular relevance to the prospect of facial transplantation. The devastating psychological impact that severe facial disfigurement can have has already been outlined in this document. In such circumstances, the desire for facial transplantation is obviously understandable, including the willingness to incur high risks for the chance of a better quality of life. Yet even if facial transplantation were a standard surgical procedure, analogous, say, to other forms of transplantation, there would still be circumstances where it would not be offered because of the surgeon's perception of the poor risk-benefit ratio. So whatever the risks, there will always be the potential for conflict with patients with facial disfigurement who wish to proceed regardless of them. Such conflict may be exacerbated by the known hazards of facial

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transplantation, along with its experimental character and the unknown hazards that this may entail.

This uncertainty can pose problems for both patients and surgeons. For example, should desperate patients who wish facial transplantation be given it, however dramatic or unknown the risks? An evaluation of this question must first outline the moral and legal boundaries of good practice as regards consent to surgical care and research.

Informed Consent and Facial Transplantation

In principle, for consent to surgery to be professionally and legally acceptable, it must be adequately informed, noncoerced, and competently given (*80*).

Information. Surgeons should explain what they are proposing to do, why the proposal makes sense in light of the patient's clinical problems, and what are common side effects and potentially worrying hazards. They should also provide information, where relevant, about other surgical or nonsurgical options. Surgeons must decide how much information to disclose and decide through asking themselves what their patients should know in order to make informed choices about their personal future. Clearly, higher risks mandate more disclosure, including communication about potential risks about which there may be inadequate information. In short, surgeons are obligated to be honest about what they both know and do not know about different risks and how probable they may be.

Given the preceding discussion in this document about the surgical and psychosocial aspects of facial transplantation, the team should ensure that potential patients have a good understanding of the following:

- Information about the background to and experimental character of facial transplantation;
- The clinical and psychological criteria for deeming the candidate to be an acceptable candidate for transplantation;
- The criteria for choosing the donor face, obtaining consent from the donor family, and divulging information about the donor for clinical and research purposes;
- The process of selecting a donor and how long the wait may be for a suitable donor;
- Procedural information relating to the transplant surgery to be performed—what will be done, how, and when;
- The likely appearance (e.g., scarring, postoperative bruising, and swelling), level of function, and sensation in the new face in both the short and long term;
- The schedule for all postoperative drugs required and for how long they must be administered;
- The postoperative healing trajectory (physical and psychological) and the support that will be provided;
- The postoperative immunosuppressive regimen, short-term side effects, and the consequences of nonadherence;
- Longer-term physical and psychological risks of facial transplantation, especially those relating to immunosuppression, acute and chronic rejection, and graft failure;
- Strategy for surgical rescue in case of rejection (acute or chronic) and/or graft failure;
- Strategy of long-term psychological and social support in the context of surgical success or failure;
- Strategy of psychological and social support for the recipient's family;
- Strategy for psychological and social support for the donor's family;
- Information about alternative interventions, surgical or otherwise; and
- The fact that refusal to participate will not affect the standard of reconstructive surgery otherwise chosen by the patient.

The processes of giving information, checking understanding, and obtaining informed consent will need to be undertaken and completed some considerable time before a transplant is performed, as there will be insufficient time once a suitable donor has been identified (*63*).

The detailed explanation of alternative treatments and confirmation of the patient's understanding of them is of heightened importance for facial transplantation. Ironically, those patients who may be best placed to give valid informed consent for the procedure may also be best able over the longer term to adapt to their existing appearance and/or to further conventional surgical intervention to improve it. This will be because their autonomy will not have been significantly undermined by distress about their disfigurement. The more vulnerable patients are made by such distress, the more likely it is that this vulnerability will create psychological difficulties in obtaining valid informed consent from them. It will be crucial to identify such difficulties before allowing patients to proceed.

Noncoercion. Even if an adequate amount of information is disclosed to patients, their consent to surgery will be invalid if anyone has pressured them into choosing as they do (*81*). Surgeons have to be especially careful about coercion since their patients are so dependent on them. There is also a high potential for coercion by relatives for the same reason. The potential for coercion can be difficult for surgeons. On the one hand, most accept that the final choice for surgery should be left to the patient. On the other hand, surgeons want what they believe to be best for their patients. Therefore, there is ample room for unintentional coercion through selecting information for disclosure that overly reinforces the surgeon's beliefs. Aside from the professional exercise of self-control, various processes exist in order to minimize the danger. Where research is concerned, one important strategy is to ensure that the process of obtaining consent guarantees independence from the clinical researcher/patient's surgeon. For example, Paragraph 23 of the Helsinki Declaration states: "when obtaining informed consent for the research the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship" (*82*). This issue is especially relevant to facial transplantation because surgeons involved will inevitably be enthusiasts—rightly so—and patients will know that they are utterly dependent upon them to obtain the transplant that they desire.

Competence. Appropriate information may be noncoercively disclosed to patients in relation to proposed surgery.

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However, any consent given by them to proceed will remain invalid unless they are competent to provide it. There are four criteria for the assessment of competence. These are the capacity of patients to understand disclosed information, to remember this information, to weigh up/reason about the choices that it poses, and to believe that the information actually applies to them (*83*). Note that all of these capacities must be present, but that their presence does not mean that patients will agree with surgical recommendations. For example, patients may have the capacity to believe their surgeons but still not accept their recommendation. Competence to consent to or to refuse surgical treatment is task oriented. A patient may be competent to consent to having a small wound sutured but not competent to consent to facial transplantation. Here, the distress or depression related to personal disfigurement may be so great as to undermine the capacities to understand, remember, reason, and believe, without this necessarily entailing incompetence to consent to other forms of surgery.

For such reasons, transplant teams should exercise great care in the evaluation of competence for the purposes of consent. For example, given the fact that facial transplantation is experimental and involves high levels of both known and unknown risks, the capacity of patients just to understand appropriate information of such complexity is an insufficient criterion of competence to provide valid consent. Rather, as Paragraph 22 of the Helskinki declaration makes clear, it should be shown that patients actually do understand such information (*82*). Equally, the ability to reason—to weigh up the risks and benefits associated with transplantation—should be agreed not to have been overwhelmed by the despair associated with the experience of dramatic facial disfigurement. Such evaluations will require specialist help from psychiatrists and psychologists that should be integrated into the process of obtaining consent. Again, it is ironic that the patients most likely to benefit subjectively from reconstructive surgery are those with the high levels of autonomy demanded to consent to transplantation. This suggests the importance of ensuring that their consent is sustained over an appropriate time and that they understand that patients psychologically similar to themselves have adapted well to conventional reconstructive surgery, without the risks of facial transplantation.

Communication About Risks

As has been noted, surgeons also have a professional duty to reveal information about side effects and potential hazards, especially those that might impinge on the personal interests of patients. The availability of accurate information about the evidence for such risks—or lack of it—will be important for the purposes of this communication. Although not without its difficulties, the legal standard probably best suited to judge the adequacy of information disclosure is whether or not it is sufficient for a reasonable and prudent person in the position of the patient to plan their future in a way that they would wish (*84*). Practically, a good approach for surgeons is to ask themselves what information they would wish to be given to close and prudent family members or friends if they were in the same position as the potential research participant.

Regarding facial transplantation, there is much that is known about risks but also much that is not (e.g., the likelihood of failure for any particular individual and the psychological aftermath of such failure). Therefore, appropriate communication with potential patients should cover both of these categories of information, emphasizing the degree to which proceeding on the basis of unknown risks constitutes a personal gamble of immense magnitude. In the face of transplant failure, it will be difficult to predict the esthetic outcome of rescue attempts using conventional surgery and the psychological impact of graft loss and further rescue surgery is even more difficult to calculate and thus to communicate clearly. Given the desperation that led to the desire for facial transplantation—of accepting, for example, the inevitability of being made unwell by and dependent upon relatively dangerous immunosuppressive drugs for a lifetime—transplant failure could be devastating for even for the most psychologically resilient patient.

Ethical and Legal Issues Concerning Donor Families

Much is already known about the psychological difficulties that requested donation can pose for both the families of deceased donors and transplant surgeons (*85*). It is clear that requests by transplant coordinators or others for organ donation can add to the burden of stress and vulnerability already experienced by relatives of potential deceased donors. They may refuse to approve the removal of the requested organ, despite the existence of a valid advance directive by the deceased authorizing such removal. When refusal of this kind occurs, surgeons are loath to override it, even though it may be legal to do so. This underlines the importance of requests from potential donor families for consent or agreement for the removal of organs or tissue being communicated with the utmost sensitivity. It is also important for those seeking such consent or agreement to be transparently independent of the transplantation team itself. The moral importance of such independence is of particular relevance to facial transplantation. This is due to its experimental character and the understandable desire of transplant teams to push ahead with such a potentially important surgical innovation and being seen publicly to do so. Therefore, transplant coordinators and all other staff who might be involved in discussion with relatives will require further training to prepare them for the special requirements required in appropriately requesting facial tissue.

Legally, it will be important to confirm the validity of any advance directive from the donor authorizing the use of their facial tissue for transplantation. In the absence of such a directive, of equal importance will be obtaining explicit written consent from the appropriate available relative in a "qualifying relationship" for the removal and transplantation of related facial skin, in conformity with the Human Tissue Act (2004). Even given the existence of a valid advance directive for donorship, it will be advisable to obtain similar agreement, especially in the context of facial transplantation. Appropriate information that should be communicated includes:

- How much facial tissue will be removed and the likely appearance of the donor;
- How the facial tissue will be transplanted on the recipient;
- What the potential appearance of the recipient will be and how closely this will resemble the donor; and
- What the risks of failure are to the recipient.

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Psychologically, the donor family should also be given guidance about the unwelcome publicity that may accompany their consent to donorship and the option for further counseling and support if for whatever reason this is required (e.g., the impact of seeing the transplanted face of their relative through media contact with the recipient). Morally, the understandable desire for a new face by a potential recipient does not trump the potential harm that can accrue to a donor's relatives through lack of proper consent and subsequent care. This is why for the purposes of facial transplantation the scope of consent from relatives should be as wide as possible and not necessarily confined to the more narrow interpretation of the Human Tissue Act.

Given the reticence of many families now to agree to the removal of organs for the purposes of transplantation, it remains to be seen how many will agree to the removal of facial tissue—especially the entire face—when presented with the preceding information. There may be great difficulties in this regard, problems of which potential recipients should be informed as part of the process of obtaining informed consent. It will be impossible to predict how long they may have to wait for a potentially viable donor face and in so doing having to forego other conventional surgical approaches to improving their appearance. It will be of equal importance for surgical teams who wish to offer facial transplantation on an experimental basis not to attempt to influence existing procedures for the equitable acquisition of organs and tissue for transplantation. While the desire to help prospective patients is commendable, nothing must be done to compromise the perceived independence of these procedures by both the medical profession and the general public.

The Experimental Character of Facial Transplantation

If surgeons do not know the risks of proposed interventions, then they cannot provide adequate information to patients about them. This is why it is important for them to be able to differentiate between standard treatment for which such information is available and surgical research where it has not been obtained (*86*). There is an inevitable catch-22 involved with the latter (*87*). On the one hand, patients need to be informed about the potential hazards of participation. On the other hand, this will never be fully possible until the research has been completed. Facial transplantation is a good example. We do know enough about other forms of transplantation to predict that there will be evidence of chronic rejection in 30–50% of standard forms of transplantation over a period of five years, along with other serious risks associated with immunosuppression, such as infection and cancer. However, the psychological risks of a failed graft are not well researched and, again, must be assumed to be immense. These areas of ignorance—along with the need to refine standard surgical techniques for the purposes of transplantation—mean that any surgeon contemplating performing facial transplantation should regard the procedure as experimental and subject it to the ethical evaluation of an appropriate research ethics committee (REC) or in the United States, an appropriate institutional review board (IRB) (*88*). For convenience, we will refer here only to RECs.

The Role of RECs in Protecting Patients

RECs have the task of ensuring that proposals for research studies comply with recognized ethical standards mandated by the Helsinki Declaration (*82*). For example, they do so by reviewing the proposed study and only agreeing to it if the dignity, rights, safety, and well being of all actual or potential research participants are protected. REC approval should be obtained for all research involving clinical interventions (*89*). RECs have a responsibility to ensure that competent patients should only participate in clinical research when they have had the opportunity to give acceptable informed consent to do so. This is particularly important since such consent makes it possible to resolve the catch-22 of needing to proceed with research in order properly to establish the risk of experimental intervention (*87*). The legal propriety of any consent given for surgical research must conform to the same criteria for valid consent for standard treatment previously outlined. However, it can be argued that it should do so with even more rigour than might be legally or professionally acceptable for assessing consent to a standard surgical procedure (*90*). One reason for this is lack of knowledge about the character and degree of some risks.

The potential vulnerability of some patients may unduly influence their willingness to consent to research posing high risks. This might be because of the nature of their illness and/or their dependence on their clinicians who also happen to be researchers. For example, committees will want to check that researchers do not overestimate the potential success of the experiment or understate its risks. Thus RECs will pay particular attention to information sheets attached to consent forms, along with the clarity of the information that they provide about what is and is not known about potential risks. Equally, Paragraph 22 of the Helsinki Declaration reiterates the importance of ensuring not just that research participants have been given appropriate information about the proposed intervention but they "have understood the information" (*82*).

Further, RECs have a duty to ensure that in their view, the risk-benefit ratio of participating in research is reasonable. This is so that patients are not asked to consent to proposals by clinical researchers that are unacceptably hazardous in the view of the collective wisdom of the REC members, based on their professional and personal experience. In doing so, for example, they will rigorously scrutinize animal studies and other relevant data. They may also take advice from other independent experts. For example, Paragraph 17 of the Helsinki Declaration states that: "Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately addressed and can be satisfactorily managed." Paragraph 18 demands that: "Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject" (*82*). This apparently means that unless the REC considers that this calculation can be done appropriately, it would be unethical for them to allow an experiment to continue even when competent patients desire it.

Evaluations of risk-benefit are often uncertain. However, such uncertainty is mitigated by the fact that good RECs include members with a range of professional and lay expertise. This should minimize uncertainty as much as is reason-

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ably possible and ensure that whatever decision is reached is done so with optimal rationality, given the information available through the research protocol. Sometimes both clinicians and patients will disagree with the decisions of RECs not to allow some clinical research to proceed. But one thing is clear. It should not be allowed unless the REC accepts the appropriateness of the agreed risks compared to the agreed benefits.

In this regard, research that involves very high risks obviously poses difficult problems for RECs. This will be particularly so in the absence of effective treatment but with the prospect of high benefit. The Helsinki Declaration provides a way forward in such deliberations. If the only option to the proposed treatment is believed to be death or more severe or permanent disability than the patient already experiences, it allows for greater flexibility in comparing risk with benefit than would be acceptable were an effective treatment already available. Paragraph 32 states: "In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy . . . The other relevant guidelines of this Declaration should be followed" (*82*).

On the face of it, Paragraph 32 of the Declaration appears to provide sufficient justification for the approval by RECs of proposals for facial transplantation. However, it does so only if the rest of the guidelines of the Declaration are followed, especially those concerning protection of research participants though independent evaluation of risk-benefit ratios and respect for their autonomy through obtaining adequate informed consent.

What the Declaration does not indicate is a way of deciding which is more important—protection from harm or respect for autonomy—when these clearly conflict. This will be when a patient wishes to proceed with a research procedure from which clear benefit may accrue but which will involve great known risks, as well as the potential for greater unknown risks. Facial transplantation reflects this conflict. For example, through the effects of immunosuppression, physically well but severely disfigured patients may be made unwell for the rest of their lives which also could be dramatically foreshortened by facial transplantation. Conversely, such patients would not qualify for transplantation unless they found life unbearable as a result of their disfigurement, wanted the procedure, and were competent to consent to it. Further potential for conflict between protection and respect exists between confident researchers and willing patients who may wish to proceed with transplantation and RECs that do not believe that proposed clinical expertise and other required support are professionally adequate.

In the face of such conflict, it would be foolish look for or expect certain answers. Again, the goal that should be sought is decision making within the REC that is as rational as possible. This is why the composition of these committees is of such importance—relevant professional expertise, lay membership, and operating procedures that will guarantee open and fair discussion. It is also important that RECs should be institutionally independent from hospitals where facial transplants are proposed. As Paragraph 13 of the Helsinki declaration makes clear, the REC "must be independent of the investigator, the sponsor, or any other kind of undue influence" (*82*).

The Moral Questionability of Facial Transplantation

In the preceding discussion, three issues have emerged about the physical and psychological risks of facial transplantation. First, the procedure itself remains highly experimental. Secondly, the procedure and its aftermath are very hazardous. Thirdly, the psychological risks for potential applicants are not well understood. We have seen that in their deliberations about the acceptability of proposals for facial transplantation—especially in their evaluation of risk in relation to benefit—both clinical researchers and RECs must take these factors into account. Therefore, let us examine them in further detail.

The Problem of Physical Safety

The implications of the highly experimental character of facial transplantation cannot be overestimated. The partial facial transplantations done in France and China have been too recent to use as good evidence about long term physical hazards. The long-term reliability of analogies with the risk data for other types of transplantation (e.g., hand) is also questionable. Aside from the dangers of immunosuppression, the most important of these risks is graft rejection. There seems little way at present to estimate the likelihood of rejection for any individual, given the volume of tissue being grafted, the small number of developed and explored animal models and continued uncertainty about the risks of immunosuppression. The general presumption must be that such risks are quite high. As has been noted earlier in this document, when the risks of acute and chronic rejection are combined, it would appear that any transplant recipient would have a long-term rejection rate of between 30–50%. Further, the risk of rejection of any further facial transplant without a complete tissue match is so likely because of sensitization that this could not be depended upon to provide a viable rescue option. Finally, the risk of unsatisfactory rescue through conventional grafting may be somewhat increased, among other things due to unexpected surgical complications relating to the failed transplant attempt and the number of further separate interventions required for an esthetically acceptable result.

Obtaining adequate informed consent to incurring these physical risks therefore appears exceedingly difficult. Doing so will entail the assimilation by potential patients of an enormous amount of information about both surgical technique and probable risks. Successful communication about the risks of immunosuppression is clearly possible and already occurs in the context of gaining consent for organ transplantation. However, the same cannot be said about communication about the risks of transplantation failure, a subject not well addressed in the literature on facial transplantation. For example, illustrations will need to be prepared for prospective patients of what failure might entail for them personally—both failure of the initial donor graft and the potential failure of further conventional grafts for the purposes of rescue. Equally, ways must be developed to ensure

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that patients have understood this information after it has been communicated and been able to weigh up the differences between these risks for their long-term appearance compared to the risks associated with conventional reconstructive techniques. Although there is literature that generally discusses the risks of transplant failure, little detail is available about the psychological impact of failure, rescue and the potential failure of rescue (*91–93*).

The Problem of Psychological Safety

There are also insufficient reliable data to estimate risks to psychological safety. We do have some evidence of the potential vulnerabilities and strengths of patients who have experienced severe facial disfigurement and received conventional surgical intervention to improve their appearance. However, there is little evidence of the potential psychological impact on patients of failed transplantation. Again, patients who are most suitable for facial transplantation will be those with optimal cognitive and emotional strength. Ironically, this may mean that despite their desire for a new face, they may already have adapted to some degree to their disfigurement. The potential loss of their old appearance, however disfigured, could therefore be incalculable. However, we have no good evidence of what "incalculable" means in this context. Indeed, even were the graft to be a technical success, patients may still be highly distressed by their new appearance, especially regarding its impact on the maintenance of already existing social networks. There may even be the possibility of a technical success but one that has abnormal side effects that could add to such distress (*60*).

How to weigh the potential for such new distress against the already existing psychological burden of disfigurement is unclear, especially in light of the uncertainty surrounding possible rejection on technical or immunological grounds. There have been interesting recent publications on the type of counseling and assessment required for selecting and preparing patients for facial transplantation. However, this does not provide an evidence base for the psychological management of transplantation failure. Psychosocially, there is a great deal that we do not understand about the risks of transplant failure, rescue, and the failure of rescue.

The Moral Acceptability of a "Leap in the Dark"

Thus far it has been shown that RECs face substantial problems in discharging their duty of protection as regards approving applications for facial transplantation. Information about the risks associated with transplant failure remains poor in some respects, particularly as regards the psychological consequences of failure and how these should be clinically managed. For this reason, it remains unclear how RECs can carry out the independent evaluation of risk-benefit ratios that is a part of their regulatory mandate. In the absence of such an evaluation—and the empirical base required to undertake it—information about some of the risks required for valid informed consent appears to be lacking. Clinicians wishing to develop protocols for facial transplantation to submit to RECs face the same issues.

Despite these difficulties, however, there is no a priori reason why prospective patients who have been shown to be sufficiently autonomous cannot be accurately informed about both known and unknown risks of transplantation—assuming that the REC has agreed the risk benefit ratio to be acceptable. Against the background of the distress caused by severe facial disfigurement the complexity of demonstrating such autonomy should not be underestimated. Yet difficulties do not entail impossibilities. Given the severity of their disfigurement and the physical and social disabilities that accompany it, patients who have acceptably been deemed competent to consent to treatment may still wish to proceed in the face of high known and unknown risks—for example, on the grounds that their lives are not worth living with their condition and that that they consider the probable results of conventional reconstructive surgery to be unacceptable. If this is so, why should respect for the autonomy of such patients not trump the clinical duty to protect them? (*91–93*).

This question now has a pertinence that it did not possess three years ago when this working party argued on ethical grounds—accepted by many others—that facial transplantation should not proceed without further research: that the risk-benefit ratio was then unacceptable and that autonomy should not be seen as trumping protection (*94–100*). Yet it is now clear that despite the known and unknown risks, some surgeons are willing to conduct facial transplantation, and some RECs in the United Kingdom and abroad are willing to approve them (*3*, *92*, *101*, *102*). It has also been shown that a significant number of patients with severe facial disability would choose facial transplantation despite the high risks (*103*). Further, during this period, there has been new research concerning the counseling of patients and the development of strategies to help autonomous candidates for transplantation make a valid informed choice to proceed (*16*). These may be some of the reasons why a few RECs have agreed that the moral argument has begun to swing in favor of deciding that some desperate though competent patients should be allowed to consent to facial transplantation despite the great risks. The agreement of other RECs may follow. If so, it will be vital for them to ensure that patients are properly informed about and understand how much is still *not* known about the potential for transplantation failure and rescue, including their own potential response to such failure. Thus, rather than to continue to maintain that there should be a prohibition on facial transplantation without more research, the working party now accepts its inevitability but endorses the urgency of establishing sound ethical principles to which REC approval should adhere before such transplantation is allowed.

If RECs allow desperate patients believed to be competent to consent to assuming the high known and unknown risks associated with facial transplantation, their endorsement of the principle of respect for autonomy does not mean that their duty of protection can be abrogated. If they decide to make such a leap in the dark, such patients will still require protection in doing so. Indeed, proper protection must be ensured since the personal stakes are so high and information about some of the risks of failure so underdeveloped. In this context, it should also be remembered that through their participation in this research and their assumption of such high risks, these patients are not just potentially benefiting themselves; they are also benefiting future generations of similarly afflicted patients as regards the potential progress of the facial transplantation program. It is clear that the management of their care in the aftermath of treatment must be planned with

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particular rigour. As part of their continued responsibility to evaluate risk-benefit ratios, RECs must ensure that any approved proposals for facial transplantation conform to the highest possible deliverable and sustainable standards of care.

It is the view of the working party that the ethical guidance thus far proposed about such standards has been helpful but lacking in some important detail, particularly about the psychological management of failure (*104*). More robust and concrete standards are required for the protection of demonstrably autonomous patients who wish a facial transplant, despite the known and unknown hazards. If adequate standards of care and protection are not in place then the moral balance is tipped back in the direction of protection rather than autonomy, even in the presence of a rational request for transplantation. Patients are not in a position to judge such adequacy. A properly constituted REC that has appropriate expertise must be convinced by transplantation protocols that standards of protection are adequate and sustainable. Only then will it be acceptable to allow competent patients to make such a dramatic and informed choice about this particular aspect of their future. The following section identifies the content of what we believe to be these minimally acceptable standards.

MINIMAL REQUIREMENTS FOR TEAMS UNDERTAKING FACIAL TRANSPLANTATION

Teams should not contemplate facial transplantations and RECs should not approve them unless an affirmative response can be given to *all* of the following questions. The acceptability of an affirmative response should be judged in relation to the relevant sections of the preceding document.

1. Does the proposing surgical unit have sufficient technical skill and experience to optimize the chances of a successful transplant? For example, there should be a consultant reconstructive surgeon with full supporting team experienced in the techniques of microsurgery. The team should be able to demonstrate a comprehensive understanding of the scope of the procedure and its implications based upon research and publications. Equally, the unit should be, and be expected to remain, a permanent component of the practice of surgery within the related hospital.
2. Does an institutional structure exist within the host hospital for integrated clinical care between the transplant team and other surgical and medical units required to optimize short- and long-term treatment? For example, all units required for optimal pre- and postoperative patient care must possess appropriate professional expertise and explicitly agree to cooperate in the provision of lifelong support for participating patients.
3. Does a comprehensive and coherent protocol exist for the selection of suitable patients for transplantation? "Suitability" will address the physical, psychological, and social attributes of the recipient, which will not only optimize the chance of surgical success but also optimize the potential for giving valid informed consent for the procedure and all aspects of its aftermath.
4. Does the REC protocol provide potential patients with adequate information on the basis of which valid informed consent can be given? Methods must be in place accurately to confirm understanding of the information and the sustained character of a choice to proceed. It is of particular importance that this information should include comprehensive explanations of the known risks of immunosuppression, as well as the risks of acute and chronic graft failure. It must be demonstrable that the patient understands what would be involved both physically and psychologically in the event of failure and attempted rescue.
5. Does the REC protocol provide adequate information for potential patients about *how little* is known about some of the risks associated with facial transplantation? This will be of particular importance for the moral and legal acceptability of any consent that is given to proceed. For example, little information exists about some of the risks following a transplant that at some point fails. These include the degree to which further conventional reconstructive surgery may be made more difficult by the initial transplant with the possibility that patients might not have a facial appearance as acceptable to them as the one they had prior to transplantation. Equally, little information exists about potential psychological risks of a successful transplant providing an appearance deemed unsatisfactory to the recipient and the potentially devastating risks of an unsuccessful transplant, with all the unpredictable physical and psychological consequences related thereto.
6. Does the surgical unit have integrated links with a team with appropriate psychological expertise (including psychiatrists and psychologists) to provide support adequate to ensure that prospective patients can give valid informed consent to facial transplantation? For example, the team should determine that the distress of the patient about their appearance will not be an impediment to their being able to understand and to weigh up the pros and cons of transplantation and thus to their being able to make a competent choice. It should be remembered that in this context, the most autonomous prospective patients may be those who have the best chance of potentially adapting to their disfigurement and thus avoiding the risks of transplantation. It is vital that evidence supporting this fact is given to prospective patients as part of the consent process.
7. In addition to the surgical team obtaining consent to the procedure, are there others involved in the process of acquiring informed consent and checking understanding who are sufficiently independent from the transplant team itself to ensure that they are not explicitly or implicitly influenced by any factors other than respect for and protection of the potential transplant patient? For example, given the understandable enthusiasm of transplant teams to achieve innovative surgical success, it is essential that risks and benefits are also presented by others with demonstrable independence. Provision should be made for a dedicated program of education and assessment of understanding that is presented in the protocol and which can be tailored to the needs of individual patients.

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8. Whether or not there is a valid advance directive, are those who will seek the consent/agreement of appropriate donor relatives for the donation of facial tissue sufficiently trained to do so? For example, coordinators and others involved with the consent/agreement process should understand how to discuss potential problems for the relatives concerning media publicity, the potential appearance of the recipient after transplantation and the possibility of transplant failure.
9. How will the psychological team provide long-term therapeutic support to the patient in the aftermath of both successful transplantation or potential and/or actual failure? Is there sufficient evidence of expertise across the team for this to be done effectively? The protocol approved by the REC should indicate a clear schedule of long term care linked to the management of potential problems of the sort already described. For example, the protocol should stipulate the schedule of support to be offered to patients waiting for surgery. In the case of successful transplantation, information should be provided about how, and for how long, patients will be followed up postoperatively in relation to indicators of depression and nonadherence to immunosuppressive medication. As regards chronic rejection or transplant failure, the protocol should articulate the ways in which this will be managed therapeutically, again in the short and long term.
10. Is the protocol clear about the mechanisms that will be in place to ensure satisfactory delivery of the duty of care toward the recipient's family? For example, preoperatively the family will require similar information about the procedure and its aftermath to that provided to the patient, along with potential psychological hazards for the family itself. Postoperatively, the recipient's family should remain within the umbrella of care for the patient, including support for the readjustment of individual members to the new appearance of the patient and for other potential psychological hazards relating to surgical complications, including graft rejection and failure.
11. Is the protocol clear about the mechanisms that will be in place to ensure satisfactory delivery of the duty of care toward the donor's family that extends beyond obtaining their consent or agreement for donation? For example, in the aftermath of surgery, media publicity surrounding the recipient will probably reveal their identity to the donor family. Indeed, their own identity may be discovered. They should anticipate these problems and understand the help that they will receive in dealing with them, as well as the obvious trauma that may be associated with seeing the new face of the recipient.
12. Can the transplant team, the psychological team, and the host hospital guarantee the long-term funding required to ensure that all patients will continue to receive the care and support specifically outlined in the protocol approved by the REC whether the transplants have been successful or unsuccessful? These patients are participants in research and not conventional medical care. For this reason, long-term follow up is essential to protect their best interests but also to ensure that optimal empirical evidence about the aftermath of surgery is properly collected and assessed. This follow-up care and research must therefore be dedicated, complex, lifelong, and inevitably expensive. Unless the financial resources sufficient for such protection and support are identified and accepted as appropriated by the REC, facial transplantation should not proceed.
13. Can the extra surgical, medical, psychological, and social care resources required for affirmative answers to the preceding questions be provided for facial transplantation by the relevant institutional payer without reducing the quality of care of other patients with facial disfigurements (among others in great need) at the host hospital? For example, if the in house psychological team required for the support of facial transplant patients perform such duties within contracted National Health Service time, this will create a shortfall that must be made up if other patients are not to suffer inequitably. Ironically, one group who might be victim to this shortfall is patients receiving conventional reconstructive facial procedures!
14. In light of the already existing shortage of transplant coordinators, can such scarcity be equitably managed in the care and support offered to the families of potential donors of facial tissue, both when they are approached to obtain consent or agreement and afterwards in the event of subsequent distress?
15. Aside from good regulatory practice in the composition of RECs to ensure appropriate and representative expertise, the membership of any such body that considers an application for facial transplantation should include experts in reconstructive surgery, immunosuppression, psychological problems posed by severe facial disfigurement and a representative of one of the organizations who provide support for those with such disfigurement. These individuals should be demonstrably independent from the transplant team proposing the transplantation, possibly through working in other hospitals. In their deliberations about specific protocols, members of the REC should be sure that they remain independent from the interests of the institution where the transplant may occur. They should equally ensure that their final decision is consistent with Paragraph 5 of the Helsinki declaration, "in medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society" (*81*).

CONCLUSIONS

Three years ago, this working party concluded that facial transplantation would constitute a major breakthrough in restoration of a quality of life to those whose faces have been severely disfigured by accident or tumor. It was therefore worthy of study. However, the working party believed that until there was further research and the prospect of better control of potential complications it would be unwise to proceed with human facial transplantation.

Since then, there has been useful progress in the understanding of the psychological problems of transplantation but there has been no change in the biological responses expected

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during and after transplantation. Although immunological tolerance has been demonstrated in animals, it has not been satisfactorily demonstrated in man. This means that conventional immunosuppression, with all its attendant difficulties, remains mandatory for both short- and long-term success.

Medium-term data is available on hand transplantation and short-term data is available for one facial transplant. The fact that two facial transplants have been carried out and that at least one institution in the United States has received ethical approval from their independent review board has caused us particularly to look again at the ethical and moral dimensions.

The working party still has considerable reservations and feels that on balance the risks cannot be quantified. We continue to advocate a cautious approach and have set out in this report 15 minimum requirements to be fulfilled before a unit or institution should contemplate undertaking facial transplantation. We believe that facial transplantation should only take place if all of these minimal requirements can be met.

If it can be demonstrated to the satisfaction of an appropriately constituted independent review committee that these minimum requirements can be met then, in our opinion, a committee might reasonably take the view that individual patients may proceed with facial transplantation in an appropriately regulated research setting.

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REFERENCES

1. Morris PJ, Bradley JA, Doyal L, et al. *Facial Transplantation. Working Party report.* London: Royal College of Surgeons; 2003.
2. Morris PJ, Bradley JA, Doyal L, et al. Facial Transplantation: A Working Party report from the Royal College of Surgeons of England: *Transplantation* 2004; 77: 330.
3. Devauchelle B, Bodet L, Lengete B, et al. First human face allograft: early report. *Lancet* 2006; 368: 203.
4. Macartney J. Face transplant for bear attack victim. *The Times* 15 April 2006; p. 9.
5. Lanzetta M, Petruzzo P, Margreiter R, et al. The International Registry on Hand and Composite Tissue Transplantation. *Transplantation* 2005; 79: 1210.
6. Thomas A. Total face and scalp replantation. *Plastic & Reconstructive Surgery* 1998; 102: 2085.
7. Buncke HJ. Microsurgical replantation of the avulsed scalp: report of 20 cases [discussion]. *Plastic & Reconstructive Surgery* 1996; 97: 1107.
8. Ustuner ET. Swine composite tissue allotransplant model for preclinical transplant studies. *Microsurgery* 2000; 20: 400.
9. Ustuner ET. Long-term composite tissue allograft survival in a porcine model with cyclosporine/mycophenolate mofetil therapy. *Transplantation* 1998; 66: 1581.
10. Ulusal BG, Ulusal AE, Ozmen S, et al. A new composite facial and scalp transplantation model in rats. *Plast Reconstr Surg* 2003; 112: 1302.
11. Unal S, Agaoglu G, Zins J, Siemionow M. New surgical approach in facial transplantation extends survival of allograft recipients. *Ann Plastic Surg* 2005; 55: 297.
12. Zhao YP, Ariji Y, Gotoh M, et al. Colour Doppler sonography of the facial artery in the anterior face. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 93: 195.
13. Renshaw A, Whitwell KA, Berger L, Butler PE. The Use of Colour Doppler Ultrasound in the Assessment of Vessels for Facial Transplantation. *Ann Plastic Surg.* In press.
14. Niranjan NS. An anatomical study of the facial artery. *Ann Plast Surg* 1988; 21: 14.
15. Soikkonen K, Wolf J, Hietanen J, Mattila K. Three main arteries of the face and their tortuosity. *Br J Oral Maxillofac Surg* 1991; 29: 395.
16. Clarke A, Butler PEM. Facial transplantation: adding to the reconstructive options after severe facial injury and disease. *Expert Opin Biol Ther* 2005; 5: 1.
17. Converse JM, Rapaport FT. The vascularization of skin autografts and homografts; an experimental study in man. *Ann Surg* 1956; 143: 306.
18. Rapaport FT, Converse JM. The immune response to multiple-set skin homografts; an experimental study in man. *Ann Surg* 1958; 147: 273.
19. Ceppellini R, Mattius PL, Scudeller G, Visetti M. Experimental allotransplantation in man. I. The role of HL-A system in different genetic combinations. *Transplant Proc* 1969; 1: 385.
20. Dausset J, Paraport FT, Legrand L, et al. [Studies on transplantation

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antigens (HL-A) by means of skin grafts from 90 children onto their fathers]. *Nouv Rev Fr Hamatol* 1969; 9: 215.
21. Dubernard JM, Petruzzo P, Lanzetta M, et al. Functional results of the first human double-hand transplantation. *Ann Surg* 2003; 238: 128.
22. Kanitakis J, Jullien D, Petruzzo P, et al. Clinicopathologic features of graft rejection of the first human hand allograft. *Transplantation* 2003; 76: 688.
23. Levi DM, Tzakis AG, Kato T, et al. Transplantation of the abdominal wall. *Lancet* 2003; 361: 2173.
24. Morelon E. Presentation at World Transplant Congress, Boston, July 2006.
25. Joosten SA, Van Kooten C, Paul LC. Pathogenesis of chronic allograft rejection. *Transplant Int* 2003; 16: 137.
26. Nankivell BJ, Borrows RJ, Fung CL, et al. The natural history of chronic allograft nephropathy. *N Engl J Med* 2003; 349: 2326.
27. Miller LW. Cardiovascular toxicities of immunosuppressvive agents. *Am J Transplantation* 2002; 2: 807.
28. Tomson CV. Cardiovascular complications of renal transplantation. In: *Kidney transplantation: principles and practice.* 5th Ed. Morris PJ, ed. Philadelphia: WB Saunders; 2001.
29. Sheil AGR. Cancer in dialysis and transplant patients. In *Kidney transplantation: principles and practice.* 5th Ed. Morris PJ, ed. Philadelphia: WB Saunders; 2001.
30. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 2004; 4: 222.
31. Opelz G, Naujokat C, Dabuek V, et al. Disassociation between risk of graft loss and risk of non-Hodgkin lymphoma with induction agents in renal transplant recipients. *Transplantation* 2006; 15: 1227.
32. Dubernard J, Owen E, Lanzetta M, Hakim N. What is happening with hand transplants? *Lancet* 2001; 357: 1711.
33. Butler JA, Peveler RC, Roderick P, et al. Frequency and impact of nonadherence to immunsuppressants after renal transplantation: a systematic review. *Transplantation* 2004; 77: 769.
34. Nevins TE, Matas AJ. Medication noncompliance: another iceberg's tip. *Transplantation* 2004; 77: 776.
35. Butler JA, Peveler RC, Roderick P, et al. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation* 2004; 77: 786.
36. Auchincloss H. In search of the elusive holy grail: the mechanisms and prospects for achieving clinical transplantation tolerance. *Am J Transplantation* 2001; 1: 6.
37. Bushell A, Wood KJ. Permanent survival of organ transplants without immunosuppresion: Experimental approaches and possibilities for tolerance induction in clinical transplantation. *Expert Rev Med* 1999: 1–31.
38. Demir Y, Ozmen, Klimczak A, et al. Tolerance induction in composite facial allograft transplantation in the rat model. *Plast Reconstr Surg* 2004; 114: 1790.
39. Siemionow M, Demir Y, Mukherjee AL, Klimczak A. Development and maintenance of donor-specific chimerism in semi-allogenic and fully major histocompatibility complex mismatched facial allograft transplants. *Transplantation* 2005; 79: 558.
40. Siemionow M, Izycki DM, Zielinski M. Donor-specific tolerance in fully major histocompatibility complex-mismatched limb allograft transplants under an anti-alphabeta T-cell receptor monoclonal antibody and cyclosporine A protocol. *Transplantation* 2003; 76: 1,662.
41. O'Carroll R, Couston M, Cossar J, et al. Psychological outcome and quality of life following liver transplantation: A prospective, national, single-center study. *Liver Transplantation*, 9, 2003; 7: 712.
42. Grady K, Naftel D, White-Williams C, et al. Predictors of Quality of Life at 5 to 6 years after heart transplantation. *J Heart Lung Transplant* 24; 9: 1431.
43. Ziegelmann J, Griva K, Hankins M, et al. The transplant effects questionnaire: the development of a questionnaire for assessing the multidimensional outcome of organ transplantation. *Br J Health Psychol* 2002; 7: 393.
44. Gribbin J, Gribbin M. *Being Human.* London: Phoenix Press; 1995.
45. Bradbury E. Understanding the problems. In: Lansdown R, Rumsey N, Bradbury E, Carr A, Partridge J, eds. *Visibly Different: Coping with Disfigurement.* London: Butterworth-Heineman; 1997.
46. Klapheke, M. Transplantation of the human hand: psychiatric implications. *Bulletin of the Menninger Clinic* 1999; 63: 2159.
47. Schuind F, Van Holder C, Mouraux D, et al. The first Belgian hand transplantation – 37 month term results. *J Hand Surg* 2006; 31B: 4371.
48. Farrer R. Psychological considerations in face transplantation. *Int J Surg* 2004; 2: 77.
49. Bruce V, Young A. *In the Eye of the Beholder: the Science of Face Perception.* Oxford: Oxford University Press; 1998.
50. Rumsey N, Harcourt D. Body image and disfigurement: Issues and intervention. *Body Image* 2004; 1: 83.
51. Macgregor F. *After Plastic Surgery: Adaptation and adjustment.* New York: JF Bergin; 1979.
52. Rumsey N, Harcourt D. *The Psychology of Appearance.* Milton Keyes: Open University Press; 2005.
53. Crerand C, Cash T, Whitaker L. Cosmetic surgery of the face. Sarwer D, Pruzinsky T, Cash T, et al., eds. *Psychological Aspects of Reconstructive and Cosmetic Plastic Surgery: Clinical, Empirical & Ethical Perspectives.* Philadelphia: Lippincott, Williams & Wilkins. 2006.
54. Pruzinsky T, Sarwer D, Cash T, et al. Multiple Perspectives on the Psychology of Plastic Surgery. Sarwer D, Pruzinsky T, Cash T, et al. *Psychological Aspects of Reconstructive and Cosmetic Plastic Surgery: Clinical, Empirical & Ethical Perspectives.* Philadelphia: Lippincott, Williams & Wilkins. 2006.
55. Kleve L, Rumsey N, Wyn-Williams M, White P. The effectiveness of cognitive-behavioural interventions provided at Outlook: a disfigurement support unit. *J Eval Clin Practice* 2002; 8: 387.
56. Newell R. *Body Image & Disfigurement Care.* London: Routledge; 2000.
57. Kapp-Simon K. Psychological interventions for the adolescent with cleft lip and palate. *Cleft Palate Craniofacial J* 1995; 32: 104.
58. Robinson E, Rumsey N, Partridge J. An evaluation of the impact of social interaction skills training for facially disfigured people. *Br J Plastic Surg* 1996; 49: 281.
59. Blakeney P, Thomas C, Holzer C, et al. Efficacy of a short-term intensive social skills training program for burned adolescents. *J Burn Care Rehab* 2005; 26: 546.
60. Peters T, Spinola K, West J, et al. Differences in patient and transplant professional perceptions of immunosuppression-induced cosmetic side effects. *Transplantation* 2004; 78: 537.
61. Simmons P. Ethical considerations in composite tissue allotransplantation. *Microsurgery* 2000; 20: 458.
62. Pruzinsky T, Edgerton M. Psychological Understanding and Management of the Plastic Surgery Patient. In Georgiade N, Georgiade C, Riefkohl R, Barwick W. *Essentials of Plastic, Maxillofacial & Reconstructive Surgery.* Baltimore: Williams and Wilkins, 1997.
63. Brill S, Clarke A, Veale D, Butler P. Psychological management and body image issues in facial transplantation. *Body Image* 2006; 3: 1.
64. Wiggins O, Barker J. Patient selection for facial transplantation III: Ethical considerations. *Int J Surg* 2004; 2: 119.
65. Weinstein N. Unrealistic optimism about susceptibility to health problems: Conclusions from a community wide sample. *J Behav Med* 1987; 10: 481.
66. Jones J. Concerns about human hand transplantation in the 21st Century. *J Hand Surg* 2002; 27A: 771.
67. Achille M, Ouellette A, Fournier S, et al. Impact of stress, distress and feelings of indebtedness on adherence to immunosuppressants following kidney transplantation. *Clin Transplant* 2006; 20: 301.
68. Dew M, Dunbar-Jacob J, Switzer G, et al. Biopsychosocial perspective on transplantation. In: Rodrigue J, ed. *Adherence to the Medical Regimen in Transplantation.* New York: Kluwer Academic; 2001.
69. Connor M, Norman P. *Predicting Health Behaviour.* Maidenhead: Open University Press; 2005.
70. Dew M, Myaskovsky L, Switzer G, et al. Profiles and predictors of the course of psychological distress across four years after heart transplantation. *Psychol Med* 2005; 1: 217.
71. Dew M, Goycoolea J, Switzer JG, Allen A. Quality of life in organ transplantation: effects on adult recipients and their families. In: Trzepacz P, DiMartini A, eds. *The Transplant Patient: Biological, Psychiatric & Ethical Issues in Organ Transplantation.* Cambridge: Cambridge University Press; 2000.
72. Rapisarda F, Tranantino A, DeVecchi A, et al. Dialysis & kidney transplantation: Similarities and differences in the psychological aspects of non-compliance. *Transplantation Proceedings* 2006; 38: 1006.
73. Toure G, Meningaud J-P, Bertrand J-C, Herve C. Facial transplantation: A comprehensive review of the literature. *J Oral Maxillofacial Surg* 2006; 64: 789.

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74. Kelly M, Butler P. Patient selection for facial transplantation I: Anatomical & surgical considerations. *Int J Surg* 2004; 2: 114.
75. Siebert C. Making Faces. *The New York Times*; 9 March 2003.
76. Doyal L. Consent for surgical treatment. In: Kirk RM, Ribbans WJ. *Clinical Surgery in General.* London, Edinburgh: 2003: 155.
77. General Medical Council. *Good Medical Practice.* London: GMC; 2006.
78. Burke v GMC [2005]. WL 1860209, para 31.
79. Re J [1991] Fam 33, [1990] 3 All ER 930; Re J [1993] Fam 15, [1992] 4 All ER 614; Re R [1992] Fam 11, (1991) 7BMLR 147. Also see: Mason JK, McCall Smith RA, Laurie GT. *Law and Medical Ethics*, Edinburgh, 2002: 317; 481.
80. Montgomery J. *Health Care Law.* Oxford: Oxford University Press; 2003: 227.
81. Re T [1992]. 4 All ER 649, CA.
82. World Medical Association. *Declaration of Helsinki*, 2004. Available at: www.wma.net/e/policy/b3.htm. Accessed 31 October 2006.
83. Jackson E. *Medical Law.* Oxford: Oxford University Press, 2006: 192–203. Also see: Mental Capacity Act 2005, Sections 2–3. Available at: www. opsi.gov.uk/acts/acts2005/20050009.htm. Accessed 1 November 2006.
84. Jackson E. *Medical Law.* Oxford: Oxford University Press; 2006: 267. Also see: British Medical Association, Medical Ethics Today. London, BMJ Books, 2004: 71.
85. Human Tissue Authority, Code of Practice – Donation of Organs, Tissue and Cells for Transplantation. 2006. Available at: www.hta.gov. uk/_db/_documents/2006-07-04_Approved_by_Parliament_-_Code_of-_Practice_2_-_Donation_of_Solid_Organs.pdf. Accessed 2 November 2006.
86. Senate of Surgery. *The Surgeon's Duty of Care: Guidance for Surgeons on Ethical and Legal Issues.* London: Royal College of Surgeons; 1997: 1–34.
87. Doyal L. Journals should not publish research to which patients have not given fully informed consent – with three exceptions. *BMJ* 1997; 314: 1107.
88. General Medical Council, *Research: the role and responsibilities of doctors.* London: GMC; 2002.
89. Further information on RECs. Available at www.corec.org.uk/index.htm. Accessed 2 November 2006.
90. Kennedy I, Grubb A. *Medical Law – texts and materials.* London: Butterworths; 2000: 1710.
91. Wiggins P, Barker JH, Serge M, et al. On the ethics of facial transplantation research. *Am J Bioeth* 2004; 4: 1.
92. Agich G, Siemionow M. Until they have faces: the ethic of facial allograft transplantation. *J Med Ethics* 2005; 31: 707.
93. Butler PEM, Hettiaratchy S, Clarke. Managing the risks of facial transplantation. *Lancet* 2006; 368: 662.
94. Strong C. Should we be putting a good face of facial transplantation? *Am J Bioethics* 2004; 4: 13.
95. Caplan A. Facing ourselves. *Am J Bioethics* 2004; 4: 18.
96. Baylis F. A face is not just like a hand: pace Barker. *Am J Bioethics* 2004; 4: 30.
97. Masche K, Trump E. Facial transplantation research: a need for additional deliberation. *Am J Bioethics* 2004; 4: 33.
98. Huxtable R, Woodley J. Gaining face or losing face? Framing the debate of face transplants. *Bioethics* 2005; 19: 2005.
99. Clarke A, Butler P. Face transplantation: psychological assessment and preparation for surgery. *Psychol Health Med* 2004; 9: 315.
100. Clark PA. Face transplantation: an ethical perspective. *Medical Scientific Monitor* 2005; 11: RA41.
101. Hall C. Full-face transplant gets go-ahead. *The Daily Telegraph,* 26 October 2006. Hawkes N. British doctors seek patient for world's first full-face transplant. *The Times*, 26 October 2006.
102. Clark PA. Face transplantation: a medical perspective. *Medical Scientific Monitor* 2005; 11: RA1.
103. Barker JH, Furr A, Cunningham M, et al. Investigation of risk acceptance in facial transplantation. *Plastic Reproductive Surg* 2006; 118: 663.
104. ASRM/ASPS. Facial transplantation – ASMS/ASPS guiding principles. Available at: www.microsurg.org/ftGuidelines.pdf. Accessed 1 November 2006.

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