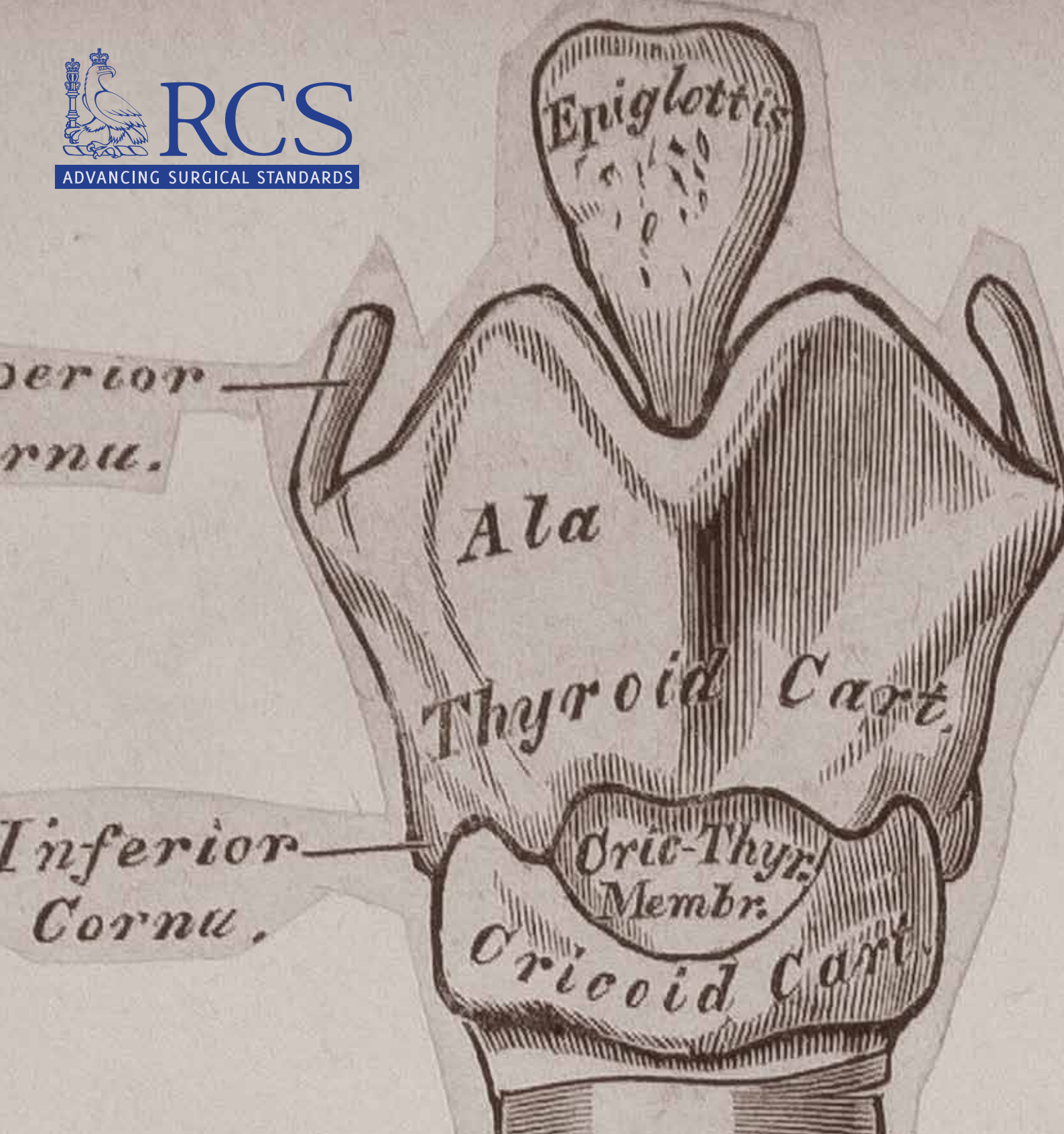




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ADVANCING SURGICAL STANDARDS



Laryngeal transplantation

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The cover image of this document is taken from the India proofs of the first edition of Gray's Anatomy, held in the College archives.

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Foreword

Transplantation continues to progress at a rapid pace but still remains one of the most challenging areas of modern medicine. Since the first kidney transplant over 50 years ago we are now able to transplant solid organs such as kidneys, livers and hearts with good short and long-term outcomes for patients. Many advances in the surgical aspects over the last half century would not have been made possible without our understanding of how the immune system responds to a transplanted organ and the development of corresponding immunosuppressive treatments that prevent rejection.

I hope the guidance in this report will be helpful to those involved in pioneering this operation in the UK and will also provide useful information to patients who may benefit in the future from this procedure. Some of the contents of this

report will also be applicable to other areas of transplantation. I appreciate that a new transplant procedure brings into sharp focus many ethical, psychological and societal questions, which I believe this report addresses in order to inform the wider debate.

I would like to thank the working group for bringing their wide range of expertise to this work. I recommend it as a good summary of this new area of surgery as well as a source of guidance to those involved in pioneering the operation to ensure that this procedure delivers the best possible outcomes for patients.

John Black

President, The Royal College of Surgeons of England

Executive summary

The aim of laryngeal transplantation is to restore a physical and functioning organ, to replace a lost or irreparably injured larynx (voice box) and to allow the recipient to achieve 'normal' or 'acceptable' stoma (tracheostoma), free breathing, swallowing and voice. The first successful operation was a total laryngeal transplantation performed by Marshall Strome in Ohio, USA, in 1998. Since that pioneering procedure only one other human total laryngeal transplant has been undertaken worldwide but never, so far, in the UK.

Like all surgical procedures, laryngeal transplantation carries risks and burdens as well as benefits. Laryngeal transplantation is aimed at improving quality of life rather than saving life and it carries potentially lifelong medical implications. Although immunosuppressive therapy is ever improving, trauma patients would be the ideal candidates for early laryngeal transplantation. The assessment and selection of laryngeal transplant candidates is important, ideally with the medical and psychological criteria being defined in advance of the procedure by a multi-disciplinary team. The risks involved in laryngeal transplantation warrant a thorough disclosure and a detailed consent form. Patient confidentiality should be upheld, unless the patient consents to revealing otherwise protected information.

The working party believes that there is a potential for laryngeal transplantation to improve the quality of life of an individual who has lost or irreparably damaged his or her larynx. In the decade since the first (and only) published transplantation was conducted, there have been advances in both surgical technology and immunosuppression that make the short and long-term outcomes for recipients more predictable.

This report recommends that laryngeal transplantation only be contemplated in patients who have suffered irreversible trauma or injury to their larynx or patients who, as a result of a large benign or low-grade malignant tumour, have undergone treatment by way of a total laryngectomy. At present, because of the increased risk of a second cancer, patients who have been treated for locally advanced or recurrent throat cancer should not be considered suitable.

The report also highlights that recent successes in specific sites, such as arm and face transplantation, indicate that there can be a reduced need for intensive immunosuppression. The report also makes specific recommendations that the transplant team provide and monitor detailed functional and psychological outcomes pre and post-operatively.

1 Background

Transplantation is one of the most challenging and complex areas of modern medicine. The field of transplantation medicine continues to progress at a rapid pace, with improvements in the outcomes of established transplants (such as heart, kidney and liver) as well as new areas (such as face, arm and hand), which are still in their infancy.

Advances in transplantation have only been possible by corresponding developments in our understanding of how the immune system responds to transplanted organs and tissues and the effect on the viability of the transplant. Of particular importance has been the development of immunosuppressive treatments that

prevent rejection, thereby maintaining viability of the transplanted organ.

One area of transplantation that has received much attention in the surgical literature is the potential to transplant a voice box (larynx). The College set up a working group to consider the progress of laryngeal transplantation and whether such surgery ought to be performed in the UK, given the current state of knowledge and its future.

This report provides guidance to those involved in pioneering the operation in the UK as well as adding information to the wider debate in this new area of transplantation.

1902	Alexis Carrel demonstrates a method of joining blood vessels to make organ transplant feasible in France
1905	First reported cornea transplant by Eduard Zirm takes place in Moravia (now Czech Republic)
1954	First successful kidney transplant operation performed by Joseph Murray in Boston, USA
1963	First liver transplant performed by Thomas Starzl in Denver, USA
1967	First heart transplant operation performed by Christiaan Barnard in South Africa
1983	First combined heart and lung transplant performed by Magdi Yacoub, UK
1994	NHS Organ Donor Register established in the UK
1998	First hand transplant performed by Clint Hallam, France First laryngeal transplantation performed by Marshall Strome, Ohio, USA
2001	First complete double arm transplant carried out by Edgar Biemer and Christoph Hoehnke, Germany
2005	First partial face transplant carried out by Bernard Devauchelle and Jean-Michel Dubernard, France
2008	First stem-cell airway transplant performed by Paolo Macchiarini, Spain, and Martin Birchall, UK
2010	First full-face transplant carried out by Joan Pere Barret, Spain

Table 1 Modern tissue transplantation

2 Laryngeal transplantation

The aim of laryngeal transplantation is to give the recipient normal breathing, swallowing and voice production. Laboratory research providing pre-clinical information on laryngeal transplantation has been documented since the 1960s and continues to be documented and published. The first total laryngeal transplant operation was carried out in the Cleveland Clinic, USA, in 1998 under the leadership of Professor Marshall Strome. Since that pioneering procedure relatively few documented human laryngeal transplants have been undertaken.

Potential recipients of laryngeal transplants are those who have suffered trauma, not correctable with conventional surgical techniques, and who have no useable voice (aphonic). Other potential recipients include those with large benign or low-grade malignant tumours of the larynx and who five years post laryngectomy are considered cured. These groups of potential patients are relatively few in number. Many more are potential patients who have locally advanced throat (laryngeal or hypopharyngeal) cancer but who at present are not considered suitable candidates because of the high-recurrence cancer risk associated with systemic immunosuppression. The latest research provides some optimism that this barrier is not insurmountable.

Laboratory and clinical research have provided some of the technical and immunological answers essential before clinical work could be considered and have highlighted remaining challenges. These problems include restoring neural control to the larynx (re-innervation), the need for organ-specific immunosuppression strategies to prevent rejection, the development of improved devices that provide electrical stimulation of paralysed laryngeal muscles (pacing devices) and organ-sparing techniques.

How the larynx works

The larynx is another name for the voice box. Its position in the neck changes from childhood to adulthood. The larynx is contained within a tube that grows to approximately 5cm in length. It sits at the entrance of the windpipe (trachea) in the neck, in front of the food pipe (gullet or oesophagus). The larynx is positioned behind and alongside the lump in the front of the neck known commonly as the Adam's apple.

The larynx is where the breathing and digestive systems separate. Its primary functions are to direct the air into the lungs when breathing, to protect the trachea when swallowing and to make voice (phonation). During breathing, the larynx is relaxed, leaving the air passage fully open so air can move through the space without making any sound. When swallowing, the larynx closes (the vocal folds adduct) and a part of the larynx called the epiglottis closes tightly over the trachea. These simultaneous actions stop food and saliva going into the lungs. The vocal cords are two bands of muscle that form a 'V' shape inside the larynx. These vibrate together when air passes between them. This produces the sound of the voice. The vocal cord area is clinically called the glottis, above the cords is the supraglottis and below the cords is the subglottis.

The larynx is made of several pieces of a smooth, shiny tissue called cartilage. The cartilage is surrounded by fibrous tissue. The largest cartilage of the larynx is the Adam's apple (thyroid cartilage). Additionally, laryngeal closure enables an effective cough, clearing the lower respiratory passage and allowing increased abdominal pressure necessary for bowel function, urination and childbirth.

The basic functions of the larynx (protective, respiratory and phonatory) are derived from sophisticated nervous control

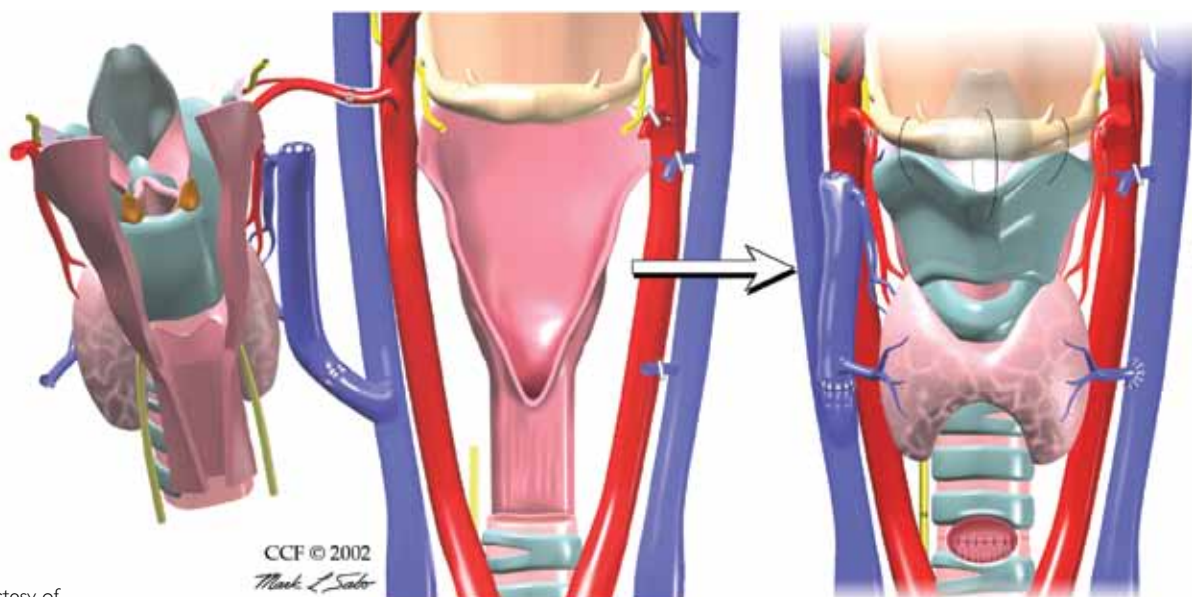


Image courtesy of
Mark Sabo,
Cleveland Clinic

Figure 2.1 The 1998 surgical technique of laryngeal transplantation

(described in more detail below). The protective function is entirely reflexive and involuntary. In contrast, respiration and phonation can also be voluntarily controlled.

Which parts need to be transplanted?

Despite 40 years of research, there has only been one documented human total laryngeal transplant, which continues to function more than 13 years after transplantation. Advances in tissue engineering, stem-cell technology and nanotechnology all offer the possibility of creating 'off the shelf' tissues and organs, some time in the future. However, given the complexity and multiplicity of functions, it remains hard to see how such an approach would replicate the potential solution offered by a successful transplantation. In theory, depending on which laryngeal function is being replaced or restored, it is currently theoretically possible that a partial laryngeal transplant would suffice and restore function. However, whatever tissue is used or transplanted, successful grafting requires the re-innervation of nerves and re-anastomosis of blood vessels.

BLOOD SUPPLY

The larynx has two arterial blood supplies. The superior laryngeal artery predominantly supplies the supraglottis and the inferior artery supplies the subglottis, though a connection (anastomosis) exists between these branches.

NERVE SUPPLY

The entire larynx is stimulated (innervated) by one nerve (vagus nerve), which is on both sides of the neck (bilateral). The superior laryngeal nerve (a branch of the vagus) divides into an internal and an external branch. The external nerve innervates the cricothyroid muscle, which tightens the vocal cords. The internal nerve enters the larynx to be distributed to the laryngeal mucosa above the vocal cords, supplying sensory and secretory stimulation (innervation). The inferior laryngeal nerve supplies all of the intrinsic muscles of the larynx except for the cricothyroid. For efficient and effective laryngeal function, sensory nerves are required to provide local tissue sensation and initiate reflex functions, and motor nerves, to create appropriate movements in response to the reflexes and produce sound.

Initial work connecting the donor and recipient nerves to restore function by primary anastomosis led to poor results, including misdirected nerves (laryngeal synkinesis) and total loss of function. Over the past decade a range of techniques for selective re-innervation have been attempted, with mixed results, but slow progress has been achieved. In addition to restoration of motor input to the larynx, sensory restoration is key for airway protection.

Primary nerve re-anastomosis techniques have improved greatly in the last decade, with decreasing innervation intervals and greater numbers of surviving neuronal elements. When patients have undergone a total laryngectomy for tumour, safe oncological

techniques involving wide excision may result in removal of a significant portion of the donor nerves. Thus nerve interposition grafts may be necessary. **Progress in our understanding of nerve regeneration continues and is one way in which laryngeal transplantation can become a viable and widely available surgical procedure.** Pacing devices have been shown to be beneficial in improving neuromuscular deficits, such as control of gait, and have also been used allowing for functional electrical stimulation to be applied to paralysed laryngeal muscles, thus providing an alternative source for restoring function to non-functioning vocal cords.

Functional outcomes of laryngeal transplantation

The ultimate aim of laryngeal transplantation is to provide the patient with normal breathing function (without the need for a small opening in the windpipe – tracheostomy), normal swallowing function and normal voice production. This requires the transplanted larynx to have sufficient voluntary movement for vocal fold adduction (coming together) and abduction (moving apart) (for breathing and voice) and laryngeal elevation (for swallowing). In addition, laryngeal sensory function is necessary to facilitate detection of food and secretions in the laryngeal area, which may otherwise be aspirated. More detail on the main functional outcomes is provided below:

BREATHING

At rest and during physical activity the vocal folds need to be sufficiently separated (abducted) to allow for adequate inspiration and expiration. The need to create an adequate airway through the glottis while also enabling maximum voice and minimum chance of aspiration is the ultimate challenge to this procedure. Clearly, successful functional outcomes require optimum sensory and motor function of the laryngeal structures.

SWALLOWING

A functioning larynx is essential (a) to provide glottal closure to prevent food or fluid from entering the trachea and (b) to facilitate timely opening of the crico-pharyngeal sphincter to allow food and drink to pass into the oesophagus. Again, sufficient motor control should in theory mean that normal swallowing physiology is possible following laryngeal transplantation. It is unclear whether these laryngeal movements will be sufficiently timely and coordinated compared with normal laryngeal excursion during swallowing.

VOICE AND SPEECH QUALITY

Laryngeal transplantation provides a new vibratory source for the patient's voice. However, the patient's 'energy source' for voicing (pulmonary expiratory air) and the patient's sound resonating chamber (the pharynx, naso-pharynx and oral cavity) will be the same as before he or she required surgery (his or her pre-morbid state). Therefore 'normal' voice quality is a theoretically possible outcome. **It is unclear how the patient with a transplanted larynx will sound in comparison**

with his or her original (pre-morbid) voice quality. The patient’s accent is essentially formed by his or her lips, cheeks, tongue and palate (the articulators) and therefore will remain intact. It is less certain how the more subtle (but equally important) features of the human voice (eg rhythm, stress and intonation – also known as prosodic features) will present following laryngeal transplantation since these features require additional fine motor control.

Alternative techniques for voice restoration

When a patient undergoes surgical removal of the larynx, there are several current options of ‘voice restoration’ available that do not involve transplantation. These are (a) oesophageal voice (b) electro-larynx voice and (c) tracheo-oesophageal voice (fistula voice). These are briefly summarised in the table below:

	Sound activator	Vibratory source	Articulators
Oesophageal voice	Air voluntarily introduced into upper oesophagus and then expelled	Pharyngo-oesophageal sphincter	Lips, tongue, soft palate
Electro-larynx voice	Battery driven	Tone generator	Lips, tongue, soft palate
Tracheo-oesophageal voice	Pulmonary air re-directed through prosthesis	Pharyngo-oesophageal sphincter	Lips, tongue, soft palate

Table 2.1 Summary of current voice restoration options

We are not aware of any current research into the implantation of a mechanical or ‘artificial’ larynx into the laryngectomised patient. Current mechanical or electrolarynx devices use a handheld vibrating machine, which is placed externally on the cheek or neck. It enables the user to be understood although the sound is not designed to sound like a human voice and is monotonous and electronic.

Most of the research in the field of voice restoration has been devoted to maximising the practice of surgical voice restoration programmes for patients who have undergone a laryngectomy. As a consequence, the literature provides many reports of relatively small incremental advances in surgical technique, prosthesis design and management of complications with these patients. However, surgical voice restoration, by definition, is unable to match the goals potentially offered by laryngeal transplantation – ie normal voice, swallowing and stoma-free breathing.

Previous laryngeal transplantations

In the late 1980s, Marshall Strome and colleagues developed a research programme to explore the feasibility of laryngeal transplantation. The work was initially developed in an animal model in which the sequences of the transplantation were studied in detail. In 1998 the group performed the first human-to-human total laryngeal transplantation in a man who had sustained a severe laryngeal trauma that had occurred in a motorised vehicle accident.

The whole of the pharyngo-laryngeal complex was taken from the donor and was transplanted into the recipient, ten hours after removal. The recipient was able to speak his first words on the third day after the operation. He suffered two episodes of rejection at fifteen months and six years after the operation but both were successfully managed by medication. The patient opted to retain his tracheotomy for reassurance though clinically this should not have been necessary. Options that would allow the closure of the tracheostoma following the transplantation are available such as a laser cordotomy (a technique to remove excess vocal cord mucosal tissue). At a conference in 2010 Professor Strome presented voice recordings from the patient eleven years after transplantation, which showed that the voice quality had changed little. The patient believes the operation has ‘immeasurably’ improved his quality of life.

In addition to the Strome case, the working party has been made aware of additional reports of further work involving partial and total laryngeal transplantation. These cases have yet to be reported and subjected to peer review, acceptance and publication. We look forward to analysing and commenting on such cases when the publications become available.

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3 Immunology

Transplanted materials that include a diverse range of tissues (such as skin, muscle, tendons, nerves and vessels) are known as composite tissue allografts. These are complicated to manage in transplantation as they bring about various levels of immune response. Skin is considered a major barrier to composite tissue allografts due to the high immune response it generates in the recipient. However, over the past decade there have been major advances in treatments to overcome the immunological rejection of transplanted organs or tissues. For example, such advances have led to successful partial and full-face transplants, which previously had not been possible in part due to the absence of suitable immunosuppressive treatments.

Advances in immunology and suppression

The main risk with organ and tissue transplantation is rejection. The field of hand transplantation has successfully addressed many issues relevant to laryngeal transplantation. By following the lessons learned in renal, hepatic and cardiac transplantation, the various hand transplantation teams have achieved what was previously considered by many as impossible. The development of the field has included careful weighing of the risk/benefit of upper-limb transplantation in relation to potential long-term toxic effects of immunosuppressive therapies.

Early risk of infection has been well controlled with prophylactic antibiotics and antiviral agents in all organ transplantation and to the best of our knowledge infection has not been encountered in the cases reported in the literature. The possible development of superficial skin malignancies, Epstein–Barr virus-associated lymphomas (less than 1% in renal transplant) and cervical carcinomas is, despite its extremely low incidence, a major stimulus to development of operative tolerance to allografts in the future.

Rejection rates

Clinical transplantation of the upper extremity has been performed in several centres and acute rejection when diagnosed can often be successfully treated. It is clear that composition of the graft, ie skin, muscle, nerves, bone, etc, as exemplified by upper-limb transplantation, is a form of complex allograft that behaves in many ways similarly to immediately vascularised solid-organ allografts. The technical aspects have been well developed for many years on the basis of successful autografts. The rejection rate will probably be in the range of 8% to 10% but this does not mean loss of the graft. These rejections are easily reversible with the right immunosuppressive regimen, which includes methylprednisolone and monoclonal antibodies.

Long-term effects

Long-term immunosuppression means lifelong. All transplants need lifelong immunosuppression otherwise they will be rejected almost immediately. This requires compliance with drug regimens by the recipient. Current immunosuppressive protocols using new agents have led to over 90% of grafts

surviving after the first year and much-reduced side effects for the recipient. It is likely in the very near future that the immune system of most patients will be regulated by a combination of immunosuppressive therapies to make transplantation safer than it is today.

A regimen that involves one dose of alemtuzumab on the day of transplant and long-term tacrolimus monotherapy should be effective to prevent rejection and should allow long-term survival of laryngeal transplants. This regimen is currently used in many transplant centres involving the transplantation of different organs. Long-term survival of over 95% would be expected based on the experience of arm transplantation, which is another composite tissue allograft. The expected correlation in behaviour between the two transplants allows us to extrapolate from one composite allograft to another. Research is ongoing to reduce the risks associated with immunosuppression in composite tissue allografts further.

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4 Psychological and social issues

Effective communication is fundamental to psychosocial wellbeing and approximately one-third of our communication takes place through verbal channels. In addition, the voice is a key aspect of identity, with markers reflecting upbringing and education. People who have undergone laryngectomy, even those with tracheoesophageal prostheses or an electro-larynx may feel they have lost a crucial aspect of their identity and can become socially isolated and/or depressed. Levels of satisfaction with current post-laryngeal procedures are not high. Clements *et al* (1997) reported that only 33% of those with oesophageal speech were satisfied with the quality of their communication, with 40% of patients satisfied with speech derived from an electrolarynx and 55% of those with who had undergone tracheoesophageal punctures. The potential psychological gains that may be achieved through the restoration of the function and form of the larynx are therefore considerable.

The growth of transplantation surgery in recent years has led to an increase in studies examining the actual and potential psychological responses of recipients, which should be considered in the context of laryngeal transplantation. As there are only minor health problems associated with the absence of the larynx, unlike some other forms of transplantation, the primary focus of the proposed procedure is to enhance quality of life through an improved ability to communicate.

Patient selection

The assessment of the suitability of potential patients to undergo a laryngeal transplant should include psychological aspects.

Patients should be motivated to undergo the procedure by self-interest rather than requesting transplant surgery in response to the agendas of their families or their treatment providers. The patient's level of cognitive functioning should be sufficiently good to enable him or her to understand and assimilate potentially complex risk/benefit information and to make a competent choice about undergoing the procedure. Levels of understanding of the risks of lifelong immunosuppression, the demands of the long-term post-operative drug regimen and of changes in habitual patterns of behaviour necessary to minimise the risks associated with compromised immune functioning (for example, changes to diet to reduce risk of diabetes; reductions in sun exposure to reduce the risk of skin carcinomas) should be carefully checked. Some degree of non-adherence is surprisingly common (levels of up to 46% have been reported in the literature) and the achievement and maintenance of the levels of adherence necessary to keep the risk of rejection acceptably low is acknowledged to be challenging.

During the pre-operative phase potential patients should be encouraged to adopt realistic expectations of the probable outcomes of surgery, as these have been shown to be associated with positive post-operative outcomes in related research. Patients may be motivated to seek surgery in the expectation

that the transplant will result in a full restoration of their original voice quality, function and range. Although near-normal speech may be possible, subtle or significant differences in voice quality and some restrictions in function are likely. Patients should also be aware of the probable extent and positioning of post-operative scarring, as if visible, this is likely to attract unwanted questioning from others in social situations.

Treatment teams should be aware that in the early days of this procedure, media attention is likely to be considerable (see section 7). Media coverage may result in potential patients, friends and family members developing unrealistic expectations of the post-operative benefits and the associated risks. Publicity will also raise the hopes of those for whom the procedure is unsuitable (eg patients with cancer), who may come forward to request treatment. Teams should include help and support for those who are deemed unsuitable for the procedure in their capacity planning.

Treatment decision making

Potential patients will vary in the extent to which they will be willing to trade the risks associated with potentially lifelong immunosuppression for the possibility of improved communication. Unlike some other forms of transplantation, the motivation to seek a laryngeal transplant will relate to improving quality of life rather than extending life expectancy. Some studies have explored the levels of risk potential patients might find acceptable. An early study by Potter and Birchall identified that a strong majority of laryngectomees would find transplant an acceptable procedure, particularly if they could be reassured the procedure was 'safe' and the voice could be re-established. 58% would accept the procedure including a significant risk to life; 50% would accept the procedure even if their voice could not be guaranteed. However, 20% would not accept the operation even if it were safe and simple.

A more recent study by Reynolds and colleagues indicated that laryngectomees ($n=53$) may be a relatively risk-averse group in comparison with healthy controls ($n=64$) and previous organ transplant recipients ($n=42$). The authors found that laryngectomees were generally unwilling to trade decreases in survival time for improvements in quality of life, despite the fact that their levels of satisfaction with alternative forms of communication were not high and the potential gains in communication considerable. The study also showed that those who had previously undergone laryngectomy would accept higher levels of risk when considering other forms of transplantation.

Post-operative issues

Significant psychological difficulties including anxiety, depression and stress reactions have been reported in several groups of transplant patients both during the post-operative period and in the months and years that follow. More research is needed

to understand this distress fully, though a substantial proportion may be accounted for by ongoing fears of rejection and the side effects of immunosuppression.

In the early post-transplant phase, psychological support should be available to facilitate the process of regaining laryngeal speech. Excitement about this form of communication may be tempered for some by an emotional reaction related to receiving a transplanted organ. Patients may need help to resolve complex feelings about the donor (for example, gratitude and guilt) and in a minority of cases may attribute any differences between their newly acquired and pre-morbid voice qualities to characteristics of the donor.

Fears about the viability of the transplant and of rejection

Although the consequences of the failure of a transplant are rarely life-threatening the patient is likely to be fearful of the possibility of rejection and the potential failure of the graft. As with any new transplantation procedure, in the early stages of development the functional outcomes are unpredictable. The patient must be prepared for a realistic outcome by the transplant team and informed of other possible eventualities through the consent process (see section 5).

Following the transplant, the surgical team will encourage patients to self-monitor for potential signs of rejection and recipients may feel a heavy burden of personal responsibility for the success or failure of the procedure. This focus on signs and symptoms may heighten levels of anxiety and fear, and may lead to hyper-vigilance for signs of rejection such as pain and/or swelling in the throat. The patient may also experience anxiety in relation to real or potential side effects of immunosuppression. Intensive psychological support will be necessary at times of threatened or real rejection and if the graft fails.

Integrating the transplant into an existing body image

Some patients may experience difficulty integrating their new voice into their sense of personal identity. They may be anxious about the real or imagined reactions of others post discharge and may need ongoing support to accommodate and benefit fully from changes in their capacity to communicate. Postoperative scarring may be visible to others. Strategies may need to be developed to deal effectively with the reactions and questions of others to the audible and visible signs of the transplant and to optimise the social functioning of the patient.

Adherence to post-transplant treatment regimens

In recipients of other transplants, levels of adherence to drug regimens and levels of success in modifying risk behaviours (eg diet, alcohol, smoking, exposure to sun) have been shown to relate to a complex interplay of factors including the age and educational level of the recipient, satisfaction with the outcome of the transplant, beliefs about the consequences of non-adherence, side effects of the regimen psychosocial status

and levels of support from family and friends. As raised levels of distress and perceived stress are also thought to contribute to non-adherence to immunological regimens in other groups of transplant patients, active efforts to promote psychological wellbeing are indicated. These should include strategies to cope with any side effects of immunosuppression.

There has been relatively little research on the effects of transplantation on the families of recipients. The post-transplant period is nonetheless likely to be stressful. The quality of support available to transplant recipients is widely acknowledged to contribute to their psychological adjustment and levels of adherence to immunosuppressive regimen. Families would benefit from advice about how best to encourage patients to develop effective new ways of communicating and to prepare responses to questions from others about their new voice. Supporters of the recipient will need to understand the importance of adherence to the immunological regimen and will appreciate practical strategies to help them to maximise adherence in the recipient.

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5 Ethico-legal issues

Risks and benefits of laryngeal transplantation

Like all surgical procedures, laryngeal transplantation carries risks and burdens. To adhere to the ethical principles of beneficence (ie acting in the best interests of the patient) and non-maleficence (ie not causing net harm to the patient) the benefits of the intervention must be deemed to outweigh the risks and burdens. Surgeons should not perform procedures that they reasonably believe will result in net harm to the patient.

It is not possible to stipulate with confidence that the benefits of the procedure outweigh the risks and burdens, especially as uncertainty remains about the exact probability of developing complications and the degree of improvement in voice and swallowing. Laryngeal transplantation is a burdensome procedure with potentially lifelong medical implications aimed at improving quality of life rather saving life. However, recent progress in immunology has considerably reduced the burden of immunosuppression and the probability of graft rejection (see section 3). Furthermore, as the larynx is a non-vital organ, total rejection of the transplanted larynx with subsequent excision – the worst case scenario – is not incompatible with life.

Some patients may reasonably and autonomously decide that in the context of their values and in spite of the statistical uncertainties the potential benefits of laryngeal transplantation outweigh the risks and burdens. In light of the potential medical benefits and the proportionate risks, the procedure is not contrary to clinical integrity. When considering a laryngeal transplant the aim is to achieve stoma-free breathing, non-aspirating swallow and then voice, in that order. While they are all interrelated the restoration of voice may only be as a result of one vocal cord moving or even neither; swallowing as such may or may not be improved but may still overflow and continue to aspirate. Ability to laugh and cough may be a function of only partial laryngeal function and the patient may still have difficulties with swallowing and aspiration.

For those who wish to opt for laryngeal transplantation the priority is to minimise the risks and burdens associated with the intervention and its after-effects and ensure that the patient understands and freely consents to the procedure and its implications.

Recruitment and consent process

Although immunosuppressive therapy is ever improving, trauma patients would be the ideal candidates for early laryngeal transplantation. **It is recommended that the multi-disciplinary team define in advance the medical and psychological criteria for selecting patients for laryngeal transplantation.** This will allow a more objective method of selection at the time of recruiting patients.

A widely accepted definition of consent is 'a voluntary, uncoerced decision, made by a sufficiently competent or

autonomous person on the basis of adequate information and deliberation, to accept rather than reject some proposed course of action' (Gillon, 1985). Below is a discussion of the three main components of consent: information, voluntariness and competence.

INFORMATION

The inevitable uncertainties about the risks and benefits of an experimental procedure such as laryngeal transplantation present a challenge to the provision of adequate information to patients. Therefore clinicians obtaining consent must be open and honest about the uncertainties as well as the known risks and benefits of the procedure and the post-operative regimen. The high risks involved in laryngeal transplantation warrant a thorough disclosure and a detailed consent form. As in other situations the clinicians should make sure that the information is conveyed in a manner understandable to the particular patient. The patient should also be provided with printed information about the procedure, again written in clear and comprehensible language, so that the patient can read details of the intervention in his or her own time and seek the opinion of others.

RECRUITMENT AND VOLUNTARINESS

During recruitment, the potential patient must be free from undue pressure from the clinicians involved in recruitment.

Performing a laryngeal transplantation, especially if it is the first in the UK, will confer prestige on the institution, the medical team involved and the surgical profession. This can lead to overt or covert pressure to perform the procedure. **It should never be forgotten that the clinicians' first priority should be the welfare of the patient.** They should not cede to any pressure if this means the patient may not give valid consent or patient care may be adversely affected.

Clinicians recruiting a recipient must also be aware that friends, relatives or other third parties may unduly influence patients. If this is suspected, efforts must be made to consult the patient alone to establish the patient's true wishes.

To ensure that the patient truly wants and understands the intervention, it is strongly recommended that there should be a 'cooling-off period' of a minimum of one month but ideally longer between the detailed explanation of the procedure to the patient and his or her final authorisation of the procedure. This period will allow the patient to consider more freely the implications of the procedure, consider the alternatives, read any relevant literature, discuss the options with friends and relatives, and ask any questions to the healthcare team.

Consent is a dynamic process, which means that the patient can withdraw his or her consent at any time before the operation, even if the consent form has been signed and without the need to provide any reasons. The patient must be informed of this

possibility and reassured that the medical team would not look unfavourably at a change of mind. The team may stress that they would much prefer that the procedure be postponed or cancelled than it be performed with the patient feeling unsure about the decision.

While the recipient must be carefully selected on medical and psychological grounds, the donor also requires careful selection to maximise the probability of success and minimise adverse consequences (eg no pre-existing laryngeal pathology). Care should also be taken in obtaining agreement from the donor's relatives. It should be emphasised that the recipient will not have the same or even a similar voice to the deceased donor. The discussion should of course be conducted in a sensitive manner and, to minimise the possibility of manipulation or coercion, by a suitably qualified person who is independent of the operative or post-operative team. As the transplant coordinators and other staff may not be familiar with laryngeal transplantation, they may need to be specially trained to conduct these discussions.

Although the law currently allows the removal of the larynx from a deceased patient who has given prior approval for organ retrieval, even in the face of refusal by relatives the committee recommends that retrieval not be performed if the relatives of the prospective donor object. This is because the relatives may receive considerable media attention following transplantation. This may be distressing to them, the recipient, his or her relatives and the medical team. It may also damage the reputation of the institution and the medical profession generally.

COMPETENCE

The Mental Capacity Act 2005 states that in order to have capacity patients must be able to:

1. understand the disclosed information
2. retain it for long enough to make the decision
3. weigh up the reasons for and against the proposed intervention
4. communicate their decision

As consent is task-specific, patients must be sufficiently competent to consent to the complex and potentially long-term intervention that is laryngeal transplantation.

Research ethics

A treatment involving a single patient can constitute research if there is a 'clear intent before treating the patient to use systematically collected data that would not ordinarily be collected in the course of clinical practice in reporting and publishing a case study' (Kagarise and Sheldon, 2001).

The committee recommends that the medical team proposing the procedure first present their proposal to their institution's clinical ethics committee (CEC) (if the institution has one. This involves discussing details of the project with the CEC. The vast

majority of CECs do not instruct the clinician on what to do but provide advice that the clinician may accept or reject. The team should then submit a formal application to a research ethics committee (REC). Unlike CECs, RECs are independent of the institution. The REC will ascertain among other things whether the 'importance of the objective outweighs the inherent risks and burdens to the subject' (paragraph 18, Declaration of Helsinki).

It should be noted that the Helsinki Declaration appears to permit research on laryngeal transplantation, with suitable protections:

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 [paragraph 32].

The benefits of laryngeal transplantation cannot currently be achieved by other, less invasive means and those benefits for some patients will help re-establish their overall health and alleviate the suffering caused by the inability to speak or swallow normally. If the CEC or REC feels unable to review the application because of insufficient clinical or ethical expertise, it should seek such expertise externally.

To share their experiences, positive and negative, with the scientific community, the medical team has a duty to write up and publish the results in peer-reviewed journals, remembering that the unique nature of the case means that specific consent for publication from the patient will be necessary.

Key references and further reading

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Service implications

Performing a laryngeal transplantation requires not only the commitment of the surgeons involved in the procedure but also of other clinicians and staff who will be involved in various aspects of the patient's pre-operative and post-operative care. In addition, for the procedure to be able to take place, commitment from the health service for resource to be allocated to be able to do this also needs to be in place.

Assessing patient suitability

A thorough assessment of the potential patient should be undertaken. This assessment should include an evaluation of the psychological suitability of the candidate to deal with the challenges of transplantation and subsequent rehabilitation, his or her motivation to undergo the procedure and expectations of the physical, functional and psychological outcomes. As adherence to a post-operative immunosuppressive regimen is crucial to the successful outcome of the transplant and as some degree of non-adherence is common in patients undergoing other types of transplant, it is advisable to check the adherence credentials of potential patients in relation to previous medication regimen or other forms of treatment.

The team should also have the capacity to provide access to psychological support for those not deemed suitable for the procedure once the selection process is completed. For those accepted as candidates for laryngeal transplantation and for their families, appropriate support should be available during the potentially long wait for a donor and to prepare them for the procedure once a donor has been identified. Psychological support will also be necessary during the post-operative period (for example, to facilitate the development of new communication strategies), prior to discharge (to develop strategies to deal with the potential responses from others and to address fears about leaving the safety of the ward) and during a prolonged follow-up period (monitoring psychological and social adaptation; dealing with ongoing fears of rejection; resolving problems with communication or the responses of others; and promoting adherence to postoperative treatment regimens).

In the case of early transplants, media interest in the patient, the patient's family and in the donor family is likely to be considerable and may well be invasive. Additional support should be available to all parties in dealing with this interest.

Training of surgical and peri-operative teams

One way to minimise the risks of operative and post-operative harm is by providing thorough training to those involved in patient care. Developing competence is a moral requirement, falling under the broad principle of beneficence. Edmund Pellegrino, the physician and ethicist, notes that 'the vulnerability of the patient, and the trust patients must ultimately place in the physician's skill, are the foundation for the obligation to be competent in performance as well as in knowledge'.

The procedure itself is long and complex. Surgeons in the operating team must have proved and recognised experience in microsurgery, notably of nerves and vessels, and reconstructive surgery. The committee strongly recommends the surgical team perform the procedure on cadavers until they are comfortable with the procedure before performing a laryngeal transplantation on a live person. Operating on animal models is not sufficient to capture the nuances of performing a human laryngeal transplant.

The institution in which the operation will be performed must have adequate pre and post-operative care with the relevant professional multidisciplinary expertise needed to provide a high level of care for the patient. This includes the means to support the patient, medically and psychologically, in the short, medium and long term.

The team who performs the laryngeal transplantation will also require expertise in functional outcome measurement. Since this is a new procedure **it is incumbent upon the transplant team to provide detailed functional outcomes at pre and post-operation stages.** The following set of outcome measures is recommended:

- | | |
|------------------|--|
| Voice outcomes | <ul style="list-style-type: none"> a. The GRABS perceptual rating scale b. Vocal handicap index c. Basic acoustic analysis (eg jitter, shimmer, HNR) |
| Swallow outcomes | <ul style="list-style-type: none"> a. MD Anderson Dysphagia Inventory b. Swallowing performance status scale c. 100ml water swallow test d. Flexible endoscopic evaluation of swallowing e. Videofluoroscopic swallow studies |

It is strongly recommended that all of these measures be performed pre-transplantation and at regular intervals or until voice and swallowing outcomes have stabilised. Measures of patient wellbeing and distress (eg anxiety and quality of life) should be monitored before and after transplantation and at follow-up. The extent to which patients' expectations of outcome are met and their perceptions of the treatment burden should also be recorded and reported in the early phases of laryngeal transplantation.

Advance care planning and follow-up requirements

The surgical intervention is one step in a long therapeutic process. As with all high-risk procedures it is advisable to consider advance care planning, exploring the patient's expectations, hopes, and worries. The medical team needs to anticipate adverse scenarios, such as graft rejection and infection, and prepare adequately for these eventualities. The contingency plans must be shared and, if appropriate, negotiated with the

patient in a sensitive manner as part of the consent process. Any specific wishes by the patient about future care must be documented. The patient must also be offered the possibility of appointing a lasting power of attorney, as described by the Mental Capacity Act 2005, who will help the medical team make 'best interest' decisions in the unlikely event that the patient loses capacity or is unable to communicate his or her wishes post-operatively.

The institution must have facilities and staff available to deal with the acute and chronic problems that may arise post transplantation. There should be regular follow-up to check on the patient's progress. It is thus important that the institution proposing the procedure, as well as the patient, medical team and other stakeholders, appreciate that a laryngeal transplantation is a long-term commitment that does not end with the final suture.

It is very likely that the patient will require specialist speech and voice therapy post transplantation. Simply transplanting the organ (larynx) and expecting it to function normally is unrealistic. Voice therapy is likely to be focused on coordination of breathing (control of expiratory airflow) with vibratory phonation. Mastery of pitch and volume control of the new larynx may also be required. Swallowing therapy is likely to be focused on coordination of laryngeal closure with the pharyngeal stage of swallow. It is likely that this programme of speech/voice therapy will be intensive (daily) and for at least one month post transplantation.

Key references and further reading

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7 Other considerations

Dealing with the media

A total laryngeal transplant is a major medical achievement and it is probable that there will be considerable media interest following the first laryngeal transplantation (and possibly the first few transplants) in the UK. The patient, his or her relatives, the donor's relatives and the medical team should be prepared for public attention. Patient confidentiality should be upheld unless the patient consents to revealing otherwise secret information. It is possible, however, that even if clinicians maintain confidentiality, the identity of the patient, the relatives, the donor and the donor's relatives will be unearthed by

journalists. This should be explained to the patient and the donor's relatives when obtaining consent. The institution should offer media training to these individuals and should have means, through a press office or other such department, to manage the media attention.

The anticipated media attention provides an additional reason to ensure that the institution's processes in conducting one of the world's first laryngeal transplants, from recruitment to surgical training to post-operative follow-up, are transparent and clinically, morally and legally robust.

8 Conclusions and recommendations

The working party believes that there is a real potential for laryngeal transplantation to improve the quality of life of an individual who has lost or irreparably damaged his or her larynx. In the decade since the first and only published transplantation was conducted, there have been advances in both surgical technology and immunosuppression. This has resulted in a more predictable improved short and long-term outcome for recipients. The working party is particularly aware of the importance of selecting the correct patients for such a procedure and ensuring that they and their families comprehensively and fully understand the risks and benefits of laryngeal transplantation and its associated treatments.

Below is a summary of the working party's key recommendations:

- > Potential recipients of a laryngeal transplantation should be only those who have suffered irreversible trauma or injury to their larynx or patients who as a result of a large benign or a low-grade malignant tumour have undergone treatment by way of a total laryngectomy. Presently in the UK a total laryngectomy is most frequently performed on patients with locally advanced or recurrent squamous cell carcinoma (cancer). In light of the present state of knowledge and the associated risk of immunotherapy, such patients are considered unsuitable for laryngeal transplantation because of the high risk of further tumour recurrence. Further research is required before such patients can be considered suitable.
- > Transplantation of the laryngeal organ itself is currently possible but further work in the area of nerve regeneration

remains ongoing and is essential if the transplanted larynx can become a functional (breathing, voice and swallowing) and universal surgical procedure.

- > Experience gained from performing heart, liver and kidney (solid organs) transplant has led to a revolution in the knowledge of the immunology and surgical techniques that underpin organ transplantation. Recent successes in specific sites such as arm and face transplantation indicate that there can be a reduced need for intensive immunosuppression in the short and long term, a feature that may be likely to be replicated in laryngeal transplantation.
- > The multi-disciplinary care team will need to define in advance of performing a laryngeal transplant the medical and psychological criteria for the selection of suitable patients. It is recommended that a psychologist and/or a psychiatrist be a core-member of such a selection team.
- > Since laryngeal transplantation is a 'new procedure' it is incumbent upon the transplant team to provide and monitor detailed functional and psychological outcomes at pre and post-operation stages.
- > Given the novelty, risks and uncertainties of laryngeal transplantation, the non-life threatening nature of the underlying condition, the anticipated media attention, and the research and publications likely to be generated from the procedure, the medical team should strive at all times to act in accordance with the highest ethical standards and fulfil their fundamental moral obligation to act in the best interests of the patient.

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Laryngeal transplantation

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