

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction

Inserting a titanium implant that is not covered by soft tissue for orofacial reconstruction

Titanium implants can be inserted to replace bones in the face as part of orofacial reconstruction, that is, rebuilding the face when there is severe damage to the bones or deformity. This is most commonly needed after injury or surgery to remove tumours, or to treat deformities of the face that have been present from birth.

In this procedure, the implants are customised (made specially to fit the person). An accurate model is made of the bones of the person's face. The model is used as a template to make the implant, which is then fixed in position using titanium screws during an operation. The implant is not covered by soft tissue.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in December 2012 and updated in May 2013.

Procedure name

- Insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction

Specialist societies

- British Association of Oral and Maxillofacial Surgeons

- Craniofacial Society of Great Britain and Ireland
- British Association of Head and Neck Oncologists.

Description

Indications and current treatment

This overview is about the use of titanium implants for complex facial reconstruction, often involving multiple surfaces, including bony and cartilaginous structures, without soft tissue cover and without the expectation of substantial soft tissue cover. It does not refer to the use of titanium orbital floor/roof/wall reconstruction, malar (cheekbone) implants, titanium miniplate/microplate/reconstruction plate techniques or the use of total temporomandibular joint prostheses where implants are covered or expected to become substantially covered with soft tissue.

Various materials are used to strengthen or replace parts of the facial skeleton after severe orofacial trauma, surgery for orofacial tumours or occasionally for treating congenital facial abnormalities. Materials that have been used include autologous grafts; alloplastic materials such as silicone, titanium or hydroxyapatite; composites (for example, titanium mesh embedded in porous polyethylene); and tissue-engineered bone. Traditionally, autologous materials have been used for the repair of large orbital and facial fractures. Limitations of autologous grafting include prolonged operating times, long hospital stay, increased postoperative discomfort and donor site complications. There is also a variable rate of resorption and consequently clinical outcomes may be unpredictable.

The traditional method of preparing titanium implants for facial reconstruction is to bend and cut titanium mesh during the operation. Positioning the implant in the appropriate site requires an accurate assessment of shape and fit, and a number of insertion attempts may be necessary before correct implant shape is achieved. The use of computer-aided design and computer-aided manufacturing (CAD-CAM) techniques to produce customised implants before the operation aims to facilitate the implantation process. This reduces operating time and in some cases reduces the number of operations needed; it may improve safety (for example in areas of restricted access such as around the optic nerve), and outcomes.

What the procedure involves

The design and construction of custom-made implants can be achieved by a number of different techniques. In most cases, customised implants are designed and manufactured using CT scan data by CAD-CAM and 3-dimensional printing techniques. In some cases a model is constructed on which the implant is shaped and made, either directly or indirectly. To improve facial symmetry, unilateral defects are repaired by creating a skull model or computer image in which the unaffected side has been mirrored.

With the patient under general anaesthesia the sterilised titanium implant is fixed to adjacent bone using titanium screws. Precise details of the operation will depend on where the implant is to be used and the integrity of surrounding structures.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction. Searches were conducted of the following databases, covering the period from their commencement to 18 March 2013: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients needing complex orofacial reconstruction.
Intervention/test	Insertion of customised exposed titanium implants.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on 17 patients from 1 case series and 2 case reports¹⁻³.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction

Abbreviations used: THORP, titanium-coated hollow screw reconstruction plate																									
Study details	Key efficacy findings	Key safety findings	Comments																						
Peckitt (1999)¹ Case series UK Recruitment period: 1996–1999 Study population: patients with head and neck tumours. n=14 Mean age: not reported Sex: not reported Patient selection criteria: not reported Technique: different implant types were used, all based on custom-designed skull models. Some solid titanium implants were computer-milled. In other patients, a titanium-coated hollow screw reconstruction plate (THORP) system was used. Average follow-up: 2 years Conflict of interest/source of funding: the author is the Director of ComputerGen Implants Ltd.	Number of patients analysed: 14 Overall outcomes It was reported that the maxilla, hemimandible and nose were successfully reconstructed without needing to raise flaps. After 2 years of follow-up, all patients remained disease-free and had an acceptable quality of life. Attempts to reconstruct the subtotal mandible in 2 patients failed because of lack of soft tissue adherence. Both patients underwent further conventional procedures after the implants were removed. Speech Speech was described as excellent in 1 patient and unaffected in 1 patient. Swallowing Swallowing was described as excellent in 1 patient and unaffected in 1 patient. Also, 1 patient was described as ‘able to chew’, and 2 patients had a fully restored dentition. Appearance Appearance was described as excellent in 3 patients. Vision ‘Return of normal vision to one eye’ occurred in 1 patient.	<table><tr><th colspan="2">Complications (Unless stated, timescales were not reported)</th></tr><tr><th></th><th>n</th></tr><tr><td>Post-operative bleeding. Nasal packs were used to arrest the bleed in 1 patient, and were removed after 20 hours. In another patient the bleed occurred at the site of their feeding tube. A laparoscopic procedure was needed.</td><td>2</td></tr><tr><td>Disseminated intravascular coagulation (patient underwent further conventional procedures after the implant was removed)</td><td>1</td></tr><tr><td>Lip retraction, separation of the soft palate from the implant, and obliteration of the buccal sulcus.</td><td>1</td></tr><tr><td>Implant failure (caused by scar contracture), needing further conventional procedures.</td><td>2</td></tr><tr><td>Fistulae – After 2 years, 1 pinhole fistula developed at the site of a THORP rivet head. This was closed with a simple lateral rotation flap. - 1 orocervical fistula developed in a patient with arterial pathology. Four flap procedures (with hyperbaric oxygen therapy) were unsuccessful. The fistula was closed using titanium chain mail with a solid titanium diaphragm. - 1 fistula closed with an infrahyoid flap, and did not recur. - 1 fistula successfully closed (method not described) after treatment with hyperbaric oxygen.</td><td>4</td></tr><tr><td>Transient discomfort and redness (after radiotherapy) – 2 years after. Related to increased motility of tissues against THORP rivet head. Acute tissue inflammation was treated with antibiotics and hyperbaric oxygen.</td><td>1</td></tr><tr><td>Infection (methicillin-resistant <i>Staphylococcus aureus</i> [MRSA]) leading to removal of THORP implant.</td><td>1</td></tr><tr><td>Residual nerve weakness in buccal branch of facial nerve.</td><td>1</td></tr><tr><td>Trismus (inability to open the mouth normally) –</td><td>1</td></tr></table>	Complications (Unless stated, timescales were not reported)			n	Post-operative bleeding. Nasal packs were used to arrest the bleed in 1 patient, and were removed after 20 hours. In another patient the bleed occurred at the site of their feeding tube. A laparoscopic procedure was needed.	2	Disseminated intravascular coagulation (patient underwent further conventional procedures after the implant was removed)	1	Lip retraction , separation of the soft palate from the implant, and obliteration of the buccal sulcus.	1	Implant failure (caused by scar contracture), needing further conventional procedures.	2	Fistulae – After 2 years, 1 pinhole fistula developed at the site of a THORP rivet head. This was closed with a simple lateral rotation flap. - 1 orocervical fistula developed in a patient with arterial pathology. Four flap procedures (with hyperbaric oxygen therapy) were unsuccessful. The fistula was closed using titanium chain mail with a solid titanium diaphragm. - 1 fistula closed with an infrahyoid flap, and did not recur. - 1 fistula successfully closed (method not described) after treatment with hyperbaric oxygen.	4	Transient discomfort and redness (after radiotherapy) – 2 years after. Related to increased motility of tissues against THORP rivet head. Acute tissue inflammation was treated with antibiotics and hyperbaric oxygen.	1	Infection (methicillin-resistant <i>Staphylococcus aureus</i> [MRSA]) leading to removal of THORP implant.	1	Residual nerve weakness in buccal branch of facial nerve.	1	Trismus (inability to open the mouth normally) –	1	Follow-up issues: • Timescales for development of complications were not all reported. • Some patients had multiple complications. • It was not clear how many of the patients who received a THORP implant had a plate with a buccal placement. Study design issues: • Selection of patients for inclusion appears to have been subjective. • The study implied that 1 patient did not have a customised skull model made. It has been assumed that the corresponding implant was custom-made, this is not clear. • Full efficacy data were not available. The reporting of outcomes appears to be highly selective. Most complications listed occurred with THORP implants. • Biased reporting is possible because of the author’s close involvement with a company that manufactures implants. Study population issues: • Procedures were carried out in different orofacial areas (maxilla, mandible, orbit or nose). • 53.3% (8/14) patients were treated using the THORP system. Other issues: • These implants were inserted with deliberate exposure of nasal and oral titanium surfaces. • It was reported that a postoperative dental malocclusion included
Complications (Unless stated, timescales were not reported)																									
	n																								
Post-operative bleeding. Nasal packs were used to arrest the bleed in 1 patient, and were removed after 20 hours. In another patient the bleed occurred at the site of their feeding tube. A laparoscopic procedure was needed.	2																								
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Trismus (inability to open the mouth normally) –	1																								

Abbreviations used: THORP, titanium-coated hollow screw reconstruction plate				
Study details	Key efficacy findings	Key safety findings		Comments
	Healthcare resources The author proposed that use of the single-stage reconstruction technique leads to a reduction in theatre time, less need for intensive care, and earlier discharge from hospital.	physiotherapy was instigated. Ulceration of the THORP implant through the skin. 1 patient had an acrylic cover plate fitted over the exposed section. In another patient who had received radiotherapy, at 1 year an exposed plate was trimmed (showing evidence of osteoradionecrosis), and closure was achieved with a trapezius flap. Loosening of the reconstruction plate caused some tissue irritation .	'All patients with buccal placement of the plate'	maintenance of an existing crossbite in 1 patient. It was assumed that this was intentional, rather than a surgical complication.

Abbreviations used: THORP, titanium-coated hollow screw reconstruction plate			
Study details	Key efficacy findings	Key safety findings	Comments
Raghavan (2006)² Case reports UK Recruitment period: not reported Study population: patients in whom large titanium implants have been used in nasal reconstruction n=2 Mean age: 47 years Sex: 0% (0/2) male Patient selection criteria: previously inserted large titanium implants for nasal reconstruction, with subsequent complications. Technique: large, customised, solid titanium implants were used. The implant in case 1 had been prepared using computer-assisted design and was not covered by an internal vascularised layer. The implant in case 2 was described as titanium scaffolding without an internal lining. Follow-up: not reported Conflict of interest/source of funding: not reported	Not reported	Case report 1 – Complications Soft tissue contraction caused the implant to protrude through the tip of the nose. During 5 surgical procedures the tip of the implant was cut as the soft tissue retracted, leading to an unfavourable facial appearance; the patient became a recluse. At time of the sixth procedure, the implant projected into the left nostril. Pus, granulation tissue and scar tissue was found around the implant site. The implant was found to be fractured and was removed. After 1 further procedure, the patient was happy with the cosmetic result at final follow-up, 2 years after the final corrective surgical procedure. Case report 2 – Complications A palatal perforation occurred following an attempt to cauterise a bleeding point on the palate. The titanium implant became exposed over the right medial canthus, both internally and externally. Eight operations were carried out to cover the implant at the exposed site with local rotation flaps but all attempts failed. The zygomatic branch of the facial nerve was weak. Many attempts (absolute number not recorded) were made to correct the patient's columella, tip of nose and collapsed ala.	Follow-up issues: - The patient in case report 1 was referred to the authors 3 years after the implant was placed (5 years after the trauma occurred), and was followed up for 2 years after corrective surgery. - The period of time that had elapsed since the original procedure in case report 2 was not stated. The study refers to some previous attempts to rectify complications, but at the time of publication the patient had deferred her decision to undergo further surgery to cover the defect. Study design issues: - The report describes serious complications that had occurred postoperatively in patients who had been treated using large titanium implants at another hospital. The patients were referred to the authors after the complications had arisen, and after attempts to rectify the problems had not been successful. Details about the original procedures are therefore limited. - The number of patients who have undergone successful nasal reconstruction procedures using large titanium implants was not reported.

Abbreviations used: THORP, titanium-coated hollow screw reconstruction plate			
Study details	Key efficacy findings	Key safety findings	Comments
Dawood A (2012)³ Case report UK Recruitment period: not reported Study population: patient in whom a titanium implant has been used for nasal reconstruction n=1 Age: not reported Sex: female Patient selection criteria: not reported Technique: customised bifunctional titanium implants (Nobel Biocare) were used (designed and milled using computer-aided design/computer-assisted manufacturing technology). The implant was placed via an intraoral approach and was designed to provide anchorage at both its ends, making it possible to simultaneously stabilise nasal and dental prostheses. Follow-up: not reported Conflict of interest/source of funding: not reported	'The implant greatly facilitated the surgical and prosthetic management for the simultaneous provision of nasal and oral prostheses'	No safety outcomes were reported.	The authors noted that the tissue response of the nasal mucosa to titanium implants does not appear to have been adequately studied or reported. The paper presents limited patient outcome data but has been included because it describes a new kind of customised exposed titanium implant.

Efficacy

In a case series of 14 patients, it was reported that the maxilla, hemimandible and nose were successfully reconstructed without needing to raise flaps for coverage. After 2 years of follow-up, all patients remained disease-free and had an acceptable quality of life. Appearance was described as excellent in 3/14 of patients¹. Attempts to reconstruct the subtotal mandible in 2 patients failed because of lack of soft tissue adherence. Both patients underwent further conventional procedures after the implants were removed.

Safety

Disseminated intravascular coagulation

Disseminated intravascular coagulation was reported in 1 patient in a case series of 14 patients who had undergone reconstruction following removal of head and neck tumours.

Implant exposure

Ulceration of THORP implants through the skin occurred in 'all patients with buccal placement of the plate' in the case series of 14 patients who were treated for head and neck cancer. Eight patients had been treated using THORP, however it was not reported how many of them had buccal placement of the implant. It was noted that 1 patient was treated by fitting an acrylic cover plate over the exposed section of the THORP implant. The same study reported failure of implants in 2 patients because of scar contracture; they were subsequently treated with conventional procedures¹.

Unintentional implant exposures also occurred in 2 patients described in case reports in a postoperative study of complications that occurred after insertion of large titanium implants for nasal reconstruction. Both patients needed a number of additional procedures².

Infection

Infection (methicillin-resistant *Staphylococcus aureus* [MRSA]), needing removal of the THORP implant was reported in 1 patient in the case series of 14 patients treated for head and neck cancer¹.

Fistulae

Fistulae were reported in 4 patients in the case series of 14 patients who had undergone reconstruction following removal of head and neck tumours. Two of the fistulae were closed with relatively simple flap procedures, and a third was closed using adjuvant hyperbaric oxygen therapy. The fourth fistula was found after 2 years at the site of one of the rivet heads on the THORP implant. This orocervical fistula failed to close after 4 flap procedures and hyperbaric oxygen

therapy; eventually titanium chain mail with a solid titanium diaphragm was used to close the fistula¹.

Bleeding and haematomas

Postoperative bleeds occurred in 2 patients from the case series of 14 patients who had facial reconstruction procedures following tumour removal. A laparoscopic procedure was needed to stop a bleed from the site of a feeding tube. The other bleed was arrested with nasal packs.

Validity and generalisability of the studies

- The aim of this overview is to summarise studies of exposed customised titanium implants for complex orofacial reconstruction, without soft tissue cover. In practice, it was often difficult to identify which studies met this particular scope – only 1 of the papers referred to in this report specifically stated that areas of the implants were intentionally left exposed¹.
- The term ‘customised’ has not been defined, and there are a number of possible methods of customising a titanium implant for an individual, each of which may have a different degree of accuracy and/or clinical success. Studies were excluded from this report if it was clear that the implant had not been tailored to the individual patient’s anatomy, or if computerised techniques had not been used in the implant design process. Computer-assisted design (and computer-assisted manufacture) may refer to the production of the skull model, or the implant, or both.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

Insertion of customised titanium implants, with soft tissue cover, for orofacial reconstruction. NICE interventional procedures guidance 449 (2013). Available from www.nice.org.uk/guidance/IPG449

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr S Dover, Mr D Koppel, Mr I Martin (British Association of Oral and Maxillofacial Surgeons), Mr C Kerawala (British Association of Head and Neck Oncologists).

- All 4 Specialist Advisers consider the procedure to be definitely novel and of uncertain safety and efficacy.
- Conventional biological reconstruction (local flaps, pedicled flaps or free tissue transfer) would be a comparator to the procedure.
- Fewer than 10% of specialists are engaged in this area of work.
- Theoretical adverse effects include recurrent infection, bone infection, possibly septicaemia, externalisation, bone resorption, loosening of the implant, poor aesthetics and failure of the prosthesis.
- Adverse events reported in the literature are infection and implant loss.
- Key efficacy outcomes include reduced operating time, reduced morbidity, prosthesis removal/long-term retention rates (1 year), fixation (screw) removal rates, survival rates (for patients with cancer).
- Training in computer-aided design is necessary.
- All 4 Specialist Advisers consider the potential impact on the NHS to be minor, in terms of numbers of patient eligible for treatment and use of resources.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

None other than those described above.

References

1. Peckitt NS (1999) Stereoscopic lithography: customized titanium implants in orofacial reconstruction. *British Journal of Oral and Maxillofacial Surgeons* 37: 353–69.
2. Raghavan U, Jones NS (2006) The complications of giant titanium implants in nasal reconstruction. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 59: 74–9.
3. Dawood A, Tanner S, Hutchison I (2012) A new implant for nasal reconstruction. *International Journal of Oral and Maxillofacial Implants* 27: e90–2

Appendix A: Additional papers on insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Schubert W, Gear AJL, Lee C et al. (2002) Incorporation of titanium mesh in orbital and midface reconstruction. Plastic and reconstructive surgery 110: 1022–30.	n=8	The titanium mesh underwent progressive incorporation with soft tissue that was then resurfaced by indigenous cells, including respiratory epithelia and goblet cells. This phenomenon occurred despite communication with the nasal-oral-pharyngeal area and paranasal sinuses.	It is likely that the implants were not customised.

Appendix B: Related NICE guidance for insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction

Guidance	Recommendations
Interventional procedures	Insertion of customised titanium implants, with soft tissue cover, for orofacial reconstruction. NICE interventional procedures guidance 449 (2013). 1.1 Current evidence on the efficacy and safety of customised titanium implant insertion for orofacial reconstruction, including reconstruction of the orbital floor, where implants are covered or expected to become substantially covered with soft tissue, is adequate for this procedure to be used with normal arrangements for clinical governance, consent and audit or research. This guidance does not cover complex orofacial reconstruction involving multiple bony and cartilaginous structures, with little or no soft tissue cover.

Appendix C: Literature search for insertion of customised exposed titanium implants, without soft tissue cover, for complex orofacial reconstruction

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	18/03/2013	Issue 2 of 12, February 2013
Database of Abstracts of Reviews of Effects – DARE (CRD website)	18/03/2013	Issue 1 of 4, January 2013
HTA database (CRD website)	18/03/2013	Issue 1 of 4, January 2013
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	18/03/2013	Issue 1 of 12, January 2013
MEDLINE (Ovid)	18/03/2013	1946 to March Week 1 2013
MEDLINE In-Process (Ovid)	18/03/2013	March 15, 2013
EMBASE (Ovid)	18/03/2013	1974 to 2013 Week 11
CINAHL (NLH Search 2.0/EBSCOhost)	18/03/2013	1981 to present
JournalTOCS	18/03/2013	n/a

Trial sources searched

- Current Controlled Trials *metaRegister* of Controlled Trials – *mRCT*
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched

- National Institute for Health and Care Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Titanium/
2	titanium*.tw.
3	1 or 2
4	"Prostheses and Implants"/
5	Maxillofacial Prosthesis/
6	Maxillofacial Prosthesis Implantation/
7	Bone Plates/
8	(prothes* or implant* or screw* or mesh* or template* or plate*).tw.
9	or/4-8
10	3 and 9
11	branemark.tw.
12	10 or 11
13	Computer-Aided Design/
14	((computer* adj3 aided* adj3 design*) or CAD or (computer*-aided* adj3 design*)).tw.
15	Magnetic Resonance Imaging/
16	((magnet* adj3 resonanc* adj3 imag*) or MRI).tw.
17	((Computer* adj3 aid* adj3 manufact*) or CAM).tw.
18	stereoscopic*.tw.
19	stereolithograph*.tw.
20	Tomography/
21	(computer* adj3 tomograph*).tw.
22	or/13-21
23	3 and 22
24	(custom* or bespok* or tailor* or individual* or biomodel*).tw.
25	3 and 24
26	12 or 23 or 25
27	((orbit* or orofac* or face* or facial* or nose* or nasal* or sinus* or mandib* or palat*) adj3 (reconstruct* or rebuild* or repair*)).tw.

28	((orofacial* or oro-facial*) adj3 (reconstruct* or rebuild* or repair*)).tw.
29	((craniofac* or cranio-facial*) adj3 (reconstruct* or rebuild* or repair*)).tw.
30	Facial Neoplasms/
31	exp Skull Neoplasms/
32	Facial Injuries/ or Maxillofacial Injuries/
33	Nose/in
34	Skull/in
35	Mouth/in
36	((face* or facial* or skull* or jaw* or chin* or mouth* or nose* or mandibul* or maxill*) adj3 (injur* or anomal* or deform* or damage* or trauma* or fractur* or break* or broke* or defect* or diseas*)).ti.
37	((face or facial or mouth* or nose*) adj3 (neoplasm\$ or cancer\$ or carcinoma\$ or adenocarcinom\$ or tumour\$ or tumor\$ or malignan\$)).tw.
38	exp Face/ or exp Facial bones/ or Skull/
39	skull fractures/
40	fractures, bone/
41	Reconstructive surgical procedures/
42	39 or 40 or 41
43	38 and 42
44	(congenit* adj3 fac* adj3 (anomal* or abnormal*)).tw.
45	(Orbit* adj3 floor* adj3 fract*).tw.
46	(blow* adj3 out adj3 fract*).tw.
47	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 43 or 44 or 45 or 46
48	26 and 47
49	animals/ not humans/
50	48 not 49
51	limit 50 to english language