NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of insertion of customised titanium implants, with soft tissue cover, for orofacial reconstruction

Inserting a titanium implant for orofacial reconstruction

Titanium implants can be inserted to replace broken bones in the face as part of orofacial reconstruction, that is, rebuilding the face when there is severe damage to the bones. This is most commonly needed after injury or surgery to remove tumours.

Some 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.

Introduction

The National Institute for Health and Clinical 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 July 2012 and updated in January 2013.

Procedure name

- Customised titanium implant insertion for orofacial reconstruction

Specialist societies

- British Association of Oral and Maxillofacial Surgeons
- Craniofacial Society of Great Britain and Ireland.

Description

Indications and current treatment

For the purposes of this review major, complex facial reconstruction involving multiple surfaces and bony and cartilaginous structures with little or no skin or epithelial coverage has not been included.

Various materials are used to strengthen or replace parts of the facial skeleton after severe orofacial trauma, removal of 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 bone regenerated using tissue engineering. Traditionally, autologous materials have been used for the repair of large orbital and facial fractures. Limitations of autologous grafting include increased operating times, prolonged hospital stay, increased postoperative discomfort and donor site morbidity. There is also a variable rate of resorption and consequently clinical outcomes may be unpredictable.

The classical method of forming 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. Using computer-aided design and computer-aided manufacturing (CAD-CAM) techniques to produce customised implants before the operation aims to facilitate the implantation process, because less manipulation of soft tissues is needed. This reduces the operating time and in some cases reduces the number of operations, improves safety (for example in areas of limited visibility such as around the optic nerve), and improves outcomes.

What the procedure involves

The first step in making the customised titanium implant is to create a precise anatomical model of the patient's skull or 3-dimensional simulated computer image, using computed tomography, or cone-beam computed tomography scans, and CAD-CAM techniques. The implant is then produced from this model. 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 surgical details will depend on where the implant is to be used and the extent of surrounding trauma. In most cases the implant is covered, either using existing soft tissue from the area or by transplant of flap tissue from a donor site. Implants abutting onto areas such as the sinuses can be left exposed as epithelialisation is thought to occur with time.

Outcome measures

Visual function

Ophthalmological and orthoptic examinations assess preoperative and postoperative enophthalmos (recession of the eye globe within the orbit), diplopia (double vision), or ocular motility. Enophthalmos can occur if orbital volume increases without a corresponding change in volume of orbital contents, for example because of a blowout fracture of the walls or floor of the orbit. Forward displacement (bulging) of the eye globe is known as exophthalmos or proptosis. Globe positioning can be measured using Hertel's exophthalmometry; a difference of 2 millimetres or more (between affected and unaffected globes) is classified as enophthalmos. Orbital volume is measured in cubic centimetres (cm^3). Enophthalmos is sometimes associated with hypoglobus, which is downward displacement of the eye globe; this is measured in millimetres.

Diplopia can occur at various positions of gaze (most commonly on upgaze); the unit of measurement is a prism dioptre. A binocular single vision screen can be used to assess the areas of the examined field in which the patient reports double images. Vertical visual disparity measures the difference in relative globe position in degrees, and affects depth perception. Ocular motility depends on correct functioning of the extra-ocular muscles, and can be affected by muscle entrapment. Motility is measured in millimetres.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to exposed customised titanium implant insertion for orofacial reconstruction. Searches were conducted of the following databases, covering the period from their commencement to 21 November 2012: 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 with orofacial trauma, orofacial tumours or congenital facial anomalies.
Intervention/test	Customised titanium implant insertion.
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 252 patients from 3 non-randomised comparative studies[1–3] and 5 case series[4–8].

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 titanium implants, with soft tissue cover for orofacial reconstruction

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

Study details

He D (2012)[1]

Non-randomised comparative study

China

Recruitment period: 2008–10

Study population: patients with delayed orbitozygomatic fractures with enophthalmos

n=**64 (39 traditional versus 14 customised versus 11 customised with navigation)**

Mean age: 33 years (range 7–58)

Sex: 84.4% (54/64) male

Patient selection criteria: delayed repair of orbitozygomatic fractures with enophthalmos. All patients had facial asymmetry.

Technique: materials used for reconstruction were 54.7% (35/64) titanium mesh only, 18.8% (12/64) Medpor only, 7.8% hydroxyapatite only (5/64), 15.6% titanium mesh with Medpor (10/64), and 3.1% titanium mesh with hydroxyapatite (2/64). For the customised groups, titanium mesh and plates were shaped against a custom-designed skull model. The navigation group also had computer-assisted navigation-guidance.

Follow-up: **1 month**

Conflict of interest/source of funding: supported by the Science and Technology Commission of Shanghai, Shanghai Leading Academic Discipline Project, National Natural Science Foundation of China, Cooperated Foundation of Medical and Engineering Science of Shanghai Jiao Tong University and PuJiang Talent Program.

Key efficacy findings

Number of patients analysed: **64 (included 25 customised)**

Enophthalmos (posterior displacement of the eyeball)

	Traditional % (n)	Customised % (n)	Customised with navigation % (n)
Good globe projection (enophthalmos ≤2 mm)	59.0 (23/39)	64.3 (9/14)	90.9 (10/11)
Mild enophthalmos (≤3 mm)	15.4 (6/39)	21.4 (3/14)	9.1 (1/11)
Moderate enophthalmos (≤4 mm)	5.1 (2/39)	0.0 (0/14)	0.0 (0/11)
Ocular prosthesis required	20.5 (8/39)	14.3 (2/14)	0.0 (0/11)

Diplopia

After surgery, 98.0% (48/49) of patients with diplopia and ocular globe movement disturbance had improved.

Facial appearance

	Traditional % (n)	Customised % (n)	Customised with navigation % (n)
Perfect reduction of zygoma	74.4 (29/39)[a]	85.7 (12/14)[b]	100.0 (11/11)

[a]The other 25.6% (10/39) had 1–4 zygomatic buttresses comminuted, which affected the accuracy of reduction.[b] In the remaining 14.3% (2/14), inadequate zygomatic projection was attributed to comminuted zygomatic body fractures.

Key safety findings

Complications

Complication	% (n)	Treatment
Temporal-region atrophy (included 3 patients with mild preoperative atrophy which worsened after surgery)	6.3 (4/64)	Abdominal fat was grafted for augmentation
Lower-eyelid ectropion	4.7 (3/64)	Resolved after massage in the long-term
Oculomotor nerve palsy	1.6 (1/64)	Strabismus surgery carried out
Infection (attributed to maxillary sinusitis)	1.6 (1/64)	Healed after drainage[c]

[c]During debridement, the titanium mesh was found to be intact and covered with fibrous tissue.

Comments

Follow-up issues:

- It was not specified when the postoperative complications (or their treatment) occurred.

Study design issues:

- Retrospective analysis.
- Postoperative CT with 3D bone reconstruction was used to evaluate the position of the zygoma after surgery. Enophthalmos was measured from pre- and postoperative CT scans by the same examiner blinded to repair type.
- Diplopia and ocular globe movement assessment was subjective.
- Reporting of complications did not differentiate between treatment groups.
- Reported percentages were apparently incorrectly calculated, and have been amended in this table.

Study population issues:

- There were 15.6% (10/64) patients who had previously been treated at other hospitals with inadequate reduction.

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

Study details

Kozakiewicz M (2011)[2]

Non-randomised comparative study

Poland

Recruitment period: 2005–8

Study population: patients who had sustained orbital fractures.

n=**24 (12 classical method versus 12 customised)**

Mean age: 37.9 years (range 14–73)

Sex: 58.3% (14/24) male

Patient selection criteria: orbital fractures without coexisting central nervous system or globe injury.

Technique: customised 0.4 mm thick titanium mesh implants were shaped and formed against patient skull models.

Follow-up: **12 months**

Conflict of interest/source of funding: supported by a grant from Ministry of Science and High Education.

Key efficacy findings

Number of patients analysed: **24 (included 12 customised)**

Early results (2 week follow-up means)

		Method	Before operation	Early results	Difference between methods	
					ANOVA	*t*-test
Loss of binocular single vision (%)		Classical	49±23	29±15	p=0.021	p=0.54
		Customised	35±24	14±16		
Vertical visual disparity (°)	Upgaze	Classical	16.58±10.22	9.92±6.72	p=0.007	p=0.12
		Customised	11.21±5.98	3.50±3.23		
	Primary globe position	Classical	5.92±6.60	2.08±2.67	Not reported	p=0.84
		Customised	3.75±4.00	0.83±1.27		
	Down gaze	Classical	5.42±9.34	5.79±8.23	Not reported	p=0.20
		Customised	8.50±10.98	5.42±5.28		

Late results (12 month follow-up means)

		Method	Before operation	Late results	Difference between methods	
					ANOVA	*t*-test
Loss of binocular single vision (%)		Classical	49±23	11±7	p=0.015	Not reported
		Customised	35±24	4±4		
Vertical visual disparity (°)	Upgaze	Classical	16.58±10.22	5.63±3.17	p=0.003	Not reported
		Customised	11.21±5.98	1.67±2.47		
	Primary globe position	Classical	5.92±6.60	0.75±0.62	p=0.012	Not reported
		Customised	3.75±4.00	0.17±0.39		
	Down gaze	Classical	5.42±9.34	2.79±4.52	p>0.05	Not reported
		Customised	8.50±10.98	2.54±3.00		

Key safety findings

Not reported

Comments

Follow-up issues:

- All patients underwent full ophthalmic and orthoptic assessment 2 weeks and 12 months after surgery.

Study design issues:

- Recruitment periods differed for patients treated by the classical method (2005–6) and those with customised implants (2007–8).
- Loss of binocular single vision (diplopia) was reported as the percentage of the examined field in which the patient reports double images.

Study population issues:

- Both groups were similar when pre-treatment ophthalmological data were compared (no p value reported).
- There were no significant differences between groups with regard to degree of injury (p=0.84) and number of affected walls (p=1.0).

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Andrades P (2009)[3]

Non-randomised comparative study
Spain
Recruitment period: 2006–8
Study population: patients with unilateral orbital fractures, and floor and/or medial wall lesions.
n=32 (20 mesh shaped intra-operatively, 12 prefabricated mesh)
Mean age: 35.7 years
Sex: 94% (30/32) male

Patient selection criteria: unilateral orbital fractures, and floor and/or wall lesions, subsequently reconstructed with titanium mesh, and with adequate follow-up using CT images. Orbital roof or lateral wall defects were excluded.

Technique: prefabricated mesh was shaped preoperatively using a skull model. Intravenous antibiotic prophylaxis was used.

Mean follow-up: 12.3 months

Conflict of interest/source of funding: None.</td>
<td>Number of patients analysed: 32 (included 12 prefabricated)
Postoperative clinical evaluation (mean follow-up = 12 months)
<table>
<tr><th></th><th>% (n)</th></tr>
<tr><td>Normal</td><td>63 (20/32)</td></tr>
<tr><td>Mild enophthalmos</td><td>25 (8/32)</td></tr>
<tr><td>Moderate enophthalmos</td><td>3 (1/32)</td></tr>
<tr><td>Severe enophthalmos and hypoglobus</td><td>3 (1/32)</td></tr>
<tr><td>Mild to moderate exophthalmos</td><td>6 (2/32)</td></tr>
</table>
Postoperative differences (between implant type)
<table>
<tr><th></th><th>Mesh shaped intra-operatively</th><th>Pre-fabricated mesh</th><th>p value</th></tr>
<tr><td>Orbital volume</td><td>1.09±1.66</td><td>0.2±0.71</td><td>0.011</td></tr>
<tr><td>Apex-globe distance</td><td>−0.90±1.80</td><td>0.00±0.43</td><td>0.007</td></tr>
<tr><td>Orbital rim area</td><td>9.15±45.9</td><td>−28.25±32.9</td><td>0.023</td></tr>
</table>
The use of prefabricated titanium mesh was the only modifiable predictive variable that showed a statistically significant association in a univariate analysis (p=0.0288).

When co-variation between study variables was performed, the use of prefabricated mesh was found to be significantly correlated with volume difference (p=0.044), apex-globe difference (p=0.019), accuracy of mesh placement (p=0.003) and clinical evaluation (p<0.001).</td>
<td>One patient developed a postoperative haematoma needing immediate evacuation, but had an uneventful recovery.</td>
<td>Study design issues:
• Retrospective analysis of medical records.
• Postoperative clinical results were presented for the cohort as a whole, and did not differentiate between outcomes for customised and non-customised treatments.
• Preoperative clinical evaluation and CT observations are not reported.
• It is not clear whether the skull model was customised for the patient – it is possible that a standard skull model was used, in which case the study may be outside of the scope of this overview.
• Clinical evaluation of globe position in the orbit was performed subjectively by an independent evaluator. It was not stated whether they were blinded to the treatment methods used.
• Clinical evaluation significantly correlated with accuracy of mesh placement (p=0.007), but not with any of the variables measured on CT scans.

Study population issues:
• Baseline characteristics were reported for the 32 patients, but not separately for the 2 groups.

Other issues:
• It was not recorded whether the patient who developed the postoperative haematoma had been in the prefabricated or non-prefabricated group.</td>
</tr>
</table>

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Lieger O (2010)[4]

Case series
UK
Recruitment period: 1997–2007
Study population: patients undergoing reconstruction of extensive orbital fractures.
n=29
Average age: 33.4 years (range 16.2–56.3)
Sex: 89.7% (26/29) male

Patient selection criteria: unilateral post-traumatic enophthalmos (a side difference of at least 2 mm) with or without diplopia.

Technique: Sheet titanium (0.5 mm thick) was pressed to shape against a counterdie, which had been created using a custom-designed skull model. All patients received perioperative prophylactic antibiotic therapy.

Mean follow-up: 14 months (range 5.5–29.0)

Conflict of interest/source of funding: None</td>
<td>Number of patients analysed: 29

Outcomes
<table>
<tr><th></th><th>Resolved % (n)</th><th>Improved % (n)</th><th>No change % (n)</th></tr>
<tr><td>Enophthalmos</td><td>69 (20/29)</td><td>31 (9/29)</td><td>0 (0/29)</td></tr>
<tr><td>Diplopia[a]</td><td>21 (5/24)</td><td>38 (9/24)</td><td>42 (10/24)</td></tr>
<tr><td>Restricted ocular motility[b]</td><td>15 (4/26)</td><td>35 (9/26)</td><td>50 (13/26)</td></tr>
</table>
[a]Two patients were blind preoperatively, 3 patients had normal binocular vision preoperatively – these have been excluded.
[b]Three patients had normal globe motility preoperatively.

Overcorrection of enophthalmos occurred in 3 patients (10.3% of 29) – these have been classified in the above table as resolved.
In 1 patient diplopia resolved although the motility of the eye globe remained unchanged. No worsening of double vision or motility was recorded in this patient.</td>
<td>During the follow-up period, 1 patient had an infection in the region of the implant. This was successfully treated with antibiotics.</td>
<td>Follow-up issues:
Whilst 32 patients met the selection criteria, 3 patients (9.4% of 32) were excluded due to insufficient follow-up.
Clinical follow-up examinations took place at 2 weeks, 4 weeks, 3 months and 6 months. Routine postoperative ophthalmological follow-up was performed between 5 months and 7 months after surgery. For the analysis the most recent examination results were used.
It was not specified when the postoperative infection occurred.
Study design issues:
Retrospective analysis of medical records.
Although enophthalmos was reported as resolved or improved in all patients, the last Hertel assessment showed a difference of 2 mm in 6.9% (2/29) patients – by definition this is still classified as enophthalmos.
Study population issues:
Primary orbital revision was performed in 10.3% (3/29) patients. These patients had sustained a zygomaticomaxillary fracture and showed delayed postoperative enophthalmos. In all other patients, no primary orbital reconstruction was performed.</td>
</tr>
</table>

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Tang W (2010)[5]

Case series
China
Recruitment period: 2005–8
Study population: patients with unilateral orbital floor fractures.
n=46
Average age: 38.7 years (range 21–65)
Sex: 60.9% (28/46) male

Patient selection criteria: unilateral orbital floor fractures that were surgically reconstructed. Exclusion criteria: orbital floor fractures without bone defects, and patients with previously unsuccessful surgical procedures.

Technique: titanium mesh was shaped against a custom-designed skull model.

Mean follow-up: 8.6 months (range 6–12)

Conflict of interest/source of funding: the work was supported by grants from the Chinese National Natural Science Foundation and the Programs of Science and Technology Commission Foundation of Sichuan Province, China.</td>
<td>Number of patients analysed: 46 (19 fresh fractures versus 27 old fractures)

Outcomes
<table><tr><th></th><th>Resolved % (n)</th><th>Unresolved % (n)</th></tr><tr><td>Enophthalmos</td><td>61 (25/41)</td><td>39 (16/41)</td></tr><tr><td>Fresh</td><td>64 (9/14)</td><td>36 (5/14)</td></tr><tr><td>Old</td><td>59 (16/27)</td><td>41 (11/27)</td></tr><tr><td>Diplopia</td><td>44 (7/16)</td><td>56 (9/16)</td></tr><tr><td>Fresh</td><td>67 (4/6)</td><td>33 (2/6)</td></tr><tr><td>Old</td><td>30 (3/10)</td><td>70 (7/10)</td></tr></table>
The change in orbital volume between pre- and postoperative measurements was significant for both fresh and old fractures (p<0.05).

Postoperatively, the correlation between enophthalmos and change in orbital volume measurements was found to be significant in patients with old fractures (p=0.016; r=0.924), but not in patients with fresh fractures (p=0.284).</td>
<td>None reported.</td>
<td>Study design issues:
The authors did not record whether data were collected prospectively or retrospectively.
The aim was to assess the features of orbital wall fractures of different stages. Fractures were classified as fresh or old depending on whether they had been sustained within 2 weeks of the study.
Paired t-tests were used to analyse discrepancies between injured and uninjured sides, and between pre- and postoperative orbital volume. Spearman rank correlation analysis was used to compare the relationships between enophthalmos and difference in orbital volume.
Study population issues:
The preoperative orbital volume differed between uninjured and injured sides (p<0.05).
The difference in orbital volume (between affected and unaffected eyes) was greater in patients with old fractures (p=0.011) than those with fresh fractures (p=0.171).
Preoperatively in patients with old fractures, enophthalmos was positively correlated with a difference in orbital volume (r=0.976).</td>
</tr>
</table>

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

Study details

Mustafa SF (2011)[6]

Case series

UK

Recruitment period: 2003–8

Study population: patients with orbital wall defects.

n=**22**

Mean age: 30.9 years (range 15–64)

Sex: 86.4% (19/22) male

Patient selection criteria: severe comminution, large defects with little or no posterior bony support, or secondary reconstruction.

Technique: different customised implant types were used: titanium mesh was shaped against a custom-designed skull model, or sheet titanium (0.25 mm or 0.5 mm) was pressed to shape against a counterdie which had been created using a custom-designed skull model.

Mean follow-up: **9.5 months (range 2–38)**

Conflict of interest/source of funding: None

Key efficacy findings

Number of patients analysed: **22**

Outcomes

	Resolved % (n)	Improved % (n)	Unresolved % (n)
Enophthalmos	81.8 (9/11)	18.2 (2/11)	0.0 (0/11)
Enophthalmos with hypoglobus[a]	80.0 (4/5)	20.0 (1/5)	0.0 (0/5)
Diplopia	64.7 (11/17)[b]	29.4 (5/17)	5.9 (1/17)[c]

[a]Three of the 5 patients who had enophthalmos with hypoglobus also had diplopia. In all 3 patients with both diplopia and hypoglobus, diplopia recovered or improved following surgery.

[b]Of the patients whose diplopia resolved, the resolution occurred within1 day for 27.3% (3/11) patients, within 7 days for 9.0% (1/11) patients, within 30 days for 9.0% (1/11) patients and within 8 months for 9.0% (1/11) patients. Time to resolution was not specified for the remaining 45.5% (5/11) patients, although the study states that 90.0% (10/11) patients reported early resolution of their diplopia.

[c]One patient with preoperative diplopia required ocular muscle surgery after the reconstruction procedure.

Key safety findings

Complications

	% (n)	Treatment
Scleral show	9.0 (2/22)	Settled later (1 patient) Not reported for 1 patient
Temporary ectropion	4.5 (1/22)	Resolved
Ectropion with severe lid injuries	4.5 (1/22)	Not reported
Mild elevation of right globe	4.5 (1/22)	Subsequently settled
Discomfort (pain and irritation) and palpable screw and plate rim at inferior orbital margin[d]	4.5 (1/22)	Further surgery to trim, shorten and smooth the plate flange, and to remove 1 of 3 screws.
Visual deterioration Initially had complete resolution following surgery, but then developed a sudden onset subjective decrease in visual acuity (with no perception of light after 8 hours).	4.5 (1/22)	The plate was removed 24 hours post-procedure but did not resolve. Spontaneously recovered after 1 week.

[d]These complications occurred after a secondary procedure (the initial operation had been carried out 9 months earlier by a different department).

Comments

Follow-up issues:

- Follow-up periods differed between each patient.
- It was not reported how the temporary ectropion resolved.
- Most of the time periods between operation and complication and/or its resolution were not reported.

Study design issues:

- Retrospective analysis of medical records.

Study population issues:

- Secondary procedures were carried out in 9.1% (2/22) patients.
- 13.6% (3/22) patients had neither enophthalmos nor diplopia. 40.9% (9/22) patients had both enophthalmos and diplopia.

Other issues:

- The results presented 1 patient as having preoperative enophthalmos and no enophthalmos postoperatively, but did not describe this as either resolved or improved. This has been categorised as resolved in this overview.
- Another patient was listed as having no enophthalmos preoperatively, but 'resolved' enophthalmos postoperatively. The same patient is reported to have preoperative diplopia but no postoperative diplopia; this was not described as either 'resolved' or 'improved'. It has been assumed that these outcomes were reported incorrectly (by exchanging results for enophthalmos and diplopia), and have been amended in the efficacy outcomes table.

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

Study details

Sun J (2011)[7]

Case series

China

Recruitment period: 2001–8

Study population: patients who had undergone reconstruction of high maxillectomy defects with fibula osteomyocutaneous flaps in combination with titanium mesh or a zygomatic implant.

n=**20**

Average age: 42.6 years (range 23–63)

Sex: 70% (14/20) male

Patient selection criteria: reconstruction of high maxillectomy defects (Brown class 3), with fibula osteomyocutaneous flaps in combination with titanium mesh or a zygomatic implant.

Technique: for primary reconstructions, a high maxillectomy was simulated on a custom-designed skull model. For secondary reconstructions, a custom-designed skull replica was generated using a mirror image of the contralateral maxilla. A skin paddle of a fibula osteomyocutaneous flap was applied to restore the palatal soft tissue. Reconstruction was carried out in the following combinations:

	n
Osteomyocutaneous flap + titanium mesh	16
Osteomyocutaneous flap + radial forearm flap + titanium mesh	3
Osteomyocutaneous flap + radial forearm flap + zygomatic implant	1
Total number of flaps	24

Average follow-up: **34.7 months (range 9–83)**

Conflict of interest/source of funding: None

Key efficacy findings

Number of patients analysed: **20**

Aesthetic assessment at 6 months

Composite scores were obtained from assessments by both patients and surgeons for facial symmetry, concavity of the cheek, globe position, and facial scars:

	% (n)
Excellent	75 (15/20)
Good	20 (4/20)
Fair	5 (1/20)
Poor	0 (0/20)

Speech intelligibility at 6 months

Intelligible speech was acquired in 95% (19/20) patients.

Masticatory function

All patients tolerated a regular or soft diet postoperatively. One patient received implant-borne dental prostheses and 9 patients wore removable partial dentures. Average postoperative occlusal force was 61.4 (±10.3)% of preoperative force.

Key safety findings

Complications

	% (n)	Treatment
Loss of flap. Six months after secondary reconstruction the patient was found to have an exposed and necrotic fibula.	4.2 (1/24)	The necrotic fibula portion was removed in a further procedure; the titanium mesh was preserved.
Partial fibular osteoradionecrosis.	5.0 (1/20)	Additional debridement to remove the necrotic portion was carried out 2 years after reconstruction.
Exposure of titanium mesh: - oral cavity after 36 months - infraorbital skin after 4 months	 5.3 (1/19) 5.3 (1/19)	Additional surgery to remove exposed mesh and cover residual mesh with a flap.
Oronasal fistulae (at edge of palatal skin paddles).	10.5 (2/19)	Sealed with removable partial dentures.

These complications were all found in patients who underwent radiotherapy.

One patient (5.0% of 20) developed local recurrence of a tumour 13 months postoperatively and died as a result.

Comments

Study design issues:

- Retrospective analysis of medical records from consecutive patients.
- 7% (15/20) of patients received preoperative or postoperative radiotherapy.
- Dental rehabilitation was delayed in 50% (10/20) of patients because of economic reasons or patient refusal.

Study population issues:

- 45% (9/20) patients underwent immediate reconstruction after ablative tumour surgery, whereas 55% (11/20) of patients underwent secondary reconstruction.

Abbreviations used: CT, computed tomography; MRSA, methicillin-resistant Staphylococcus aureus; THORP, titanium-coated hollow-screw reconstruction plate

Study details

Bell RB (2009)[8]

Case series

USA

Recruitment period: 2007–8

Study population: patients with complex primary or secondary unilateral post-traumatic and post-ablative orbital deformities, who had undergone computer-assisted reconstruction.

n=**15**

Mean age: 37.3 years (range 17–67)

Sex: 73.3% (11/15) male

Patient selection criteria: unilateral, clinically significant disruption of the internal and/or external orbit that involved more than one orbital wall or an isolated orbital roof, and that resulted in (or had the potential to result in) enophthalmos, diplopia, ocular dysmotility or facial asymmetry. Exclusions: patients who underwent reconstruction using traditional techniques.

Technique: titanium mesh was shaped against a custom-designed skull model. Computer-assisted intra-operative navigation was used to assess the accuracy of positioning of the implant.

Follow-up: **not reported**

Conflict of interest/source of funding: not reported.

Key efficacy findings

Number of patients analysed: **15**

Outcomes

	Resolved % (n)	Unresolved % (n)
Enophthalmos/ Proptosis[a]	75 (9/12)	25 (3/12)
Diplopia	67 (8/12)	25 (3/12)
Ocular dysmotility	71 (5/7)	29 (2/7)
Facial asymmetry: - malar depression - excessive malar prominence	100 (6/6) 100 (2/2)	0 (0/6) 0 (0/2)

[a]Sub-optimal correction of globe projection occurred in 3 patients undergoing secondary enophthalmos repair, because of severe intraconal soft-tissue scarring.

Operative success

Good % (n)	Fair % (n)	Poor % (n)
53 (8/15)	40 (6/15)	7 (1/15)

Key safety findings

Complications

	% (n)	Treatment (outcome)
Intraconal soft-tissue scarring (posterior to the equator of the globe), limited ocular motility and persistent diplopia.	7 (1/15)	Revisional surgery for extraocular muscle entrapment (Diplopia improved)
Decreased visual acuity – transient loss of visual acuity occurred when the mesh plate encroached on the optic nerve.	7 (1/15)	Reoperation (Complete recovery – favourable functional and aesthetic results)
Inaccurate plate placement. Complications that were observed as a result of inaccurate placement were not specified.	7 (1/15)	Reoperation (Complete recovery – favourable functional and aesthetic results)
Lower lid retraction with increased scleral show	7 (1/15)	None reported

Comments

Follow-up issues:

- No follow-up information was provided after the initial postoperative period.
- Postoperative diplopia information was not available for 1 of the 12 patients who had pre-operative diplopia.
- Suboptimal restoration of enophthalmos was, for the purposes of this study, not considered a complication. This implies that there were other adverse consequences to the 'inaccurate plate placement' described.

Study design issues:

- Retrospective analysis of medical records from consecutive patients.
- The authors did not describe how outcomes were measured, other than stating that pre- and postoperative CT images were compared and subjectively analysed by the primary surgeon (who was also the main author).
- A poor operative outcome was defined as clinically perceptible enophthalmos, persistent diplopia, facial asymmetry/malar flattening, or ocular dysmotility.

Study population issues:

- 40% (6/15) patients had undergone previous orbital surgery using conventional techniques.

Efficacy

Enophthalmos

A non-randomised comparative study of 64 patients with facial asymmetry who had orbitozygomatic reconstruction reported enophthalmos as good (less than 2 mm), mild (less than 3 mm), moderate (less than 4 mm) and 'ocular prosthesis required', in groups treated with implants produced by different methods. At 1-month follow-up, enophthalmos with the traditional method was reported as good in 59% (23/39) of patients, mild in 15% (6/39) of patients, moderate in 5% (2/39) of patients, and 21% (8/39) of patients needed an ocular prosthesis. Combining results for both customised groups, enophthalmos was reported as good in 76% (19/25) of patients, mild in 16% (4/25), and 8% (2/25) of patients needed an ocular prosthesis[1]. A non-randomised comparative study of 32 patients (treated with mesh that was either shaped intra-operatively or prefabricated against a skull model) found that the use of prefabricated mesh was found to be a predictive variable in correction of orbital volume ($p=0.011$)[3]. A case series of 29 patients reported that enophthalmos resolved in 69% (20/29) of patients, and improved in 31% (9/29) of patients at a mean follow-up of 14 months. However it was noted that overcorrection of enophthalmos occurred in 10% (3/29) of patients[4].

Diplopia and vertical visual disparity

A non-randomised comparative study of 24 patients measured diplopia in patients treated with either the customised or classical implantation methods. At 12-months follow-up, the customised implant group showed significantly better reduction of binocular single vision loss area ($p=0.015$), correction of primary globe position in vertical visual disparity ($p=0.012$) and improvement in upgaze disparity ($p=0.003$) compared with the classical implant group, but no significant difference in downgaze disparity ($p>0.05$)[2]. The case series of 29 patients reported that diplopia resolved in 21% (5/24) of patients, improved in 37% (9/24) of patients and did not change in 42% (10/24) of patients, with a mean follow-up of 14 months for the study[4].

Ocular motility

The case series of 29 patients reported that restricted ocular motility resolved in 15% (4/26) of patients, improved in 35% (9/26) of patients and did not change in 50% (13/26) of patients, with a mean follow-up for the study of 14 months[4]. A case series of 15 patients who underwent orbital reconstruction reported that ocular dysmotility resolved in 5 of 7 patients; the follow-up period in this study was not reported[8].

Facial appearance

The non-randomised comparative study of 64 patients with facial asymmetry who had orbitozygomatic reconstruction reported perfect reduction of the zygoma in 74% (29/39) of the patients treated by the traditional method, and 92% (23/25) of patients treated using custom-designed implants (including 11 procedures that used computer-assisted navigation)[1]. A case series of 20 patients who had reconstruction of high maxillary defects included an assessment of facial symmetry, concavity of the cheek, position of the globe, and facial scars. Aesthetic assessment scores were recorded as excellent in 75% (15/20) of patients, good in 20% (4/20), fair in 5% (1/20) and poor in 0%[7]. In the case series of 15 orbital reconstruction patients, facial symmetry was restored in 100% (8/8) of patients who had either excessive malar prominence or a malar depression[8].

Speech intelligibility

The case series of 20 patients who had reconstruction of high maxillary defects were subjectively assessed for speech intelligibility. At the 6-month postoperative visit, 95% (19/20) of patients had intelligible speech[7].

Masticatory function

The case series of 20 patients measured occlusal forces in 10 patients who had undergone dental rehabilitation after reconstruction of high maxillary defects. The average total postoperative occlusal force was 61.4±10.3% of the preoperative force. Dental restoration in the other 10 patients had not yet been undertaken, but it was recorded that all patients were able to tolerate a regular or soft diet[7].

Further surgery

In a case series of 22 patients with orbital defects, 1 (6%) of 17 patients with preoperative diplopia needed ocular motor surgery after the initial procedure. The mean follow-up for the study was 9.5 months; this particular patient was followed-up for 24 months[6].

Safety

Implant exposure

Titanium mesh became unintentionally exposed in 2 patients in the case series of 20 patients who had undergone reconstruction of high maxillary defects using titanium mesh or a zygomatic implant. The mesh became exposed in the oral cavity of 1 patient at 36 months, and through the infraorbital skin in 1 patient at 4 months postoperatively. Both had further surgery[7].

A palpable plate rim was found in 1 patient in the case series of 22 orbital reconstructions. The patient developed pain and irritation at the inferior orbital margin, where she was able to feel the plate flange and screw (the period of time

between surgery and complication was not reported). The flange was trimmed and the screw removed in a further operation[6].

Infection

Infection because of maxillary sinusitis was reported in 1 patient in the non-randomised comparative study of 64 patients. This resolved after debridement and drainage[1]. Infection in the region of the implant was observed in 1 patient in the case series of 29 patients who had undergone extensive orbital reconstruction[4].

Necrosis

Necrosis can occur in tissue that has been exposed to radiation, and may be associated with peri-implantitis. Loss of a fibula osteomyocutaneous flap (used in combination with titanium mesh) occurred because of vascular compromise in 1 patient in the case series of 20 patients who had undergone maxillary reconstruction in combination with a titanium mesh or zygomatic implant. At the 6-month follow-up visit the fibula was found to be exposed and necrotic, needing further surgery. Partial fibular osteoradionecrosis occurred in 1 other patient in the same case series of 20 patients 2 years after reconstruction; additional debridement was carried out. The complications in this study all occurred in patients who had undergone radiotherapy[7].

Fistulae

Oronasal fistulae were reported in 2 patients in the case series of 20 patients who had undergone maxillary reconstruction. The fistulae were detected at the edge of palatal skin paddles, 1 year after surgery[7].

Bleeding and haematomas

A postoperative haematoma developed in 1 patient from the non-randomised comparative study of 32 patients (it was not recorded whether this patient had received a customised implant)[3].

Scleral show and ectropion

Scleral show is excessive exposure of the lower white of the eye, and can be associated with ectropion (where all or part of the lower eyelid turns outwards). Problems associated with these conditions include epiphora (overflow of tears), lagophthalmos (inability to close the eyelids), thickening and keratinisation of the conjunctiva, and ocular irritation. Lower eyelid ectropion was reported in 3 patients in the non-randomised comparative study of 64 patients[1]. Scleral show was observed in 2 patients in the case series of 22 patients who underwent orbital reconstruction; ectropion was reported in 2 patients in the same study[6]. Lower lid retraction with increased scleral show was reported in 1 patient in the case series of 15 patients who had undergone orbital reconstruction[8].

Visual deterioration

Visual deterioration occurred in 1 patient in the case series of 22 patients. The patient developed a sudden-onset subjective decrease in visual acuity, with no perception of light after 8 hours. This did not resolve when the plate was first removed (24 hours post-procedure), but spontaneously resolved after 1 week[6]. Transient loss of visual acuity occurred in 1 patient in the case series of 15 patients who had undergone orbital reconstruction, which was attributed to the mesh plate encroaching on the optic nerve. Reoperation led to complete recovery[8].

Intraconal scarring with persistent diplopia

In patients with severe scarring of soft tissues posterior to the equator of the eye globe (within the cone of extraocular muscles that support the globe), the globe cannot be projected without significant inferior rotation. Intraconal scarring, limited ocular motility and persistent diplopia were reported in 1 patient from the case series of 15 patients with orbital defects. Diplopia improved after revisional surgery[8].

Nerve damage

Oculomotor nerve palsy occurred in 1 patient in the non-randomised comparative study of 64 patients with a follow-up period of 1 month; surgery was carried out to correct the resulting strabismus (squint)[1].

Validity and generalisability of the studies

- The age of patients included in the studies ranged from 7 to 73 years. Approximately 77% (196/254) patients were male. This calculation includes 71 patients who had been treated by the classical method of forming titanium mesh in the 3 non-randomised comparative studies[1–3]. Follow-up beyond the immediate postoperative period was not reported for 1 study[4]. Average follow-up periods for the remainder ranged from 8.6 months[5], to an average of 34.7 months[7].
- 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.
- The defects in these studies occurred in different orofacial areas with related procedural differences, and will not all be directly comparable. Three of the non-randomised comparative studies[1–3] and 4 of the case series[4–8] involved procedures in the orbital areas, and 1 case series related to high maxillary defect reconstructions[7], Assessment criteria and measurement tools were not

stated for all of the studies, and some reported the use of different measures than others for a particular condition. For example, in the case series of 29 patients, the extent of enophthalmos was quantified using a Hertel exophthalmometer[4], whereas in the case series of 15 patients who underwent orbital reconstruction, enophthalmos was subjectively evaluated[8]. Therefore, classification of the presence, absence, or extent of the condition/defect therefore may not always be directly comparable between studies.

- Two of the studies appeared to focus more on the accuracy of reconstruction (orbital volume in particular) than they did on the clinical outcomes for patients, and therefore may have omitted pertinent details[3, 5].
- There may be a number of complications that were not reported. One non-randomised comparative study of 24 patients (12 of whom had received customised implants)[2], and 1 case series study of 46 patients[5], did not refer to any safety implications. One other case series of 15 patients did not specify that any follow-up examinations took place beyond the initial postoperative period[8]. These 3 studies were all of patients who had undergone orbital reconstruction.

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

- Exposed customised titanium implants for orofacial reconstruction. NICE interventional procedures guidance 28 (2003). Available from www.nice.org.uk/guidance/IPG28

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 Stephen Dover and Mr Ian Martin (British Association of Oral and Maxillofacial Surgeons).

- Two Specialist Advisers considered that the title did not describe the procedure adequately. One Adviser stated that the title is confusing as it covers a number of different areas. The other Specialist Adviser commented

that ‘exposed’ needs to be defined, and that the implant type needs to be clarified.

- One Specialist Adviser explained that endosseous implants (which are partially inserted into bone) had been used extensively and successfully, although most were not custom made. On the other hand, customised, exposed, subperiosteal implants (placed onto the bone but beneath the membrane that covers the bone) had been used with very limited success.
- Computer-assisted design and computer-assisted manufacturing have facilitated the production of customised subperiosteal implants. These techniques are taught in large specialist centres for producing conventional prostheses, but their adoption into mainstream practice was considered to be extremely unlikely.
- One Adviser stated that the technique of creating customised titanium implants which are completely covered by vascularised tissues is not controversial. However it is thought it to be highly unlikely that the technique involving large areas of exposed titanium would be widely adopted.
- Suggested measures of efficacy included implant and prosthesis survival rates; and functional outcomes such as speech, eating, and return to normal daily activities. Appropriate quality of life assessment tools may be used.
- Theoretical adverse events included infection; bleeding; pain; life-threatening sepsis; bone resorption; failure, externalisation, loosening or loss of implants; and failure of the prosthesis.
- One Adviser noted that studies in the literature are limited to case reports and some small case series reported over a short timescale. Anecdotal reports indicate that grafts have been lost because of postoperative infection.
- One Specialist Adviser believed that potential costs to the NHS would be substantial because of requirements for highly skilled computer and manufacturing technology, and expensive products. Another Adviser noted that a number of subperiosteal implants had been removed at considerable expense to the NHS and at considerable disadvantage to the patient.

- Factors to be taken into account included the length of hospital stay, readmission rates, cost of procedure, cost of fabrication, insertion and long-term maintenance, the availability of professionals for servicing and maintenance, and indications over those of conventional implants. One Adviser noted that there were other well-established techniques with proven outcomes and quality of life indicators.
- Both Specialist Advisers felt that the potential impact of the controversial procedures on the NHS is minor, in terms of numbers of patients 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

- Limitations of the overview and reasons for including/excluding studies are described in the validity and generalisability section.
- Articles describing implants that were used primarily for cranial reconstruction, dental restoration, or temporomandibular joint reconstruction were excluded. However other reconstruction procedures sometimes affect these areas. For example, some of the bones at the base of the skull also form orbital walls (such as the sphenoid bone), and mandibular reconstructions may be completed by insertion of dental implants.
- It may be helpful to discuss and clarify the scope of the guidance, particularly which orofacial areas are of most relevance in relation to intentional exposure of the implant.

References

1. He D, Li Z, Shi W et al. (2012) Orbitozygomatic fractures with enophthalmos: analysis of 64 cases treated late. Journal of Oral and Maxillofacial Surgery 70(3): 562–77

2. Kozakiewicz M, Elgalal M, Piotr L et al. (2011) Treatment with individual orbital wall implants in humans – 1-year ophthalmologic evaluation. Journal of Cranio-Maxillo-Facial Surgery 39(1): 30–6

3. Andrades P, Hernandez D, Falguera MI et al. (2009) Degrees of tolerance in post-traumatic orbital volume correction: the role of prefabricated mesh. Journal of Oral and Maxillofacial Surgery 67(11): 2404–11

4. Lieger O, Richards R, Liu M et al. (2010) Computer-assisted design and manufacture of implants in the late reconstruction of extensive orbital fractures. Archives of Facial Plastic Surgery 12(3): 186–91

5. Tang W, Guo L, Long J et al. (2010) Individual design and rapid prototyping in reconstruction of orbital wall defects. Journal of Oral and Maxillofacial Surgery 68(3): 562–70

6. Mustafa SF, Evans PL, Bocca A et al. (2011) Customized titanium reconstruction of post-traumatic orbital wall defects: a review of 22 cases. International Journal of Oral and Maxillofacial Surgery 40(12): 1357–62

7. Sun J, Shen Y, Li J et al. (2011) Reconstruction of high maxillectomy defects with the fibula osteomyocutaneous flap in combination with titanium mesh or a zygomatic implant. Plastic and Reconstructive Surgery 127(1): 150–60

8. Bell RB, Markiewicz MR (2009) Computer-assisted planning, stereolithographic modeling, and intraoperative navigation for complex orbital reconstruction: a descriptive study in a preliminary cohort. Journal of Oral and Maxillofacial Surgery 67(12): 2559–70

Appendix A: Additional papers on insertion of customised titanium implants, with soft tissue cover for 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
Abbott JR, Netherway DJ, Wingate PG et al. (1998) Computer generated mandibular model: surgical role. Australian Dental Journal 43(5): 373–8	n=1 Follow-up: 4 years (approximately)	Titanium casing was custom-manufactured to fit directly against the lower body of the mandible, supporting a vascularised iliac bone crest graft. Infection occurred with the loss of a tooth, and exposure of a dental implant led to a compromise with the final prosthesis design. The authors concluded that computer-assisted production of a life-size skull model based upon CT data facilitates planning prior to surgery.	Case report. No new efficacy or safety information.
Feng F, Wang H, Guan X et al. (2011) Mirror imaging and preshaped titanium plates in the treatment of unilateral malar and zygomatic arch fractures. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology 112(2): 188–94	n=4 Follow-up: 1 month	No infection or plate exposure was observed. All patients regained a normal degree of mouth opening and occlusion. Facial contours were recovered successfully in all patients. The mirror-imaging technique and preshaped titanium plates are viable choices for the treatment of unilateral malar and zygomatic arch fractures.	Small case series. No new efficacy or safety information.
Guo L, Tian W, Feng F et al. (2009) Reconstruction of orbital floor fractures: comparison of individual prefabricated titanium implants and calvarial bone grafts. Annals of Plastic Surgery 63(6): 624–31	n=61 (26 calvarial bone grafts versus 35 individually prefabricated titanium mesh implants) Follow-up: not reported	Fractures of the orbital floor can be diagnosed in early stages and reconstructed by individual digital design and rapid prototyping techniques. In patients with fresh fractures of the orbital floor, orbital volume should be recovered as soon as possible. Individually designed titanium mesh can recover precise orbital volume in older fractures. Future studies should examine the relationships between orbital volume reconstruction and embedded position.	Sample is taken from the same cohort as Tang (2010)[4], but includes fewer patients that were treated with customised titanium implants.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Lethaus B, Kessler P, Boeckman R et al. (2010) Reconstruction of a maxillary defect with a fibula graft and titanium mesh using CAD/CAM techniques. Head and Face Medicine 6(16): 1–4	n=1 Follow-up: 3 weeks	Postoperative computed tomography scans showed that virtually planned positions of individualised titanium mesh (made by rapid prototyping) were achieved correctly. The case report demonstrates the possibilities of computer-aided design/computer-aided manufacturing applications in reconstructive surgery.	Case report. No new efficacy or safety information.
Schoen R, Metzger MC, Zizelmann C et al. (2006) Individually preformed titanium mesh implants for a true-to-original repair of orbital fractures. International journal of oral and maxillofacial surgery 35(11): 990–5	n=19 Follow-up: 10 months	Reconstruction using preformed implants in the repair of orbital injuries using titanium mesh and calvarial grafts was less time consuming, more precise and less invasive compared to 'free-hand' efforts. None of the patients demonstrated diplopia or enophthalmos during follow-up.	Study focuses on the accuracy of reconstruction – clinical outcomes are not quantified, other than an average operating time (95 minutes). No safety concerns are reported.
Swinson B, Amin M, Nair P et al. (2004) Isolated bilateral orbital floor fractures: a series of 3 cases. Journal of Oral and Maxillofacial Surgery 62(11): 1431–5	n=3 (including 1 customised implant) Follow-up: 3 months	Highlights both the unusual nature of this injury and the difficulties in management because of the lack of an uninjured contralateral side for comparison. Custom-made titanium implants milled on stereolithographic models, derived from CT data, are gaining favour for accurately restoring the orbital anatomy.	Case report. No new efficacy or safety information.
Watson RM, Coward TJ, Clark RKF et al. (2001) The contribution of imaging and digitised data to mandibular reconstruction and implant stabilised occlusal rehabilitation: a case report. British Dental Journal 190(6): 296–300	n=1 Follow-up: not reported	Use of an appropriate software package enables computer assessment of the form/dimensions. The outcome of intended surgical and restorative changes can be accurately assessed offering a more radical approach to therapy. Pre- and postoperative models can be prepared to visualise the outcome of maxillofacial rehabilitation.	Case report. No new efficacy or safety information.
Wang G, Li J, Khadka A et al. (2012) CAD/CAM and rapid prototyped titanium for reconstruction of ramus defect and condylar fracture caused by mandibular reduction. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 113(3): 356–61	n=1 Follow-up: 6 months	CT scan, rapid prototyping, reverse engineering, and computer modelling are the determinants of simplification, acceleration, and perfection of surgical planning, manufacturing of customised mesh, and immediate reconstruction. These techniques ensure less surgical time, fewer operational errors, more precise fit, and much better stability postoperatively.	Case report. No new efficacy or safety information.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Westendorff C, Kaminsky J, Ernemann U et al. (2007) Image-guided sphenoid wing meningioma resection and simultaneous computer-assisted cranio-orbital reconstruction: technical case report. Neurosurgery 60(ONS Suppl 1): e173–4	n=1 Follow-up: 12 months	The combination of computer-assisted planning using rapid prototyping techniques and image-guided surgery allowed for an extensive tumour resection precisely according to a preoperative treatment plan in a patient presenting with a large intraosseous sphenoid wing meningioma. A larger clinical series with a long-term follow-up will be needed to determine the reproducibility.	Case report. No new efficacy or safety information.
Yates JM, Wildgoose DG, van NR (2009) Correction of a mandibular asymmetry using a custom-made titanium onlay. Journal of Plastic, Reconstructive and Aesthetic Surgery 62(8): e247–50	n=1 Follow-up: not reported	The use of a custom-made titanium alloplast/prosthesis enabled successful treatment of a mandibular asymmetry. It is important to evaluate each patient on an individual basis and assess actual needs against perceived needs, and relate them to psychological factors.	Case report. No new efficacy or safety information.
Yeung RWK, Samman N, Cheung LK et al. (2007) Stereomodel-assisted fibula flap harvest and mandibular reconstruction. Journal of Oral and Maxillofacial Surgery 65(6): 1128–35	n=8 Follow-up: not reported	The clinical outcome in terms of mandibular contour and position of the reconstructed segment, as well as the facial outer appearance and symmetry, was consistently excellent. No case of instability or malposition of the graft segments was encountered.	Small case series. No new efficacy or safety information.
Zhang Y, He Y, Zhang ZY et al. (2010) Evaluation of the application of computer-aided shape-adapted fabricated titanium mesh for mirroring-reconstructing orbital walls in cases of late post-traumatic enophthalmos. Journal of Oral and Maxillofacial Surgery 68(9): 2070–5	n=21 Follow-up: 3–6 months	The application of a computer-aided individually fabricated shape-adapted titanium mesh technique to reconstruct orbital anatomy can reduce approximately 65% of the expanded orbital volume and, correspondingly, correct 50% of post-traumatic enophthalmos.	No new efficacy or safety information.
Zhou LB, Shang HT, He LS et al. (2010) Accurate reconstruction of discontinuous mandible using a reverse engineering/computer-aided design/rapid prototyping technique: a preliminary clinical study. Journal of Oral and Maxillofacial Surgery 68(9): 2115–21	n=6 Mean follow-up: 50 months	Mandibular reconstruction was facilitated using the reverse-engineering/computer-aided design/rapid prototyping technique. Satisfactory aesthetic results were achieved. However, the rigidity of the cast tray could cause severe stress shielding to the grafts, which could lead to disuse atrophy. Therefore, some modification is needed for functional reconstruction.	Small case series. No new efficacy or safety information.

Appendix B: Related NICE guidance for insertion of customised titanium implants, with soft tissue cover for orofacial reconstruction

Guidance	Recommendations
Interventional procedures	**Exposed customised titanium implants for orofacial reconstruction (current guidance). NICE interventional procedures guidance 28 (2003)** 1.1 Current evidence on the safety and efficacy of exposed customised titanium implants in orofacial reconstruction does not appear adequate to support the use of this procedure outside formal research. No further investigation is being undertaken by NICE at present. 1.2 This is not a procedure currently suitable for diffusion outside a research setting, and training should be provided only in the context of research.

Appendix C: Literature search for insertion of customised titanium implants, with soft tissue cover for orofacial reconstruction

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/11/2012	
Database of Abstracts of Reviews of Effects – DARE (CRD website)	21/11/2012	
HTA database (CRD website)	21/11/2012	
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/11/2012	
MEDLINE (Ovid)	21/11/2012	1946 to November Week 2 2012
MEDLINE In-Process (Ovid)	21/11/2012	November 20, 2012
EMBASE (Ovid)	21/11/2012	1980 to 2012 Week 46
CINAHL (NLH Search 2.0/EBSCOhost)	21/11/2012	

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	prosthes*.tw.
6	implant*.tw.
7	screw*.tw.
8	4 or 5 or 6 or 7
9	3 and 8
10	branemark.tw.

11	9 or 10
12	Computer-Aided Design/
13	((computer* adj3 aided* adj3 design*) or CAD or (computer*-aided* adj3 design*)).tw.
14	Magnetic Resonance Imaging/
15	((magnet* adj3 resonanc* adj3 imag*) or MRI).tw.
16	((Computer* adj3 aid* adj3 manufact*) or CAM).tw.
17	stereoscopic*.tw.
18	stereolithograph*.tw.
19	Tomography/
20	(computer* adj3 tomograph*).tw.
21	or/12-20
22	3 and 21
23	(custom* or bespok* or tailor* or individual* or biomodel*).tw.
24	3 and 23
25	11 or 22 or 24
26	((orbit* or orofac* or fac*) adj3 (reconstruct* or rebuild* or repair*)).tw.
27	(orofacial* or oro-facial*).tw.
28	(craniofac* or cranio-facial*).tw.
29	exp Facial Neoplasms/
30	exp Facial Injuries/
31	((fac* or skull*) adj3 (injur* or deform$)).tw.
32	((face or facial) adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.
33	((fac* or skull*) adj3 trauma*).tw.
34	exp Face/ or exp Skull/
35	(fac* or skull* or mandibul* or maxillar* or nos* or mouth*).tw.
36	34 or 35

37	fractur*.tw.
38	fractures, bone/
39	exp skull fractures/
40	37 or 38 or 39
41	36 and 40
42	(congenit* adj3 fac* adj3 (anomal* or abnormal*)).tw.
43	(Orbit* adj3 floor* adj3 fract*).tw.
44	(blow* adj3 out adj3 fract*).tw.
45	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 41 or 42 or 43 or 44
46	25 and 45
47	animals/ not humans/
48	46 not 47