![Australian Government — Medical Services Advisory Committee]

Public Summary Document

Application No. 1577 – Autologous fat grafting (AFG) for treatment of burn scars, and treatment of facial defects due to craniofacial abnormalities

Applicant: **Australian Society of Plastic Surgeons (ASPS)**

Date of MSAC consideration: **MSAC 79th Meeting, 28-29 July 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of autologous fat grafting (AFG) for treatment of burn scars, and treatment of defects due to craniofacial abnormalities was received from Australian Society of Plastic Surgeons by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding of AFG for the treatment of burn scars and treatment of defects due to craniofacial abnormalities. MSAC noted limitations in the evidence, but considered that, on balance, the totality of evidence indicated that AFG is safe, cost-effective, and has potential savings compared with higher-risk, higher-cost alternative procedures, while reducing out-of-pocket costs for patients. MSAC recommended that a review be conducted in 2 years to ensure the item is being used appropriately.

Consumer summary
The Australian Society of Plastic Surgeons applied for public funding via the Medicare Benefits Schedule (MBS) for the use of autologous fat grafting (AFG) for the treatment of burn scars, and the treatment of defects due to abnormalities in the face and head.
AFG is a type of surgery that takes fat from one part of the body (such as the thigh) using liposuction, and injects it into another part of the body (such as the face). The transferred fat adds volume to the area it is injected into, which can help correct defects. Over time, the body absorbs some of the transferred fat, so AFG is usually done several times to reach the desired effect.

Consumer summary
MSAC noted that the clinical studies on AFG were low quality, making it difficult to be sure that AFG is safe and effective. However, MSAC considered that, overall, AFG was safe and effective, compared to other more complicated surgeries.

MSAC noted the comments from consumers and practitioners, which supported AFG and identified a high clinical and psychological need. MSAC considered that AFG would be a simpler procedure than other alternatives, could improve some outcomes and reduce out-of-pocket costs for consumers.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported public funding for AFG to treat burn scars and defects in the face and head. MSAC accepted that AFG was likely to be safe, effective and cost-effective.

3.   Summary of consideration and rationale for MSAC's advice

MSAC noted the application was requesting MBS listing for AFG for the treatment of defects due to craniofacial abnormalities (Population 1) and treatment of burn scars (Population 2). MSAC noted this application arose from an MBS Review Taskforce recommendation and initially covered a broader population, which was split into MSAC Application 1575 and 1577. The linked MSAC Application 1575 is requesting MBS listing for AFG injection for the management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformities.

MSAC noted the extensive consultation responses, in which 22 plastic surgeons and 5 consumer groups were supportive of the application. MSAC noted the high clinical need in these populations, for which AFG would likely allow less complex reconstruction for patients with craniofacial abnormalities. AFG would also address psychological need; reduce pain, skin tightness and dysaesthesia; and improve mobility for patients with burn scars. MSAC also noted that MBS listing of AFG would reduce the substantial out-of-pocket costs that patients currently face for more expensive and higher-risk alternatives.

MSAC noted the very low quality of evidence on the use of AFG for the treatment of burn scars and craniofacial abnormalities leads to substantial uncertainty in clinical and economic outcomes. MSAC also noted the high degree of heterogeneity in the study populations may impact the generalisability of the findings. However, MSAC also recognised that the proposed burn scar and craniofacial defect patient populations are inherently heterogeneous, as such no two patients are the same and care is highly individualised. MSAC also noted the pre-MSAC response claimed that, because of this inherent heterogeneity, it would be unethical to treat patients in a standardised way.

For craniofacial abnormalities (Population 1), when comparing the safety of AFG to free flap surgery, MSAC noted free flap surgery is more complex and is associated with longer hospital stay (often including intensive care), and all flaps require revision after initial surgery. MSAC also noted complications arise in 12–27% of patients who received flaps, compared with 4–5% of patients who received AFG; complications following AFG are also minor, such as bruising. Despite the limited clinical evidence, MSAC considered that AFG was likely to be safer than free flap surgery for craniofacial abnormalities. For burn scars (Population 2), MSAC noted that when AFG is used to treat burn scars complications arose in

1.15% of patients following AFG, and all complications were minor; however, there were no comparative data on safety of AFG *vs.* the nominated comparator (usual care).

MSAC noted the limited data on comparative clinical effectiveness for both populations. For craniofacial abnormalities (Population 1), MSAC considered that non-inferior effectiveness had not been established, although small studies showed both patient and surgeon satisfaction, and significantly improved facial symmetry following AFG. For burn scars (Population 2), MSAC noted a non-significant difference in scar hardness and appearance (although results were from a small study, and wounds were in the same patient) and a significant improvement in movement.

MSAC noted the cost-utility analysis conducted for AFG in patients with craniofacial abnormalities. AFG was dominant, primarily driven by the cost of the comparator (free flap surgery). However, MSAC noted that the clinical data did not establish superiority or non-inferiority for AFG, and the quality-adjusted life years (QALYs) in the economic model were driven by safety rather than effectiveness. The cohort model also had highly variable outcomes. For burn scars, MSAC noted that the economic model used trial-based outcomes extrapolated to lifetime; and studies were limited, had a high risk of bias, and included different populations and procedures. The resulting incremental cost-effectiveness ratios (ICERs) were widely variable, up to $20,086 per QALY gained for face movement.

MSAC noted the modest financial and budgetary impacts for AFG for burn scars, and likely cost-savings for craniofacial abnormalities.

Overall, MSAC considered that, on balance, the totality of evidence indicated that AFG is safe, cost-effective, and has potential savings compared with higher-risk, higher-cost alternative procedures, while reducing out-of-pocket costs for patients.

MSAC noted the proposed item descriptor and considered that leakage to other populations for cosmetic reasons, although possible, was of lower risk for this application (as opposed to Application 1575). MSAC considered whether the descriptor should specify 'congenital or acquired craniofacial abnormalities' to cover these patients and whether a review be conducted to observe if leakage due to cosmetic use is occurring. MSAC considered that, given the relatively small eligible populations for this item (100–150 patients per year for craniofacial abnormalities, and 18–20 patients per year for burn scars), the likely number of patients using the service within the first 12 months would be insufficient to accurately determine whether the item is being used appropriately. MSAC therefore recommended that a review be conducted after 2 years.

MSAC also noted the item descriptor specifies at least 3 months between services, but that this is not specified in Application 1575. MSAC considered that it was good practice to allow the treated area to stabilise before performing another service, but that this did not need to be specified in the descriptor if the total number of services was capped at five. MSAC therefore recommended that 'with at least 3 months between services' be deleted from the item descriptor.

MSAC supported the following item descriptor:

Autologous fat grafting (harvesting, preparation and injection of adipocytes) as an independent procedure or in conjunction with another procedure, if:
(a) the autologous fat grafting is for:
   i.   Correction of asymmetry arising from volume and contour defects in craniofacial disorders, up to a maximum of 5 services per episode; OR
   ii.   Treatment of burn scar or associated skin graft in the context of scar contracture, contour deformity or neuropathic pain, in patients who have undergone a minimum of 3 months of topical therapies, including silicone and pressure therapy, with an unsatisfactory (minimal) level of improvement; up to a maximum of 5 services per region of the body defined as upper or lower limbs, trunk, neck or face; AND
(b) photographic and/or imaging evidence, demonstrating the clinical need for this service, is to be documented in patient notes; AND
(c) in relation to craniofacial disorders, evidence of diagnosis of the qualifying craniofacial disorder is documented in patient notes.

MBS Fee: $651.50 Benefit: 75%=$488.65

4.   Background

This is the first submission (Department contracted assessment report [DCAR]) for AFG for treatment of burn scars, and treatment of facial defects due to craniofacial abnormalities.

The request for MBS listing of AFG for treatment of burn scars and facial defects due to craniofacial abnormalities was initially submitted as part of a much broader patient population within application 1575. The broad population was deemed too large for a single application and therefore, was split into:
- Application 1575 – AFG injection for the treatment/management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity.
- Application 1577 (this application) – AFG for the treatment of craniofacial defects and burns scars.

5.   Prerequisites to implementation of any funding advice

The application indicated that regulatory requirements are not applicable to the proposed medical service. The DCAR noted that the autologous fat that is harvested and re-injected during the AFG intervention falls within the definition of autologous human cells and tissues (HCT) products excluded from some aspects of Therapeutic Goods Administration (TGA) regulation (TGA excluded autologous HCT). Exclusion from TGA regulation is not exclusion from all regulation. There is regulation by other bodies that is sufficient to mitigate possible risks that may arise as a result of manufacturing and using autologous HCT products that are excluded from TGA regulation.

Medical devices or equipment used for the manufacture of autologous HCT products (i.e. used to harvest, prepare and re-inject the autologous fat for the AFG intervention), may be regulated under the medical devices framework, where it is to be used for the treatment, diagnosis or modification of a patient's anatomy or physiological process. Such medical devices can be found listed on the Australian Register of Therapeutic Goods (ARTG; reference Table 11, p49 of the DCAR).

6.   Proposal for public funding

The proposed MBS item descriptor is provided in Table 1.

Table 1 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES

Autologous fat grafting (harvesting, preparation and injection of adipocytes) as an independent procedure or in conjunction with another procedure, if:
 	
(a) The autologous fat grafting is for:
 	
   i. Correction of asymmetry arising from volume and contour defects in craniofacial disorders, up to a maximum of 5 services per episode with at least 3 months between services; OR
 	
   ii. Treatment of burn scar or associated skin graft in the context of scar contracture, contour deformity or neuropathic pain, in patients who have undergone a minimum of 3 months of topical therapies, including silicone and pressure therapy, with an unsatisfactory (minimal) level of improvement; up to a maximum of 5 services per region of the body defined as upper or lower limbs, trunk, neck or face; with at least 3 months between services in the same region; AND
 	
(b) Photographic and/or imaging evidence, demonstrating the clinical need for this service, is to be documented in patient notes; AND
 	
(c) In relation to craniofacial disorders, evidence of diagnosis of the qualifying craniofacial disorder is documented in patient notes
 	
Multiple Operation Rule
 	
(Anaes.)

MBS Fee: $641.85 Benefit: 75%=$481.40

Source: Table 1, p18 of the DCAR.

7.   Summary of public consultation feedback/consumer Issues

In total, 27 consultation responses (22 from specialists/clinicians, 1 consumer and 4 patient support group/carers) were received. The feedback are summarised below.

Summary of Specialist/Clinician Comments

Some of the main benefits of the proposed medical service being funded were:

- Natural reconstructive surgery, smaller operation and less invasive compared to alternative procedures (such as inserting facial implants or free flaps).
- Health funds will be able to cover added out-of-pocket expenses with MBS listing and more patients could have the option to be treated in a private hospital.
- For some patients this is the only suitable option for contour correction.
- Useful adjunct to major reconstruction.
- Reduces pain and tightness in scars and reduced recovery time.
- Improved psychological wellbeing of the patient.
- Reduced psychological impact of facial deformities and potential for bullying.
- Equitable access to this service for all eligible patients.
- By having access to this intervention, patients may be less likely to resort to getting cosmetic fillers in inappropriate facilities.

The specialists considered that disadvantages of the service could include:

- Risks and complications of surgery: bruising, deformity, infection, oil cyst, fat embolism.
- Unskilled practitioners performing the procedure.
- Use for cosmetic purposes unrelated to a pathological diagnosis.

- It often requires more than one procedure to achieve adequate volume and since the resorption of fat is unpredictable.
- The results vary.

Patients require ongoing management and often need repeat therapy. Some specialists commented that the item descriptor needs to ensure it could not be used in patients undergoing reconstruction for cosmetic purposes. Many respondents considered that fat grafting is part of the standard of care and therefore, needs to be publically funded.

Summary of Consumer/Group/Carer Comments
The views towards the benefits of the proposed medical service were similar to those listed by the specialists, especially in regards to psychological wellbeing and satisfaction with the results of the surgery. Consumers also noted the advantage of the less invasive procedure, less pain and less recovery time which allowed them to return to work/school sooner.

8.   Proposed intervention's place in clinical management

Description of Proposed Intervention
AFG is the harvesting, preparation, and re-injection of autologous fat, with or without specialised fat grafting equipment. It includes live fat cells being harvested from a donor site on the patient, prepared in theatre by a variety of methods to separate and purify the fat cells, and injected back into the defective area. It relies on the fat stem cells remaining viable in the transferred site.

Description of Medical Condition(s)
AFG is proposed to treat defects arising from the following medical conditions:
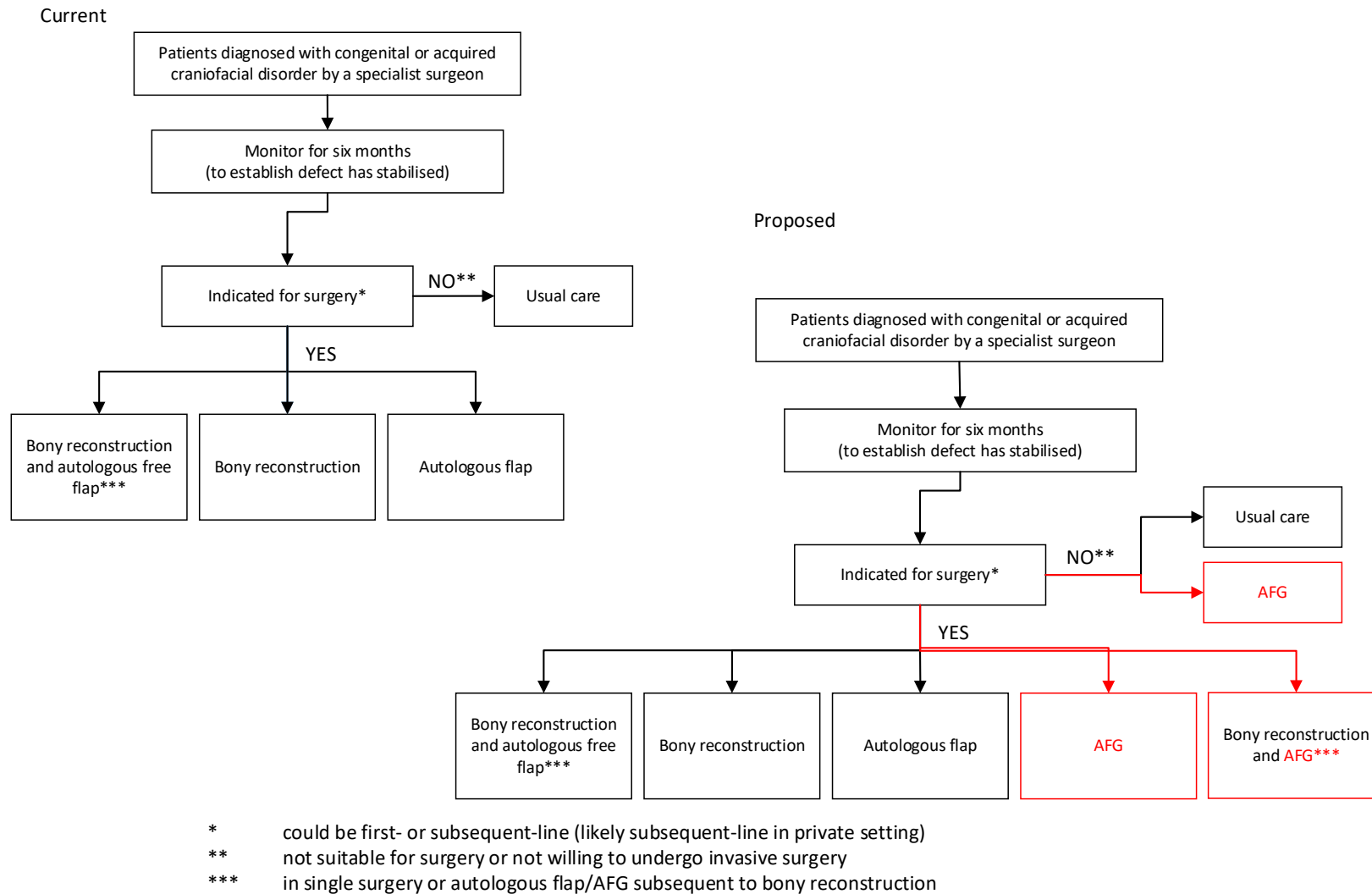
- Population 1: includes patients with craniofacial disorders with facial asymmetry, requiring reconstruction and re-contouring including:
    - Congenital craniofacial syndromes
    - Acquired craniofacial defects (e.g. cancer surgery, other surgery, lipodystrophy associated conditions, trauma).
- Population 2: includes patients with burn scars for the treatment of dysaesthesias, contracture, poor skin quality or deformity, which have shown an unsatisfactory (minimal) level of improvement following treatment with topical therapies.

Population 1 clinical management pathway
The DCAR stated that the clinical management algorithms (Figure 1) includes both patients diagnosed with congenital or acquired craniofacial disorders by a specialist surgeon. Patients are required to have had a formal diagnosis of a craniofacial disorder and to be assessed by a specialist as having a significant facial asymmetry or contour defect identified by clinical evaluation by a specialist and documented by clinical photography. At a minimum prior to surgery, patients are required to have had monitoring of their condition for a period of at least six months in order to establish that the defect has stabilised. If surgery is required, current treatment provides for significant craniofacial surgery, bony reconstruction or bony reconstruction and autologous flap or for autologous flap alone or usual care (for those unwilling to undergo surgery). Autologous fat grafting may be a first-line treatment of choice, instead of an autologous flap, as it presents significantly less morbidity and risk than major surgery or it may be used following invasive surgery to correct persisting asymmetries or deformity.
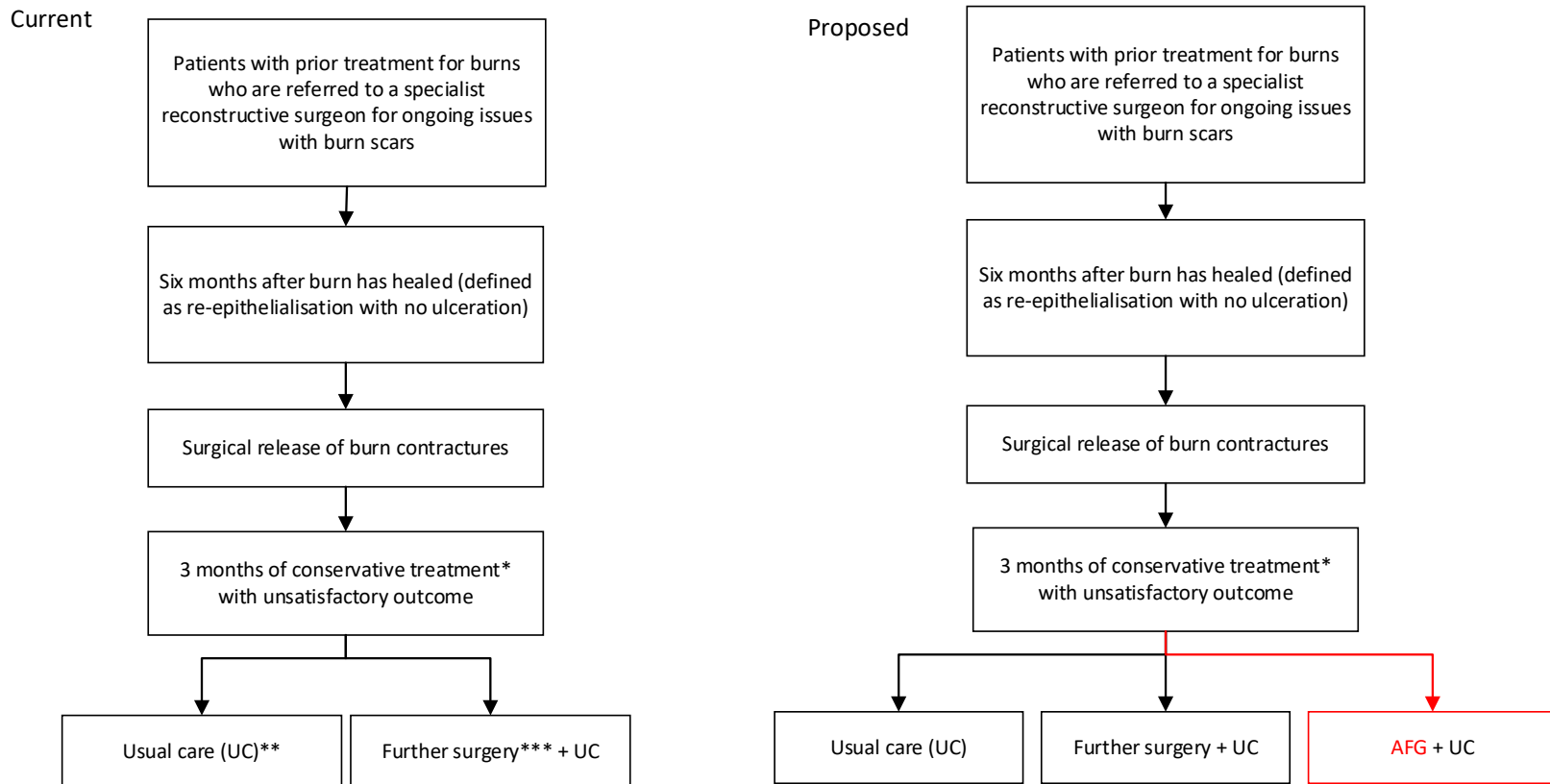
Population 2 clinical management pathway
The DCAR stated that clinical management algorithms (Figure 2) included patients with prior treatment for burns would be referred to a specialist with expertise in burns (plastic and reconstructive surgeon, general surgeon or paediatric surgeon) by a GP or other specialist. Patients would be assessed by a specialist surgeon in burns, following the complete healing of burn wounds/associated skin grafts, in order to determine suitability for surgery. In the case of acute and immature scars, patients may be monitored for a period of up to six months to determine the most appropriate time for surgery. Patients would have had at least three months of conservative treatment with an unsatisfactory outcome and surgical release of burn contracture if required. Conservative treatment is defined as at least silicone therapy, pressure garments and physiotherapy. If AFG is listed on the MBS, patients who currently have unsatisfactory outcomes from conservative treatment +/- contracture release would in addition to usual care alone, or further surgery with usual care, be able to have AFG plus usual care.

Figure 1 **Current and Proposed clinical management pathways for patients with craniofacial disorders with facial asymmetry (Population 1)**
Source: Figure 1, p 68 of the DCAR.

Current

Patients with prior treatment for burns who are referred to a specialist reconstructive surgeon for ongoing issues with burn scars

↓

Six months after burn has healed (defined as re-epithelialisation with no ulceration)

↓

Surgical release of burn contractures

↓

3 months of conservative treatment* with unsatisfactory outcome

Usual care (UC)** | Further surgery*** + UC

Proposed

Patients with prior treatment for burns who are referred to a specialist reconstructive surgeon for ongoing issues with burn scars

↓

Six months after burn has healed (defined as re-epithelialisation with no ulceration)

↓

Surgical release of burn contractures

↓

3 months of conservative treatment* with unsatisfactory outcome

Usual care (UC) | Further surgery + UC | AFG + UC

*   conservative treatment refers to silicone, pressure garments and physiotherapy (other things such as laser treatment may also be included)
**   usual care (UC) = conservative treatment e.g physiotherapy, pain relief, lotions, laser
***   for example, scar contracture release (MBS item 45519), repeat skin grafting (MBS item 45451) or pedicle flap (MBS item 45203)

Figure 2   Current and Proposed clinical management pathway for patients with burns scars and contractures (Population 2)
Source: Figure 2, p 69 of the DCAR

9.   Comparator

Population 1
The comparators for Population 1 are:
   a) bony reconstruction and free autologous flap
   b) free autologous flap reconstruction, or
   c) usual care.

The DCAR noted that the PICO referred to a group of patients included in Population 1 who, have not followed up on further invasive surgery, and would be candidates for AFG. Usual care in this instance does not refer to any specific conservative therapies. The DCAR also noted that the procedure often requires subsequent revision surgery (free autologous flap reconstruction) which was estimated at 20% of the population that received AFG in the application.

MBS items of the surgical comparators for Population 1 include MBS items 45564 and 45565.

The pre-ESC response queried "usual care" as a comparator for the AFG for craniofacial anomalies within the DCAR. The applicant questioned the appropriateness of comparing the safety of a surgical intervention to "usual care" (i.e. doing nothing) in conditions where there is a clear indication to intervene.

In the rejoinder, the assessment group clarified that the inclusion of 'usual care' as the last of the three comparators was an acknowledgement that there likely exists a population who may not have wished to pursue further existing surgery (this may be due to patients preference or patients unsuitable for lengthy general anaesthetic required for microvascular surgery) but for whom AFG may be an appropriate intervention. As noted in the DCAR, although it is acknowledged this population may exist (and contribute to unmet demand for AFG), it is a population which it is not possible to identify for the purposes of utilisation data or for evidence evaluation.

Population 2
The comparator for Population 2 is usual care, which mainly comprises conservative regimens of treatment, but may also include surgical options such as contracture release or microvascular flap procedures.

The DCAR noted that usual care for patients in Population 2 consists of many interventions such as ongoing physiotherapy, massage therapy, hydration of the scar, ultrasound and laser therapy and that the therapies that constitute usual care can differ for each patient.

MBS items for surgical operations that may be included as part of usual care and may also be used in conjunction with AFG, include MBS items 45519, 45054, 45451 and 45203. The DCAR noted that The Medicare Benefits Review Task force ([Draft Report for the Plastic and Reconstructive Surgery Clinical Committee](#)) has recommended that the proposed descriptor for item 45519 (burns contracture release) be amended and three new items be created to account for the extent of the deficit (i.e. <1%, 1-3% and >3 to <10% of total body surface).

10. Comparative safety

Population 1

Congenital craniofacial abnormalities

For Population 1, the DCAR identified two comparative studies assessing the use of AFG compared to free vascular flap transfer (free flap) to correct facial asymmetry due to congenital conditions (Table 2). A further three systematic reviews relevant to the use of AFG in Population 1 were included in the DCAR (Table 3).

Table 2 Key features of the included comparative studies comparing AFG with free flaps

Study	N	Design	Risk of bias	Patient population	Intervention group	Comparator group	Key outcomes
Schmitz 2008	18	Retrospective	High	Patients with congenital facial lipodystrophy	Treated with lipofilling/fat injection	Treated with free flap surgery	Average duration of treatment Resource use Complications Degree of patient satisfaction Clinician and researcher evaluation of cosmetic outcome
Tanna 2011	31	Retrospective	High	Children diagnosed with craniofacial macrosomia	Treated with serial autologous fat grafting	Underwent microvascular free flap surgery	Number of procedures Resource use Complications and adverse events Patient and physician satisfaction

Source: Table 17, p81 of the DCAR.

Table 3 Key features of the included systematic reviews

Systematic review	Number of studies	Number of patients	Risk of bias	Intervention	Comparator group	Key outcomes
Krastev 2018	Total = 51 Congenital = 16 Acquired = 17 HIV =14 Mixed = 4	Total = 1533 Congenital = 409 Acquired = 326 HIV =650 Mixed = 148	Low	AFG, most studies using procedures based on principles described by Coleman for reconstructive purposes.	Not applicable.	Patient and physician satisfaction Volume measurements Number of sessions Complications
Lv 2020	Total = 27 Meta-analysis = 21	Total = 1011	Low	AFG, for cosmetic or reconstructive purposes.	Not applicable.	Volume retention
Sinclair 2019	Total = 38[a] Fat graft = 8 Pedicled flap = 5 Free flap = 24 Functional reconstruction = 2 Alloplastic reconstruction = 1	Total = 251 Fat graft = 87 Pedicled flap = 13 Free flap = 129 Functional reconstruction = 9 Alloplastic reconstruction = 13	Unclear	Structural fat grafting to correct soft-tissue deficiency in hemifacial microsomia.	Pedicled flap. Free flap. Functional reconstruction. Alloplastic reconstruction.	Fat grafting Number of grafting sessions Total volume fat grafted Complication rate Facial symmetry Flaps Intra- and post-operative flap volume Pre- and post-operative symmetry scores Patient and physician satisfaction Number of procedures Complications

[a] individual papers reported on >1 procedure
Source: Table 18, p82 of the DCAR.

The DCAR stated that Schmitz (2008)[1] reported that no migration or necrosis of fat was observed in those who underwent AFG (by the Coleman procedure; n=9). Two patients in the fat graft group (n=12; including one who underwent AFG following free flap surgery) experienced post-operative swelling, which resolved progressively. In contrast, among those treated with free flap (n=7), Schmitz (2008) reported one preoperative arterial thrombosis (no flap loss), haematomas, oedema, section of the facial nerves, atrophy, and ptosis of the flap. Donor site morbidity was low and healed primarily in the free flap group. The authors also reported that all free flaps developed ptosis or atrophy and needed some further treatment, although the nature of that further treatment was not specified. All patients in the free flap group experienced post-operative swelling. One patient lost 2.5L of blood perioperatively and needed blood transfusion. One patient had facial nerve injury.

The DCAR stated that Tanna (2011)[2] reported that the complication rate for those undergoing AFG (n=21) was five per cent, with infection and surface irregularities observed; no donor-site morbidity was observed. Among the free flap group (n=10), the complication rate was reported as 12 per cent, which included haematoma and partial flap loss with fat necrosis; one patient in the free flap group had a prolonged seroma.

The DCAR noted no studies providing a comparison of the safety of AFG to usual care were identified to inform the comparative safety of AFG to this comparator for congenital craniofacial abnormalities.

Acquired craniofacial abnormalities
The DCAR noted no studies providing a comparison of the safety of AFG to free flaps or usual care were identified to inform the comparative safety of AFG to these comparators for acquired craniofacial abnormalities.

The DCAR noted that systematic reviews (summarised above in Table 3) included case series on patients with acquired craniofacial abnormalities that reported low complication rates associated with AFG use (2.8-5%), however the nature and severity of these complications was not reported. Sinclair (2019)[3] provided a comparison of fat grafting to free flaps. The authors reported that the complication rate associated with AFG was 4.2% (6 complications in 142 grafting procedures reported in seven studies). Across 17 studies, the complication rate associated with free flaps was 27.1% (16 complications in 59 free flaps). Sinclair (2019) reported an odds ratio (95% confidence interval [CI]) of 6.7 (2.4, 18.7).

The DCAR considered although AFG applied to the craniofacial region appears to be a safe procedure and the risk of hypersensitivity reactions is negligible, AFG can be complicated by morbidity in the donor site, prolonged oedema, infections, contour irregularities, and necrosis or calcification of the injected fat. Further investigation of the safety AFG when applied to the craniofacial region noted case reports of fat emboli leading to stroke and vision loss. For patients who are seeking treatment for asymmetry to the face following cancer surgery (i.e, acquired craniofacial defect), the incidence of cancer recurrence in this population would be of interest. No studies reporting such events were identified.

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[1] Schmitz S, Weis C, Morley S, Demey A, Dabernig J (2008) European Journal of Plastic Surgery. 31(6):305-10.
[2] Tanna N, Wan DC, Kawamoto HK, Bradley JP (2011) Plastic and reconstructive surgery. 127(2):802-11.
[3] Sinclair N, Gharb BB, Papay F, Rampazzo A (2019) The Journal of craniofacial surgery. 30(3):879-87.

Population 2
For Population 2, the DCAR identified one randomised controlled trial (RCT), two comparative studies, five case series and two systematic reviews relevant to the assessment of AFG for treating burn scars (summarised in Table 4).

The DCAR noted that the randomised controlled trial (Gal 2017[4], n=9) and the comparative study (Klinger 2013[5], n=20) did not report any complications associated with either the donor or the AFG sites. The non-comparative studies (Fredman 2016[6], n=7; La Padua 2018[7], n=24; Gargano 2018[8], n=12; Byrne 2016[9], n=13) reported incidences of small, asymptomatic donor-site seroma, and minor events including pain, local oedema and "skin breakdown". Patients in Byrne (2016) experienced no adverse events, however they were administered oral antibiotic therapy for five days postoperatively to prevent infection, due to previous reports of infection associated with AFG.

The DCAR suggested, based on the above, that AFG as a separate procedure is relatively safe with a rare occurrence of serious complications, and a low risk of less serious complications such as haematoma and infection of the donor or recipient site. However, based on the limited number of small size studies it appears that AFG in combination with other procedures (a simultaneous rigottomy or a subsequent laser) may be a less safe procedure. This uncertainty could only be resolved with larger size trials, if they were available.

The DCAR also noted that two systematic reviews (Riyat 2017[10], 23 studies; Negenborn 2016[11], 26 studies) of the use of AFG for the treatment of scars (not limited to burn scars) reported a complication rate (14/1222=1.15%). This number included postoperative haematoma and infection, as well as the need for further AFG sessions and surgical excision of scar tissue following unsuccessful treatment (Riyat 2017). Also included was a small number of complications such as one case of a superficial abdominal hematoma, which required percutaneous surgical drainage; four cases of infection, which were treated successfully with antibiotics and two cases of reactivation of herpes infection, which resolved in four days without leaving pigmented lesions (Negenborn 2016).

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[4] Gal S, Ramirez JI, Maguina P (2017) Burns. 43(3):486-9.
[5] Klinger M, Caviggioli F, Klinger FM, Giannasi S, Bandi V, Banzatti B, et al. (2013) The Journal of craniofacial surgery. 24(5):1610-5.
[6] Fredman R, Edkins RE, Hultman CS (2016) Annals of plastic surgery. 76:S298-S303.
[7] La Padula S, Hersant B, Meningaud JP, D'Andrea F (2018) Journal of stomatology, oral and maxillofacial surgery. 119(4):279-83.
[8] Gargano F, Schmidt S, Evangelista P, Robinson-Bostom L, Harrington DT, Rossi K, et al. (2018) JPRAS Open. 17:5-8.
[9] Byrne M, O'Donnell M, Fitzgerald L, Shelley OP (2016) Burns. 42(2):356-65.
[10] Riyat H, Touil L, Briggs M, Shokrollahi K (2017) Scars Burn Heal 3:1–16.
[11] Negenborn VL, Groen J-W, Smit JM, Niessen FB, Mullender (2016) Plastic and Reconstructive Surgery. January 31e-43e.

Table 4 Summary of the evidence available for Population 2 (burn scars)

Author	Design	N patients	Population detail	Intervention group	Comparator group	Risk of bias[a]	Outcomes
Controlled trials							
Gal 2017	RCT, double-blind	9	Paediatric burn survivors - children and young adults aged <21 years (mean age 13 years) with mature homogenous burn scars of at least 10x5cm dimension suitable for apportioning into two areas.	One half of the scar was injected with 5mL of AFG.	The other half was injected with 5mL of saline solution.	Medium-high	VSS (no scores were reported); subjective patient assessment of pigmentation, vascularity, pliability, height, "looks" and "feels".
Klinger 2013	Non-randomised CT	20	Patients aged ≥15 years with hypertrophic painful and retractile traumatic, surgical, and burn scars[d] affecting daily function, i.e. joint mobility.	One half of the scar was treated with AFG.	The other half was infiltrated with saline solution.	High	Objective test for hardness (functional deficit) was performed with a durometer. POSAS (patient and surgeon modules)
Non-comparative studies to improve burn scar appearance, functionality and pain							
Bruno 2013	Case series[b]	93[c]	Patients with a homogenous burn scars of at least 200 cm^2 suitable for apportioning into two areas.	Half of the scar area was treated with AFG performed through an intrascar infiltration	The other half of the scar area remained untreated	High	Objective histologic and immuno-histochemical measurements. VSS; NRS for subjective patient assessment. Results for the comparator site were not reported.
Xu 2018	Case series	80	Patients with hypertrophic scars resulting from severe burns received more than 1 year previously.	Autologous fat converted into chyle fat, 3 separate treatment with 3 month intervals.	Not applicable, assumed "do nothing".	High	*Ad hoc* quantitative assessment of scar "shrinkage" combined with the qualitative assessment of its texture, softness and colour.
Byrne 2016	Case series	13	Patient with burn scars that reduce range of motion of hand.	AFG (a single session).	Not applicable, assumed "do nothing".	High.	Hand function was measured with grip strength, TAM, DASH and MHQ. Patients' satisfaction was assessed with POSAS.
Fredman 2016	Case series	7	Patient with chronic, refractory neuropathic pain, who failed conventional therapy, which included pharmacologic, medical, and laser treatment of the burn scars.	2 sessions of AFG, spaced 2 months apart.	Not applicable, assumed "do nothing".	High.	5 patients filled Patient-Reported Outcomes Measurement Information System (PROMIS)

Author	Design	N patients	Population detail	Intervention group	Comparator group	Risk of bias[a]	Outcomes
Non-comparative studies assessing effectiveness of AFG in combination with another simultaneous or a subsequent intervention							
Gargano 2018	Prospective case series	12	Patients with debilitating contracted burns scars limiting range of motion that had been previously treated with scar release, skin grafts, or Z-plasties	Patients treated with the "SUFA" technique (Subcision and Fat Grafting).	Not applicable, assumed "do nothing".	High.	VSS. Joint range of motion was assessed with goniometer. Fat graft survival and skin changes were evaluated by high frequency ultrasound.
La Padua 2018	Prospective case series	24	Patients with hypertrophic scars and keloids, resulting from second and third–degree burns of the face.	A small quantity of purified fat was injected in multiple sites at the dermal-hypodermal junction of the scar. Procedure was repeated in 3 months. CO_2 laser treatment of hypertrophic burn scars was performed at the end of the fat graft.	Not applicable, assumed "do nothing"	High.	A punch biopsy from the scar tissues was performed in each patient before surgery and at one year follow-up. *Ad hoc* questionnaire about improvement in self-confidence; skin texture, softness, colour and elasticity was administered at baseline and at 1 year follow up.

Abbreviations: AFG = autologous fat graft; CT = controlled trial; DASH = the Disabilities of the Arm, Shoulder and Hand; MHQ = Michigan Hand Outcome Questionnaire; POSAS = patient and observer scar assessment scale; consists of two scales (one for the patient and one for an observer) whereby each scale has six items (relating to the scar) scored on a numeric rating scale from 1 to 10; R = retrospective; RCT = randomised controlled trial; TAM =Total Active Movement; VSS=Vancouver Scar Scale

[a] RCTs assessed by Cochrane tool for assessing risk of bias of RCTs, comparative studies by ROBINS-I; case-series were assessed with: Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about

[b] Case series design was assigned according to the result presentation as before and after AFG rather than as AFG vs no AFG. Subsequently, the declared method of the controlled trial was reclassified.

[c] Number of scars, rather than patients

[d] The controlled trial (N=20) was a part of a larger (N=694) non-controlled study (Klinger, 2013). Although the aetiology of scars in these 20 patients was not reported, the results were reproduced in Chapter 18 (Klinger, 2009), specifically concerned with burn scar remodelling. It was therefore assumed that all 20 patients had burn scars.

Source: Table 19, p83 of the DCAR.

The pre-ESC response raised concern regarding the literature search strategy used in the DCAR and claimed there was insufficient information about the screening methodology used. Further, the applicant contested why peer-reviewed articles on post-parotidectomy contour deformities (head and neck tumour defects) were excluded from the DCAR. In particular, the applicant contested why Wang, KY et al. and Yamaguchi et al. were excluded on the basis of "wrong intervention".

In the rejoinder, the assessment group clarified the screening criteria specified and justified the exclusion of Wang (2019) as the "wrong intervention" on the basis that adipose tissue was harvested and placed directly in the cavity, rather than injected, and that fat grafting was performed at the same time as the parotidectomy, rather than six months after (to establish the defect had stabilised). In regards to Yamaguchi (2017), the assessment group acknowledged that is article was incorrectly cited as being excluded on the basis of "wrong intervention" in the DCAR; it was excluded on the basis of not being a comparative study (although it was included in the Sinclair (2019) systematic review, which was included in the DCAR).

11.   Comparative effectiveness

Population 1
Congenital craniofacial abnormalities

Patient satisfaction of cosmetic outcomes
The DCAR noted that Schmitz (2008) indicated greater patient satisfaction among those treated with AFG compared with free flap surgery, while Tanna 2011 reported no differences in patient satisfaction (p>0.05). The mean patient satisfaction score was 3.7 ± 0.5 for the AFG group and 3.5 ± 0.2 for the free flap group, on a five-point scale (with 0 indicating dissatisfied or no improvement and 4 indicating totally satisfied or 100% improvement). The Krastev (2018)[12] systematic review reported that a high proportion of patients were satisfied with the results of treatment with AFG (92.2%; 95% CI: 80.8%, 97.1%), however no estimates were available for those treated with free flap.

Clinician satisfaction of cosmetic outcome
Tanna (2011) reported there were no statistically significant differences between the AFG and free flap groups with respect to physician satisfaction (p>0.05). The mean physician satisfaction scores for the AFG and free flap groups was 3.6 ± 0.2 and 3.5 ± 0.3 on a five-point scale, respectively. Krastev (2018) reported that a high proportion of surgeons were satisfied with the results of treatment with AFG (91.5%; 95% CI: 86.8%, 98.3%).

Symmetry scores
The DCAR noted that Tanna (2011) reported symmetry scores in terms of the difference of the final scores from 100%, where a value of 100 per cent was considered ideal. The symmetry scores in the AFG and free flap groups was $99\% \pm 5.4\%$ (from $75\% \pm 5.0\%$ at baseline), i.e. 1% difference and $121\% \pm 7.9\%$ (from $74\% \pm 7.1\%$ at baseline), i.e. 21% difference, respectively. The authors reported that patients treated with AFG had a post-reconstruction symmetry score significantly closer to 100 percent (p<0.05) compared with those treated with free flaps. Sinclair (2019) reported the results from Tanna (2011) and three further case series, which all reported statistically significant improvements in facial symmetry when making comparisons before and after AFG.

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[12] Krastev TK, Beugels J, Hommes J, Piatkowski A, Mathijssen I, van der Hulst R (2018) JAMA facial plastic surgery. 20(5):351-60.

Volume of AFG retention

The DCAR noted that Tanna (2011) reported that there was a statistically significantly higher amount of volume augmentation in those treated with free flaps compared with those treated with AFG. Systematic reviews by Krastev (2018) and Lv (2020)[13] reported a wide variation in volume retention, 40% to >80% at 1 year and 26% to 83% at 2 years, respectively.

Acquired craniofacial abnormalities

The DCAR considered that no comparative data was available to inform a comparison of AFG to free flap or usual care among those with acquired craniofacial abnormalities.

The systematic review of case studies (Krastev 2018) reported that a high proportion of patients and surgeons were satisfied with the results of treatment with AFG (81.5%; 95% CI: 68.0%, 90.2%) and (87.1%; 95% CI: 78.1%, 92.7%), respectively.

Population 2

Appearance of burn scars

The DCAR noted that Gal (2017) reported no statistical or clinically noticeable differences in the "look" and "feel" of burn scars, treated with AFG or saline (Table 5). The outcomes were assessed by both patients and investigators, all of whom were blinded to the treatment allocation. The trial was subsequently prematurely terminated.

Table 5 Results of RCT (Gal 2017) of AFG vs placebo (saline) to improve appearance of burn scars (N=8)

Dimensions for the scar assessment	Frequency of the responses		
	AFG site is better	No difference	Saline is better
Blinded observers			
Pigmentation	1	6	1
Vascularity	1	6	1
Pliability	3	3	2
Height	1	5	2
Blinded patients			
"Looks"	4	2	2
"Feels"	2	2	4

Abbreviations: AFG = autologous fat graft; N = number of participants
Source: Table 24, p100 of the DCAR.

Skin hardness

The DCAR noted that Klinger (2013) reported skin hardness using a Durometer (objective outcome), showing a statistically significant reduction (p<0.05) between preoperative and postoperative values in the AFG treated site while no significant reduction was observed in the control site (Table 6). The DCAR noted that flaws in the trial design (i.e. apparent lack of heterogeneity between the intervention and control parts of the scar area and no randomisation) prevented a meaningful comparison of results. The areas treated with AFG were significantly worse at baseline, however at 3 months of follow-up, the hardness of these areas became similar to the hardness of the area treated with saline (in fact, AFG site remained slightly worse).

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[13] Lv Q, Li X, Qi Y, Gu Y, Liu Z, Ma GE (2020) Aesthetic plastic surgery.

Table 6 Results of controlled trial (Klinger 2013) of AFG vs placebo (saline) to improve hardness (N=20)

Arm of the trial	Durometer mean value (baseline)	Durometer mean value (3 months)
Intervention (AFG)	40.91 (SD 11.85)	31.67 (SD 9.46)
Control (saline)	33.75 (SD 10.94)	30.72 (SD 10.77)

Abbreviations: AFG = autologous fat graft; N = number of participants; SD = standard deviation
Source: Table 25, p101 of the DCAR.

Other clinical effectiveness outcomes

The DCAR noted change in a summary Vancouver Scar Scale (VSS) score from baseline was reported by Bruno (2013)[14] for the AFG procedure and by Gargano (2018) for a "SUFA" technique (Subcision and Fat Grafting; Table 9). Bruno (2013) reported a 26 point change reduction (improvement) in VSS between baseline and the 6 month follow-up visit; however analysis of statistical significance of the difference was not conducted. Gargano (2018) reported statistical significance of the change (6 point reduction) in the VSS total scores from baseline (p=0.0025). It is not known whether this 6 point improvement would be clinically significant.

The DCAR noted that Byrne (2016) included two types of patients with decreased range of motion due to scar contracture (N=7) and with cosmetically displeasing scars (N=6). Results indicating the change from the baseline were not reported according to subgroups. For the small sample of just 13 patients the study used a battery of tests: two objective metrics were range of motion (ROM), assessed with goniometer and grip strength, assessed with dynamometer; two condition-specific instruments were the Disabilities of the Arm, Shoulder and Hand (DASH) Questionnaire and Michigan Hand Outcome Questionnaire (MHQ) (Chung 1998). The MHQ activity of daily living score, function score, work score, satisfaction score, pain score and total score, all increased following AFG but did not reach the level of statistical significance in comparison to the pre-surgery scores. Neither grip strength measurement (34.6 ±10 preoperatively *vs.* 35.8 ± 10 postoperatively) nor DASH score (18 ±14 preoperatively *vs.* 18 ± 16 postoperatively) showed improvements.

The DCAR also noted in addition to the change in ROM in hand/arm (Byrne 2016), the goniometer results for head and neck were reported in (Gargano 2018) [see Table 7 below].

Summary
The DCAR summarised the available evidence reported in the RCT and comparative studies (Table 7). In addition, some selective evidence from case studies that informed the economic evaluations was also included.

Table 7 Balance of clinical benefits of AFG, relative to free flaps (Population 1) or usual care (Population 2), and as measured by the critical patient-relevant outcomes in the key studiesa

Outcomes (units)	Participants (studies)	Quality of evidence (GRADE)[b]	AFG group/ site	Comparator (free flap/ usual care) group/site	Statistical significance of the difference	Comments
Population 1 (congenital craniofacial abnormalities)						
Patient satisfaction	Schmitz (2008, n=18) Tanna (2011, n=31)	⊕⊙⊙⊙ ⊕⊙⊙⊙	100%[c] 3.7 ± 0.5	0%[c] 3.5 ± 0.2	Not reported No statistically significant difference	Using *ad hoc* instruments; heterogeneity in the population between the studies and the arms prevented meta-analysis
Physician satisfaction	Tanna (2011, n=31)	⊕⊙⊙⊙	3.6 ± 0.2	3.5 ± 0.3	No statistically significant difference	

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[14] Bruno A, Delli Santi G, Fasciani L, Cempanari M, Palombo M, Palombo P (2013) Journal of Craniofacial Surgery. 24(5):1806-14.

Outcomes (units)	Participants (studies)	Quality of evidence (GRADE)[b]	AFG group/ site	Comparator (free flap/ usual care) group/site	Statistical significance of the difference	Comments
Symmetry scores	Tanna (2011, n=31)	⊕⊙⊙⊙	99 ± 5.4	121 ± 7.9	Significant (p<0.05)	Outcome is assessed in percent, where the value of 100% is considered ideal
Population 2 (Burn scars)						
VSS (distribution of responses)	Gal (2017, n=10)	⊕⊕⊙⊙	Distribution of physicians' assessment of pigmentation, vascularity, pliability and high of the scar areas	Said to be no difference (statistical analysis was not conducted)		The assessment was done by three categories (AFG better, saline better and no difference)
Patient assessment of the "look" and "feel" of two parts of the scar	Gal (2017, n=10)	⊕⊕⊙⊙	None of the patients had experienced obvious changes on the scar or a clear improvement on one or the other side	Said to be no difference (statistical analysis was not conducted)		Most patients hesitated and often changed their mind when asked for answers during the assessment
Skin hardness	Klinger (2031, n=20)	⊕⊙⊙⊙	40.9-31.67= 9.23 [d]	33.75-30.72= 3.03 [d]	Not reported	Objective outcome (durometer); note a big difference at the baseline
VSS (scores)	Bruno (2013) Gargano (2018)	⊕⊙⊙⊙ ⊕⊙⊙⊙	41 (34-49) to 15 (9-18)[e] 10 (9-12) to 4 (3-7)[e]	N/A N/A	Not reported Not reported	Lower values indicates better skin Combine intervention of AFG and Subcision (percutaneous release of deep scar tissues)
Range of motion	Byrne (2016) Gargano (2018)	⊕⊙⊙⊙ ⊕⊙⊙⊙	31%[f] 36.3^0 (20^0-45^0) to 61.2^0 (45^0-70^0) [e]	N/A N/A	Not reported Significant (p<0.05)	Proportion of responders. Outcomes are applicable to the subgroup (n=6) with restricted motion of neck
MHQ	Byrne (2016)	⊕⊙⊙⊙	Increase in 5 MHQ points from baseline	N/A	No statistically significant difference	Read from Fig.3 p.360.

Abbreviations: VSS=Vancouver Scar Scale; AFG=autologous fat grafting; SD=standard deviation; ROM=range of motion; TAM=total active movement; ASSH= American Society for Surgery of the Hand; MHQ = Michigan Hand Outcome Questionnaire;

[a] Included 2 case-series with outcomes used in economic evaluation
[b] GRADE Working Group grades of evidence (Guyatt et al., 2013)
[c] Proportion of "very pleased" or "satisfied" patients
[d] 3 month observation of difference from the baseline. SD of the difference was not reported
[e] follow up observation of difference from the baseline; at 6 month in Bruno (2013) and at 12 month (presumably) for Gargano (2018)
[f] Proportion of "responders" in the total sample (n=13); response is defined as improvement in ROM on the TAM scale at least to the next grade according to the ASSH gradation
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Source: Table 2, p29 of the DCAR.

Clinical claim

The clinical claim for Population 1 is non-inferiority of AFG compared to the current surgical treatment(s) for efficacy, but with superior safety. No clinical claim for patients who have not

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followed up on further invasive surgical treatment but would be eligible for AFG (where usual care would be the relevant comparator) was made in the PICO.

The clinical claim for Population 2 is superiority of AFG compared to usual care for efficacy. A claim for safety was not made in the PICO. A clinical claim for safety will depend if the comparator is usual care alone or usual care with secondary surgery.

On the basis of the benefits and harms reported in the evidence base (summarised above), the DCAR suggested that:
- for Population 1 - Congenital craniofacial abnormalities:
    - relative to free flap surgery, AFG has uncertain safety and uncertain effectiveness.
    - relative to usual care, AFG has unknown safety and unknown effectiveness.
- for Population 1 - Acquired craniofacial abnormalities:
    - relative to free flap surgery and usual care, AFG has unknown safety and unknown effectiveness.
- For Population 2 - Burn scars:
    - relative to usual care, AFG has uncertain safety and uncertain effectiveness.

Translation issues

Population 1

In the absence of a demonstrated clinical effectiveness of AFG versus the comparator, free flap transfer, the DCARs base case analysis for the congenital subpopulation was performed in terms of a highly hypothetical cost-utility analysis (CUA), where equal utility gain was assigned to successful procedures, whether AFG or a free flap surgery. This is consistent with the clinical non-inferiority claim suggested in PICO (notwithstanding that non-inferiority was not demonstrated either). The economic evaluation could be reduced to a cost comparison, however the difference in the observed complication rates (favouring AFG) was reflected in the model in two ways: as a risk of complication; by assigning a disutility on occasion of a serious adverse event. The results were reported in terms of incremental cost per quality-adjusted life year (QALY) gained.

The DCAR considered that due to the highly hypothetical nature of the modelling assumptions, the applicability and generalisability of results of the economic evaluation across subgroups of the population with congenital craniofacial deformity for whom MBS listing is sought is uncertain.

Population 2

The DCARs base case analysis was a trial-based cost-effectiveness analysis. However, in this population, scenario analyses were also conducted where the outcomes measured in the base case in terms of the proportion of "responders" were converted to QALYs and extrapolated over a life-time in a modelled economic evaluation. Given these scenario analyses are underpinned by numerous assumptions, they are considered to be of a hypothetical nature and should be interpreted with caution.

The DCAR also considered that due to the highly hypothetical nature of the modelling assumptions, the applicability and generalisability of results of the economic evaluation across subgroups of the population with burn scar contracture for whom MBS listing is sought is uncertain. Applicability is most seriously compromised by the assumption that utility values observed in Dupuytren disease population[15] would suit the burn scar contracture population

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[15] Engstrand (2014) reported utility gain of 0.09 (EuroQoL -5D) corresponding to 59% improvement in ROM from baseline in Dupuytren disease population

and generalisability is most seriously compromised by AFG being a third line (last resort or, conversely, "finishing touches") treatment with the implied comparator "do nothing".

12. Economic evaluation

Population 1

The base case model for Population 1 was a CUA of AFG *vs.* free flap surgery (Table 8).

Table 8 Summary of the base case economic evaluation (Population 1)

Perspective	Australian Health Care System
Comparator	free flap surgery
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Systematic reviews (Krastev 2018, Sinclair 2019, Lv 2020) for the number of sessions and risk of adverse events for the intervention AFG and comparator FF
Time horizon	Lifetime, starting age is 20 years
Outcomes	QALY
Methods used to generate results	Markov chain model
Health states	"Alive after surgical success", "alive with serious AE"; "alive with minor AE"; "dead"
Cycle length	12 months
Discount rate	5%
Software packages used	TreeAge Pro 2019 R2.1

Abbreviations: AE=adverse event; AFG= autologous fat graft; FF=free flap procedure
Source: Table 34, p124 of the DCAR.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the analysis, and using the base case assumptions, are shown in Table 9.

Table 9 Results of the base case CUA (Population 1)

	Cost	Incremental cost	Effectiveness (response)	Incremental effectiveness	ICER
AFG	$2,231	-$5,032	3.11	0.04	AFG dominates
Free flaps	$7,263		3.07		

Abbreviations: ICER = Incremental Cost Effectiveness Ratio
Source: Table 6, p36 of the DCAR.

The DCARs summary of the model drivers in sensitivity analyses in summarised in Table 10. The DCAR concluded that AFG being a dominant strategy was robust to the variations in risk of serious complications, variations in the values of utility gain when the same values applied to both strategies, and variations in disutility values. However, when the assumption of no difference in clinical effectiveness was relaxed by assigning the maximum utility gain (0.22, Dey 2019) to the free flap comparator arm and the base case value (0.16, Dey 2019) to the AFG arm, AFG became the less costly and less effective option (-1.13 QALYs) with corresponding ICER estimate of $4,457 saving per QALY foregone. Assigning the minimum utility gain to AFG outcomes (0.06, Dey 2019) resulted in -3.07 incremental QALYs and an ICER estimate of $1,640 saved per QALY forgone. The DCAR considered this assumption appeared plausible in the context of heterogeneity of the patients' condition, as well as patients' preferences and surgeons' skills in choosing the most suitable procedure. For example, it could be argued that a facial defect of a larger volume cannot be effectively managed with AFG and better results would be achieved with free flap surgery. From that point of view, the base case result indicating AFG dominance should not be interpreted as an

equivalent to the potential savings to the health system. Potential savings need to be apportioned to the patients whose clinical needs would equally likely be met by either AFG or free flap transfer.

Table 10 Key drivers of the model (sensitivity analysis) – Population 1

Description	Value	Impact
Utility values	Utility gain = 0.06 in both AFG and FF arms	Medium, decreases the QALY gain from 0.04 in base case to 0.01 without affecting the dominance of AFG strategy
Two-way sensitivity analysis of utility values (differential clinical effectiveness)	Utility gain = 0.22 in FF arm and Utility gain = 0.06 in AFG arm	High, AFG becomes the less costly and less effective strategy

Abbreviations: AFG = autologous fat grafting; QALY = quality-adjusted life year
Source: Table 38, p132 of the DCAR.

Population 2

The DCAR's base case model for Population 2 was a trial-based cost-effectiveness analysis (CEA) of AFG *vs.* no treatment based on Byrne 2016 (Table 11). In this small study (n=12), all patients presented with scar contraction or cosmetically displeasing scars were treated in the hospital setting with one session of AFG for secondary reconstruction (i.e. third-line treatment) as per Coleman's procedure. A summary of the DCARs cost-utility scenario analyses, which extends the model to a lifetime is summarised in Table 13. The first scenario analysis was estimated from Byrne (2016), and the second scenario analysis involved the population (N=12) with limited ROM due to scar contracture affecting face and neck, upper extremity and axilla, lower extremities and perineum Gargano (2018). In this population a combined simultaneous intervention of subcision (percutaneous release of deep scar tissues) and AFG was used: "SUFA" technique (Subcision and Fat Grafting), performed in the hospital setting. In this scenario analysis, the number of AFG procedure was assumed to be two, as the authors did not report the mean number of sessions but stated that a maximum of three sessions with an interval of 2–3 months was performed. The DCAR could not estimate a CEA from Gargano (2018), as only derived modelled utility gains could be cautiously estimated from the outcomes (degrees of improvement in ROM from the baseline) reported in the study.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the analysis, and using the base case assumptions, are presented in Table 12.

CEA-base case model

Table 11 Summary of the base case economic evaluation (Population 2)

Perspective	Australian Health Care System
Comparator	No treatment
Type of economic evaluation	Trial based cost-effectiveness analysis
Sources of evidence	Observational study (Byrne 2016)
Time horizon	12 months
Outcomes	Response rate (achieving at least 65^0 improvement in ROM on the TAM scale)
Methods used to generate results	Base case: trial-based
Health states	Not applicable
Cycle length	Not applicable
Discount rate	Not applicable
Software packages used	Not applicable (simple arithmetical calculation)

Abbreviations: ROM=range of motion; TAM=total active movement
Source: Table 40, p135 of the DCAR.

Table 12 Results of the base case CEA (conservative estimate of proportion of responders) – Population 2

	Cost	Incremental cost	Effectiveness (response)	Incremental effectiveness	ICER incremental cost per responder
AFG (single procedure)	$1,104.64	$1,104.64	0.31	0.31	$3,563.36
No treatment	$0		0		

ICER = Incremental Cost Effectiveness Ratio
Source: Table 44, p142 of the DCAR.

The DCAR considered that the results were most sensitive to the assumed 'responder rate', noting when the response rate was assumed to be 57%, the ICER decreased to $1,938.00. The DCAR did not conduct sensitivity analysis as it was considered misleading given the fundamental underlying uncertainty associated with the estimate of proportion of responders to AFG treatment. Based on the possible interpretations of the response rate it can be argued that the likely cost-effectiveness is somewhere in between the two ICER estimates of $1,938.00 and $3,563.36 per responder.

CUA-Scenario analyses

Table 13 Summary of the scenario analyses (Population 2)

Perspective	Australian Health Care System
Comparator	No treatment
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Observational studies (Byrne 2016, Gargano 2018)
Time horizon	Lifetime (60 years, starting from the baseline age of 40 years)
Outcomes	QALY
Methods used to generate results	Markov chain model
Health states	"responder"; "non-responder"; "alive with AE"; "alive without AE"; "alive with scar contracture"; "dead"
Cycle length	A year
Discount rate	5%
Software packages used	TreeAge Pro 2019 R2.1

Abbreviations: AE = adverse event; QALY = quality adjusted life year
Source: Table 41, p135 of the DCAR.

In the DCARs first scenario analysis CUA, assuming a conservative response rate of 31% in the population with scar contracture of hand and arm (Byrne 2016), the incremental cost per QALY gained is estimated at $20,086. In the second scenario analysis, in the population with scar contracture of face and neck (Gargano 2018) the incremental cost per QALY gained is estimated at $4,111 (Table 14).

Table 14 Scenario analyses results of the economic evaluation in population with scar contracture

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER Δ$/ΔQALY
AFG vs no treatment (improvement of ROM in hands/arms) (Byrne 2016)	$ $1,104.72	$1104.72	0.055	0.055	$20,086
AFG (SUFA) vs no treatment (improvement of ROM in face/neck) (Gargano 2018)	$3,288.61	$3,288.61	0.80	0.80	$4,111

Abbreviations: Δ=increment; AFG = autologous fat graft; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; ROM = range of movement
Source: Compiled from Table 46, p143 of the DCAR.

The DCAR considered that the high degree of heterogeneity in the populations from two studies (Byrne 2016 and Gargano 2018) together with incompatible procedures (a single AFG and two consecutive SUFA procedures) makes the direct comparison of ICER estimates impossible. The considerable difference in ICER estimates, which favoured SUFA over AFG despite its higher cost, were due to:
a) higher rate of responders in the population with face/neck scar (50% *vs.* 31%), which is consistent with the more aggressive treatment that produced a higher improvement in ROM, and
b) difference in the estimated utility gain associated with successful intervention (0.09 vs 0.01).

The DCAR also considered that both utility estimates were associated with a high degree of uncertainty. However, it is also possible that in the population with hand and arm scar contracture, AFG as a third-line treatment delivers only a marginal improvement, while in the population selected for more aggressive surgery a larger health benefit is both expected and likely achieved.

The DCAR noted that the modelled results were most sensitive to the assumptions about the value of utility gain, the response rate, but less sensitive to the background mortality and not sensitive to the variation in the proportion of patients experiencing adverse events.

13.   Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of AFG for use in Population 1 (congenital and acquired; Table 15) and Population 2 (burn scar; Table 16). The two nominated populations for this application are predominantly treated in public hospitals, especially for the acute or major surgical treatment of the conditions. Therefore, determining which patients are likely to switch from being treated in the public system versus the private system is difficult to determine, thus estimates of the financial implications may be based on assumptions for which there is a scarcity of data. Additionally, due to the initial surgery being done in a public hospital it is difficult to ascertain from the population descriptions where along the treatment pathway patients may be, this is especially the case for Population 1. The proportion of the Australian population with private health insurance was estimated at 44%. The 75% rebate level was used to estimate the financial implications after co-payment.

Population 1

Table 15 Total costs to the MBS associated with use of AFG in Population 1—craniofacial population (revised post ESC values)

Variable	Method	2020-21 Year 1	2021-22 Year 2	2022-23 Year 3	2023-24 Year 4	2024-25 Year 5
AFG						
Total population- congenital		94	94	94	94	94
Nos of services		168.98	168.98	168.98	168.98	168.98
Total population- acquired		492	492	492	492	492
Nos of sessions		688.27	688.27	688.27	688.27	688.27
Total Number of AFG sessions	A	857.25	857.25	857.25	857.25	857.25
Cost to MBS for AFG	B	$550,227	$550,227	$550,227	$550,227	$550,227
Co-payment subtracted	C	$412,671	$412,671	$412,671	$412,671	$412,671
Co-administered services currently MBS listed (MBS 20100) anaesthesia for AFG	D	$309.35	$309.35	$309.35	$309.35	$309.35
Costs to MBS	E=A*D	$265,191	$265,191	$265,191	$265,191	$265,191
Other MBS items for AFG						
MBS item 45564 (require follow up flap surgery)	F	117	117	117	117	117
MBS costs of flap surgery	G	$227,215	$227,215	$227,215	$227,215	$227,215
Anaesthesia (MBS 20230)	H	$131,995	$131,995	$131,995	$131,995	$131,995
Sub-total Services	I=A+F	974	974	974	974	974
Sub-total costs	J=E+G+H	$624,401	$624,401	$624,401	$624,401	$624,401
Total cost AFG	K=J+B	$1,174,629	$1,174,629	$1,174,629	$1,174,629	$1,174,629
After Co-payment	L	$880,971	$880,971	$880,971	$880,971	$880,971
Comparator						
Co-administered services currently MBS listed (substituted by AFG)	M	586	586	586	586	586
Costs to MBS (45564) ($1940.35)	N	$1,136,075	$1,136,075	$1,136,075	$1,136,075	$1,136,075
Anaesthesia (20230) ($1127)	O	$659,976	$659,976	$659,976	$659,976	$659,976
Sub-total cost	P	$1,796,051	$1,796,051	$1,796,051	$1,796,051	$1,796,051
After co-payment	Q	$1,347,038	$1,347,038	$1,347,038	$1,347,038	$1,347,038
Total Services[a]	**R=I-M**	389	389	389	389	389
Total cost to MBS[b] (savings)	**S (L-Q)**	-$466,067	-$466,067	-$466,067	-$466,067	-$466,067

[a]   the number of anaesthetic services co-administered have not been included in these estimates as both the intervention and comparator are surgical interventions (potential number of additional services)

[b]   the cost of the anaesthetic services has been included in these estimates

Text in red indicates reductions or saving

Source: Table 9, p41 of the DCAR.

Note, the DCAR revised the estimates post ESC to correct the double counting of anaesthesia costs

The DCAR noted the population estimates for use of AFG, and the consequent savings to the MBS, are likely uncertain. In addition, the cost savings for Population 1 may be overestimated as there is potentially a group of patients are unwilling to undergo further flap surgery, but willing to undertake treatment with AFG. However, their numbers could not be determined. These patients would represent a net cost to the MBS as there would be no savings from substituted services. To the degree that AFG does replace microvascular free autologous flap surgery there is likely to be savings to the MBS.

Population 2

Table 16 Total costs to the MBS associated with use of AFG in Population 2—burn scars

Variable		2020-21 Year 1	2021-22 Year 2	2022-23 Year 3	2023-24 Year 4	2024-25 Year 5
AFG						
Total population – burn scars		64	64	64	64	64
Number of AFG sessions*		127	127	127	127	127
Cost to MBS		$81,787	$81,787	$81,787	$81,787	$81,787
Co-payment subtracted	A	$61,340	$61,340	$61,340	$61,340	$61,340
Co-administered services currently MBS listed	B	127	127	127	127	127
Costs to MBS (anaesthesia MBS 20100)	C	$39,419	$39,419	$39,419	$39,419	$39,419
Co-payment subtracted	D	$29,564	$29,564	$29,564	$29,564	$29,564
Total Services		**127**	**127**	**127**	**127**	**127**
Total cost to MBS (after co-payment)	A+D	**$90,904**	**$90,904**	**$90,904**	**$90,904**	**$90,904**

*   two sessions per person on average.
Source: Table 10, p42 of the DCAR.

The DCAR noted that the MBS item descriptor allows for a maximum of five services per region of the body defined as upper or lower limbs, trunk, neck or face. Without being able to identify a typical patient it is not possible to identify whether a patient is eligible for a maximum or 5, 10 or 15 sessions and then on average how many sessions are likely. The number of sessions estimated may be an underestimate. Additionally, the total population may be an overestimate as a patient's financial status after a major burn may change significantly, impacting on their ability to keep their private health cover.

The DCAR considered that where these patients obtain relief from the application of AFG this may also result in a reduction in the need for conservative therapies such as lotions or ongoing physiotherapy, sometimes provided in a hospital, allied health or consulting room setting. These may be likely outcomes but the financial implications for government health budgets could not be determined.

14.   Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Very low quality of the evidence, leading to substantial uncertainty in clinical and economic outcomes	ESC noted the inherently low-quality evidence and outcome variation in heterogeneous populations, which leads to high levels of uncertainty in clinical and economic outcomes. However, ESC also noted the difficulties in developing high-quality evidence for these populations, and considered it would be unlikely that better quality evidence becomes available.
Comparative safety and effectiveness	AFG is probably a safe procedure; comparative safety is probably not an issue, but comparative effectiveness is at best uncertain.
Usage	Uncertain usage and estimates given AFG is mostly performed in the private sector
Uncertainties that significantly impact the economic model	Main issue is the low quality evidence base informing the economics, resulting in very uncertain ICERs. Other key

ESC key issue	ESC advice to MSAC
	uncertainties included:
	• the economics relied upon 'heroic' assumptions
	• demonstrating QALY gains based on AEs may not be appropriate
	• no adequate health-related quality of life data
Financial impact	Uncertainty regarding service numbers, uptake of AFG *vs.* comparators, and assumptions around implications for use in private *vs.* public hospitals.
Item descriptor-Alignment with application 1575 (AFG for the management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity)	ESC advised that MSAC consider aligning item descriptors for Applications 1575 and 1577; specifically, whether: - there should be a 3-month wait between multiple services - the number of services per side should be limited to 3 or 5 - there should be a maximum lifetime limit on services.

ESC discussion

ESC noted the application was requesting Medicare Benefits Schedule (MBS) listing for autologous fat grafting (AFG) for the treatment of burn scars, and facial defects due to craniofacial abnormalities. ESC noted this application is linked to MSAC Application 1575 requesting MBS listing for AFG injection for the management of defects arising from breast surgery, breast cancer treatment/prevention and congenital breast deformity.

In Application 1577: Population 1, including patients with craniofacial disorders with facial asymmetry that require reconstruction and recontouring, including 2 subpopulations: congenital acquired syndromes, and acquired craniofacial defects; and Population 2 including patients with burn scars that have shown unsatisfactory improvement after three months of topical therapies. ESC considered that these were heterogeneous groups, making it difficult to define severity; this also affects translation and the economic analysis. ESC also noted that following advice from the applicant, PASC agreed that patients with HIV-association lipodystrophy should be excluded from the proposed population.

ESC noted several safety and quality issues from a consumer perspective, including adverse events, donor sites, harvesting techniques and the likelihood of the need for repeat grafts. ESC considered that these issues could be further explored.

ESC noted the requirement in the item descriptor for imaging (photographic) evidence to be documented in the patient notes. ESC also noted the clinical management algorithms specified a monitoring period of at least six months to ensure the patient's condition had stabilised prior to surgery for Population 1, and a monitoring period up to six months prior to surgery for Population 2. ESC considered that this would minimise the risk of leakage.

ESC noted the comparators for Population 1 and 2; and noted the pre-ESC response, in which the applicant considered that usual care was not an appropriate comparator for Population 1. However, ESC considered usual care is an appropriate comparator as it reflects patient choice to pursue non-surgical options, but may be more appropriately termed 'non-surgical treatment'.

ESC reviewed the clinical study data for the two subpopulations of Population 1. Evidence for congenital craniofacial abnormalities subpopulation included two small retrospective comparative studies of AFG *vs.* free flap surgery (total n=49) at high risk of bias, and three systematic reviews (total n=2,795), largely without a comparator group, but at low risk

of bias. For the acquired craniofacial abnormalities subpopulation there were no comparative studies found comparing AFG with free flaps or usual care, making any conclusions of comparative safety and effectiveness uncertain. ESC also reviewed the clinical study data for Population 2, which included one small single randomised controlled trial (n=9), one small cohort study (n=20), five case series and two systematic reviews relevant to the assessment of AFG for treating burn scars.

Regarding comparative safety, ESC considered that AFG alone appears to be safe, although limited small studies show that possible adverse events arise (such as infection and haematoma) when AFG is used in combination with other procedures to treat facial defects. ESC queried the assessment group's conclusion of uncertain safety for congenital craniofacial abnormalities in Population 1, given that the included studies showed no increase in complications and possibly improved safety for some measures. The assessment group clarified that the nature and details of the complications were not reported in many studies, leading to the overall conclusion of uncertain safety.

Regarding comparative effectiveness, ESC noted the very low quality and quantity evidence for most outcomes, which relied upon the assessment of patient satisfaction, physician satisfaction and symmetry scores in Population 1; and patient assessment of appearance of burn scars, and objectively measured skin hardness in Population 2. ESC considered that the evidence failed to demonstrate that AFG had a meaningful clinical effect compared with the comparator, and thus agreed with the DCARs clinical claim that AFG has:

- for Population 1, congenital abnormalities –uncertain effectiveness compared with free flap surgery, and unknown effectiveness compared with usual care
- for Population 1, acquired abnormalities –unknown effectiveness compared with free flap surgery and usual care
- for Population 2, burn scars –uncertain effectiveness compared with usual care.

In the economic analysis, ESC considered that there was substantial uncertainty in the models, which was largely driven by the high uncertainty in the clinical data. ESC noted that the cost-utility analysis (CUA) of AFG *vs.* free flap for Population 1 was considered to be highly hypothetical, with the DCARs model assuming equal effectiveness compared with free flap surgery, with quality-adjusted life years (QALY) gains driven by safety outcomes. ESC noted that the model implies that AFG has superior safety, but this was not supported by the clinical data. ESC also considered that, in light of limitations of clinical evidence, a cost-comparison approach might have been more appropriate than CUA. ESC noted for Population 1, the conclusion of AFG dominance (i.e. AFG cheaper and more effective), based on the incremental cost-effectiveness ratio (ICER), was robust to variations in risk of adverse events, but was sensitive to variation in the assumption of equal effectiveness, with AFG becoming less costly and less effective than free flap procedure when the minimal utility gain was applied for AFG. ESC recognised the limited usefulness of these findings due to more fundamental problems with the CUA approach, and also noted if only costs are compared in the model (see Table 9) that AFG was cheaper than free flap surgery.

For Population 2, ESC noted the base-case model was a trial-based cost-effectiveness analysis of AFG *vs.* no treatment (or usual care) [see Table 12], with the key driver being the response rate, which ESC considered was open to interpretation. ESC also noted the additional scenario analyses, which extended the CEA model to a lifetime CUA model; however was appropriately acknowledged by the DCAR to be highly uncertain due to the many assumptions required (e.g. the extrapolation of trial-based responders to lifetime). If only costs are compared in the base case model (see Table 12), then expectantly AFG was more expensive than no AFG.

In the financial estimates, ESC noted that the numbers remain the same for every year due to the lack of epidemiological data to inform a trend. ESC requested that the assessment group check the financial data before the application is considered by MSAC, as ESC was not able to replicate the numbers. Following the meeting, the assessment group provided amended financial costs for Population 1 (see Table 15), correcting for double counting of MBS anaesthesia costs resulting in a slightly greater estimated savings to the MBS with the introduction of AFG.

ESC queried whether there are applicable clinical trials on horizon that could resolve current uncertainty due to the weak evidence base. The following upcoming clinical trials may be relevant but due to limitations in the study designs (i.e. small planned population sizes [N=40], non-comparative, non-randomised) and estimated completion dates, the studies may be insufficient to resolve the uncertainty in the comparative clinical safety and effectiveness:

- NCT03880188 - Fat to the Future, Dermal Time 2: Long Term Status of Free Dermal Fat Autografts for Complex Craniofacial Wounds (FTFDT2). Status: enrolling by invitation (estimated n=20). Estimated completion: June 2020.
- NCT03872544 - Fat to the Future, Dermal Time 3: Short Term Status of Free Dermal Fat Autografts for Complex Craniofacial Wounds (FTFDT3). Status: not yet recruiting (estimated n=20). Estimated completion: November 2025.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website