



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1608 – Amnion membrane (human tissue) for topical treatment of ophthalmic disorders (caused by disease and/or trauma), and wound dressings for skin burns and ulcers on the craniofacial area, torso, and limbs

Applicant: NSW Organ and Tissue Donation Service

Date of MSAC consideration: MSAC 81st Meeting, 31 March – 1 April 2021

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

1. Purpose of application

An application seeking MSAC’s advice to inform the Protheses List Advisory Committee (PLAC) on the comparative safety, clinical effectiveness and cost-effectiveness of human amnion membrane (AM) tissue for topical treatment of ophthalmic disorders (caused by disease and/or trauma), and wound dressings for skin burns, and ulcers on the craniofacial area, torso and limbs was received from the NSW Organ and Tissue Donation Service 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 will advise the Protheses List Advisory Committee that AM for topical treatment of ophthalmic disorders, and wound dressings for burns and ulcers on the craniofacial area, torso and limbs, was not demonstrated to be cost-effective. MSAC considered that the evidence for comparative safety and effectiveness across the three populations was uncertain, and that limitations in the clinical evidence base resulted in the inability to assess the cost-effectiveness for two populations. In regards to the economic analysis for the chronic skin wounds population, MSAC noted issues that resulted in a high and uncertain incremental cost-effectiveness ratio, and highly uncertain impact on the Protheses List (PL).

Consumer summary

The NSW Organ and Tissue Donation Service submitted an application seeking MSAC’s advice to inform the Protheses List Advisory Committee (PLAC) on the comparative safety, clinical effectiveness and cost-effectiveness of human amnion membrane to treat certain eye disorders, and as a dressing for burns and ulcers.

Consumer summary

The amnion membrane is the innermost layer of the placenta that helps protect the growing foetus in the womb. It is also known as the amniotic sac and has many properties that can help wound healing. Amnion membrane is collected from people who have had a caesarean section and agree to donate their placenta. The donated placenta is then processed to collect the amnion membrane, which is further prepared and stored, either frozen or dehydrated, for later use. This process is in accordance with the Australian code of good manufacturing practice for human tissue.

MSAC thought that the quality of clinical evidence in the application was low. This made it difficult to tell if amnion membrane was safe or effective, or if it was good value for money. MSAC also thought that the suggested price for amnion membrane was expensive.

MSAC's advice to the Commonwealth Minister for Health

MSAC will advise the PLAC that amnion membrane for topical treatment of ophthalmic disorders, and wound dressings for burns and ulcers on the craniofacial area, torso and limbs was not demonstrated to be cost-effective. This is because MSAC could not be certain that amnion membrane is safe, effective and good value for money.

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

MSAC noted the purpose of the application was to advise PLAC on the comparative safety, clinical effectiveness and cost-effectiveness of AM for the treatment of ophthalmic conditions, chronic skin wounds and acute skin wounds. This is the first time that MSAC advice has been sought to inform PLAC consideration of an application to list a human tissue product on Part B of the PL.

MSAC noted that AM is proposed to treat wounds across three broad populations: ophthalmic conditions (Population 1), chronic skin wounds (Population 2) and acute skin wounds (Population 3). MSAC noted that the populations were complex, with each population containing several subpopulations. MSAC also noted that the comparators (standard of care [SOC]) were also heterogeneous across populations and subpopulations.

For Population 1 (ophthalmic conditions), MSAC noted support for the application from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO). However, for Population 2 (chronic skin wounds) and 3 (acute skin wounds), MSAC noted relevant clinical experts in these fields (e.g. plastic surgeons, dermatologists) had not submitted consultation feedback on the application. MSAC considered there may be potential clinical need for AM in Population 2 in burns patient requiring a dermal substitute as a bridge before skin grafting (subpopulation of Population 3 [3a]), but queried the clinical need in the use of AM for graft fixation (Population 3c). In addition, MSAC noted that role of AM for the treatment of toxic epidermal necrosis (subpopulation of Population 3 [3d]) was uncertain given it is a very rare condition.

The application claimed that AM has non-inferior safety for all three populations compared with SOC, and that AM has superior efficacy (population 1 and 2)/non-inferior efficacy (population 3) compared with SOC.

MSAC noted that the clinical evidence consisted of 15 randomised clinical trials (RCTs) for Population 1, 14 RCTs for Population 2 and 8 RCTs for Population 3. However, MSAC agreed with the ESC assessment of the evidence, noting that the quality of evidence was low

or very low for Populations 1 and 3, making it difficult to evaluate. Only Population 2 had clinical data of sufficient quality for meta-analysis. MSAC also noted the lack of long-term safety data for all populations, and the short follow-up times in the included RCTs. MSAC also noted there are two ongoing clinical trials in patients with chronic ulcers (Population 2) due for completion in 2021¹.

MSAC noted that due to the limitations in the clinical evidence, an economic evaluation was not presented for Population 1 and 3. However, MSAC disagreed with the reasoning and approach to narrow the economic evaluation to only one subpopulation of Population 2 (diabetic foot ulcers [DFU]). MSAC also agreed with ESC that it was too difficult to assess the cost-effectiveness of AM when the economic modelling is limited to only one population.

MSAC noted the cost-utility analysis comparing AM with SOC in patients with DFU was based on an Australian cost-effectiveness model. MSAC agreed with ESC who considered that the model structure and translation issues were appropriate. However, MSAC noted that the cost of the AM in the model only accounted for 5 AM applications (based on average number of AM grafts used in a 12 week trial) which might not account for further use at relapse. MSAC considered this underestimated the full costs of AM, as for some chronic wounds AM is applied weekly over a number of months. MSAC also agreed with ESC and considered that the base case using a 1-year time horizon was appropriate (due to the short trial follow-up), which generated an incremental cost-effectiveness ratio (ICER) of \$97,870. MSAC considered the ICER to be high and uncertain, as it was sensitive to the price of AM and wound size, but also healing rates and utility values.

MSAC noted an epidemiological approach for each subpopulation was used to estimate the financial and budgetary impacts. MSAC agreed with ESC that the estimated uptake of AM in the three populations is highly uncertain and that the costs for the PL are likely underestimated. MSAC considered there is potential for significant cost implications if AM was listed on the PL.

MSAC noted the proposed price (\$28.93 per cm²). MSAC also noted that state and territory legislations prohibits trade for profit for human tissues, unless the tissue has been processed; however, the extent of processing required to be able to make a profit was unclear. In addition, MSAC noted that in response to ESC's request, the applicant provided further information breaking down the pathology and staffing costs included in the proposed price. The applicant also advised that cryopreservation and storage costs are captured under the equipment and staffing costs. However, MSAC was uncertain that the proposed price for AM was appropriate. In addition, MSAC also noted the applicant response indicating that if requested, a smaller 2 x 2cm² AM graft for use in ophthalmic conditions (as used in the National Health System, UK) would be considered, which may result in a subsequent reduction in cost for those indications.

MSAC noted the setting in which care could be provided for the requested populations and indications. Populations 1 and 3 could be treated in hospital, for which a PL benefit could be paid. However, Population 2 could be more likely to be treated in the community, for which a PL benefit could not be paid. MSAC considered that this could create a potential incentive for patients to be admitted to access treatment.

Usually, once a product is listed on the PL, it can be used for any indication. However, the Department confirmed that PLAC can place restrictive conditions on a listing to limit

¹ [NCT04457752](#) and [NCT02929056](#)

reimbursement to specified indications only (although this has not been done before for human tissue prostheses included in Part B of the PL).

MSAC considered that any resubmission should include:

- consultation with clinicians and relevant craft groups to identify more specific populations and review the uptake assumptions in each population
- more evidence on the effectiveness (including over the longer term) of AM in specific subpopulations, noting the outcomes of the two ongoing clinical trials in patients with chronic ulcers due for completion in 2021²
- full breakdown and justification of the unit costs which should also be compared with other products (e.g. split skin grafts) to justify the price differential
- further consideration of the location of care and unintended consequences if listed on the PL
- a revised economic analysis for population 2 (as per above issues) along with economic analyses for population 1 and 3 in order to inform whether AM is cost-effective price in any or all of the population(s).

MSAC also considered that if enough trial data was available to support the use of AM in specific subpopulations the application could be considered by population as the data becomes available.

4. Background

This is the first submission (Department Contracted Assessment Report [DCAR]) for AM (human tissue) for topical treatment of ophthalmic disorders and dressings for acute and chronic skin wounds.

A health technology assessment by MSAC was required to determine the comparative clinical and cost effectiveness of AM to inform PLAC consideration of an application to list AM on Part B of the PL because:

- AM products are novel,
- there are currently no comparators for AM products on the PL, and
- there is a lack of information to clearly justify the costs.

Two applications for AM have previously been submitted for MSAC consideration:

- [MSAC Application 1556](#) - Human tissue (topical) wound treatments – Ulcers and burns (EpiFix and EpiBurn)
- [MSAC Application 1557](#) – Human tissue (surgical) wound treatments - Laminectomy and tendon repair (AmnioFix, AmnioWrap and AmnioFix Injectable).

5. Prerequisites to implementation of any funding advice

Cryopreserved and dehydrated AM were included on the Australian Register of Therapeutic Goods (ARTG) in 2018 (Table 1). AM is obtained from donors and prepared for medical use in accordance with [Therapeutic Goods Order 88](#). Six dehydrated AM-based products used for wound healing are listed under ARTG number 307979. Two additional products registered under this number—EpiFix Injectable and AmnioFix Injectable—are injectable AM treatments for chronic plantar fasciitis and are not relevant to this application.

² [NCT04457752](#) and [NCT02929056](#)

Table 1 Cryopreserved and dehydrated AM products included on the ARTG

ARTG number Start date	Sponsor	Category	Product name	Intended use
303207 18/05/2018	South Eastern Sydney Local Health District	Biological Included Class 2	Amniotic membrane, cryopreserved	Treatment of ophthalmic disorder/ disease/ trauma, or as a wound dressing
307979 08/08/2018	Vicki Partridge Pty Ltd	Biological Included Class 2	Foetal membranes, dehydrated, irradiated (EpiFix, AmnioFix, EpiFix Fenestrated, EpiXL, EpiFix Mesh, AmnioFix Wrap)	Treatment of acute and chronic wounds to enhance healing

Source: Table 8, p17 of the DCAR

6. Proposal for public funding

As advised by clinicians, there are existing MBS items that can accommodate the delivery of AM. The application does not seek new MBS item numbers or seek to amend existing MBS item numbers.

It is noted that the applicant intends to seek listing of AM on Part B of the PL. The applicant proposed cost for AM: \$587.57 for 5cm diameter circle, \$1,446.11 for 5 x 10 cm, and \$2,892.87 for 10 x 10 cm. The applicant in the response to ESC's request indicated that the 5cm diameter circular graft is traditional in Australia. The applicant also indicated that feedback is sought from surgeons on each occasion of service and a smaller 2 x 2cm² AM graft for use in ophthalmic conditions (as used in the National Health System, UK) would be considered if requested.

7. Summary of public consultation feedback/consumer Issues

One consultation survey was received from the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) which supported the application and noted that AM products would also be beneficial in the community setting to avoid hospital admission.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

The proposed intervention is any human AM that is purported to promote healing for a range of indications. Amnion membrane is obtained from elective caesarean section births and prepared for medical use in accordance with Therapeutic Goods Order 88. The AM can be either cryopreserved or dehydrated for storage. The cryopreserved AM has an expiry of 12 months, and the dehydrated AM can have a shelf life for up to five years depending on the manufacturing process. The setting for using AM products is specific to indications. AM is more likely to be used in the operating theatre for both ophthalmic conditions and treating different wounds following surgical debridement. However, AM can be used in outpatient settings for appropriate wound types.

Description of Medical Condition(s)

The applicant proposed three populations, each with subpopulations:

Population 1 – Ophthalmic conditions

Population 1 covers a range of ophthalmic conditions, which may disrupt the corneal surface including:

- chemical, thermal and radiation burns
- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN)
- pterygium
- other ophthalmic conditions involving corneal disruption
- chronic ophthalmic wounds refractory to healing.

Of these ophthalmic conditions, pterygium has the highest frequency in the Australian population with 9,363 pterygium cases (2017/2018, Australian Institute of Health and Welfare [AIHW] 2019³). Ophthalmic wounds refractory to healing have a count of 560. Less frequent conditions include ocular burns and SJS which have a prevalence of 260 (2013/2014, (AIHW, Pointer & Tovell 2016)) and 26 (2006-2016, (Chan & Cook 2019)), respectively.

Generally, corneal epithelium turnover is quick and rapid healing is possible. However, if the healing process is delayed or disrupted, the amnion membrane product may be indicated to promote healing. Amnion membrane products are most relevant for difficult cases where there is no clear alternative treatment option. The treatment goal is a clear cornea and for difficult to treat cases reduce the risk of impaired vision or blindness.

Population 2 – Chronic skin wounds

Chronic wounds are defined as those that have been unresponsive to treatment following at least 12 weeks of SOC. It represents a considerable health and economic burden in Australia, with more than 400,000 Australians affected with associated health-care related costs more than \$3.5 billion (2% national health expenditure). The underlying aetiology of the wound is a crucial determinant of management; for this application, wounds have been classified as:

- venous insufficiency ulcers
- arterial insufficiency ulcers
- diabetic foot ulcers.

Among the patients with these skin wounds, a substantial proportion would develop into chronic wounds, and this proportion can be up to 20% across all three subpopulations.

Population 3 – Acute skin wounds

The acute skin wounds suitable for AM treatment can be severe burns that require referral to specialist burns units. The PASC defined subpopulations include:

- a) burns where patients require a dermal substitute before skin grafting
- b) treatment of graft site wound
- c) skin graft fixator
- d) treatment of TEN.

Among 1,658 skin graft procedures performed in Australia for the 2017/18 financial year, most of them could be categorised as acute skin wound, which is indicated for the first three

³ Aihw. 2019. Procedures Data Cubes, Procedures and healthcare interventions (ACHI 10th edition), Australia, 2017-18 [Online]. Australian Institute of Health and Welfare. Available: <https://www.aihw.gov.au/reports/hospitals/procedures-data-cubes/contents/data-cubes> [Accessed 16 March 2020]

subpopulation. Based on expert advice, 5 - 7.5% of skin graft patients could benefit from dermal substitute before skin grafting ([MSAC 1608 PICO Confirmation](#)). However, no data were available to estimate the treatment of toxic epidermal necrolysis.

For each subpopulation, different scenarios present for the application of AM (e.g. AM is used as a bridge to skin grafts where immediate skin grafting is not possible or where additional support is required for the skin graft).

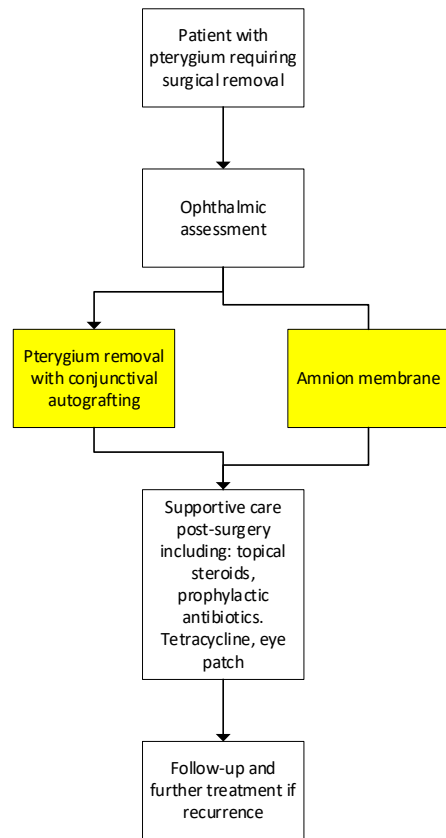
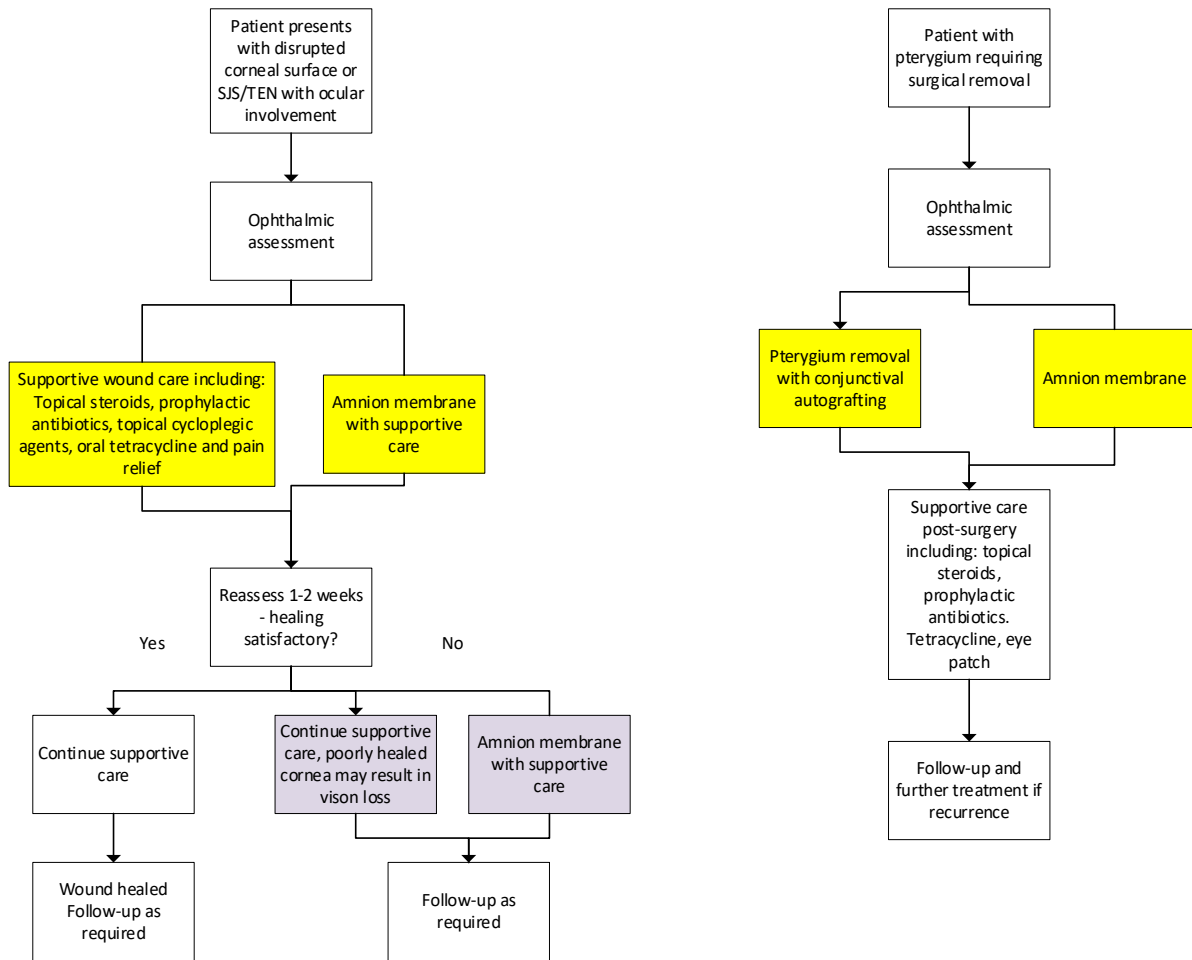
Clinical management algorithms depicting the proposed place of AM are presented for:

- Population 1 – ophthalmic conditions in Figure 1
- Population 2 – chronic wounds in Figure 2
- Population 3a – burns where patients require a dermal substitute before skin grafting can take place in Figure 3
- Population 3b – patients with a skin graft donor site wound in Figure 4
- Population 3c - patients requiring a skin graft fixator in Figure 5
- Population 3d - patients with TEN skin lesions requiring dressing in Figure 6.

It is noted that these clinical management algorithms are a representation only as not all conditions can be captured in the flowchart.

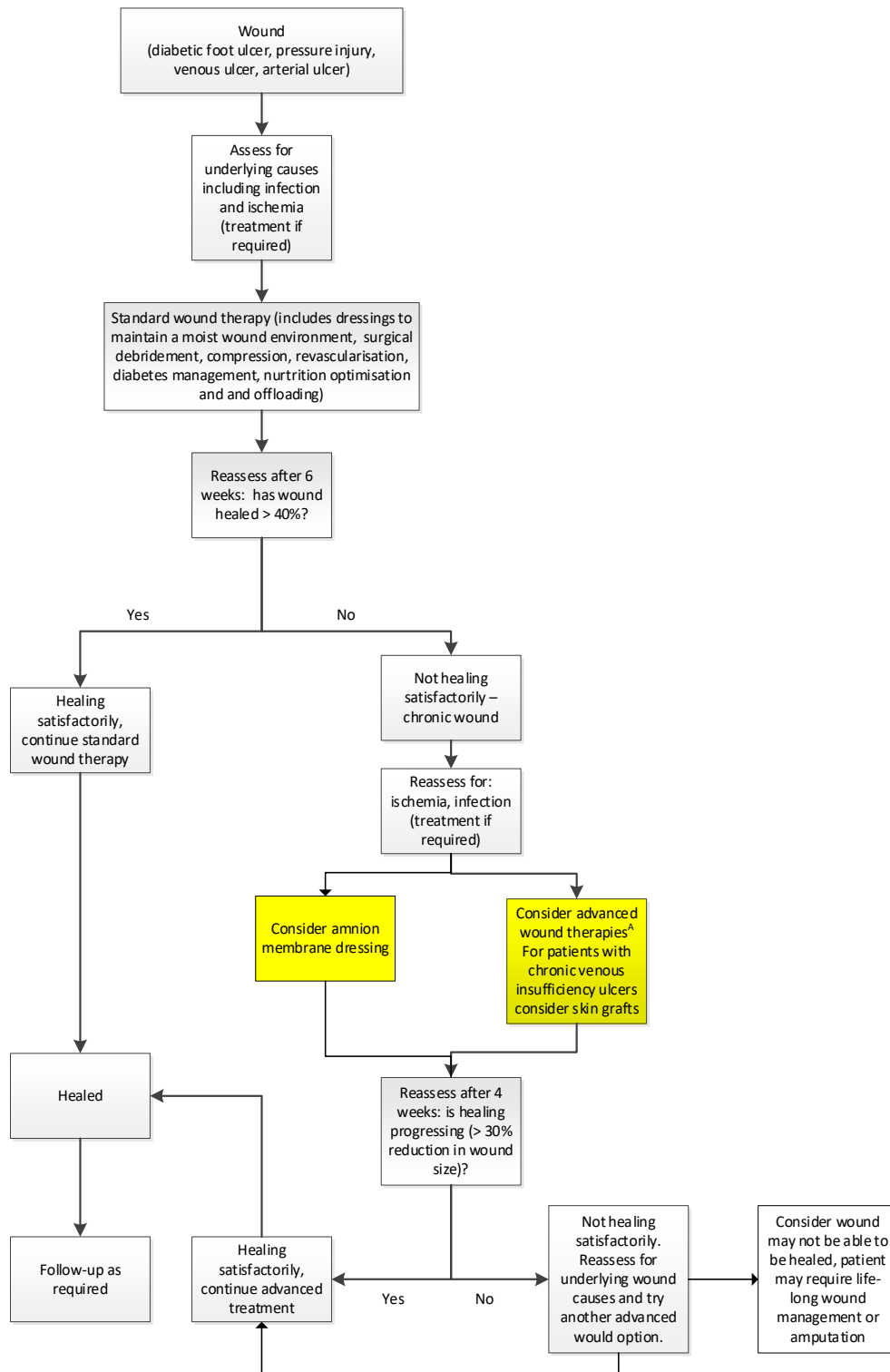
Compared to the generically defined SOC, AM delivery settings may be different for some populations and subgroups. For ophthalmic conditions, the delivery of AM and SOC are likely to remain unchanged where most of the treatments would occur in hospitals regardless. For chronic skin ulcers, the treatment delivery may be different between the intervention and the comparator. AM may occur outside of the hospital in the community setting. However, it was assumed approximately 50% of patients with a ‘difficult to heal’ chronic skin wound would be treated in hospital. For Population 3, all treatment would still occur in hospitals; hence no difference between the AM and the SOC in terms of the setting for treatment delivery.

Figure 1 Proposed clinical management algorithm for Population 1



Source: Figure 2, p31 of the DCAR; produced by the Assessment Group based on published evidence and expert advice (Associate Professor of Ophthalmology, 2020, Bunya and Chang, 2019, Gupta et al., 2014, Hemmati and Colby, 2020, Hsu et al., 2012, Nouredin and Yeung, 2016, Sharma et al., 2016, Slenz and Hemmati, 2013, Wander and Kroger, 2020)
 Abbreviations: SJS = Stevens-Johnson Syndrome, TEN = Toxic Epidermal Necrosis.

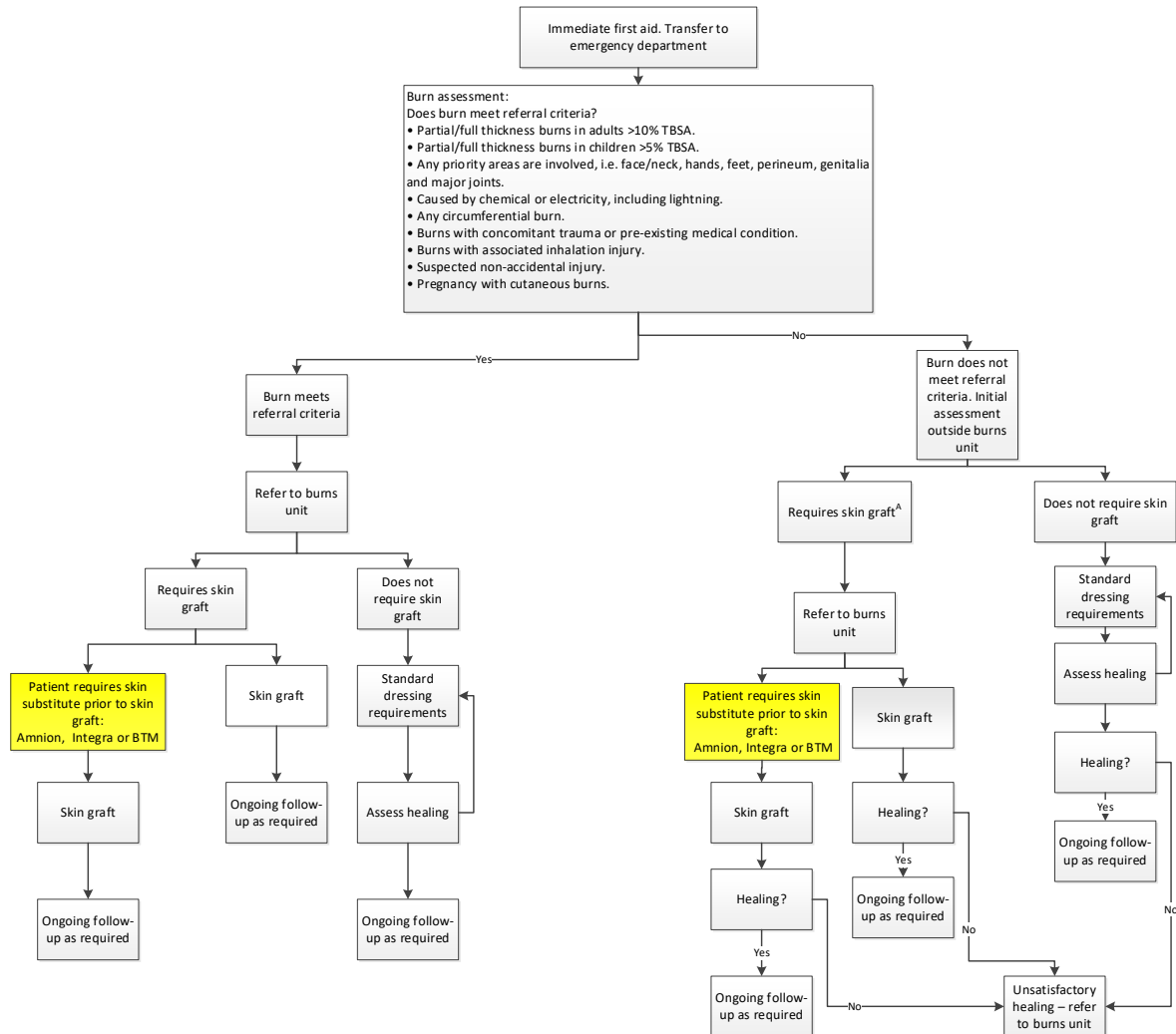
Figure 2 Proposed clinical management algorithm for Population 2



Source: Figure 4, p33 of the DCAR; Algorithm developed based on expert advice, published literature and guidelines (DoH identified Expert 2020; IWGDF 2019; NICE 2019 a, 2019 b; Personal communication, PoVS 2020; Personal communication, ps 2020)

Note: A: Expert advice indicated that UrgoStart dressings are used in Australia.

Figure 3 Proposed clinical management algorithm for Population 3a: burns where patients require a dermal substitute before skin grafting can take place

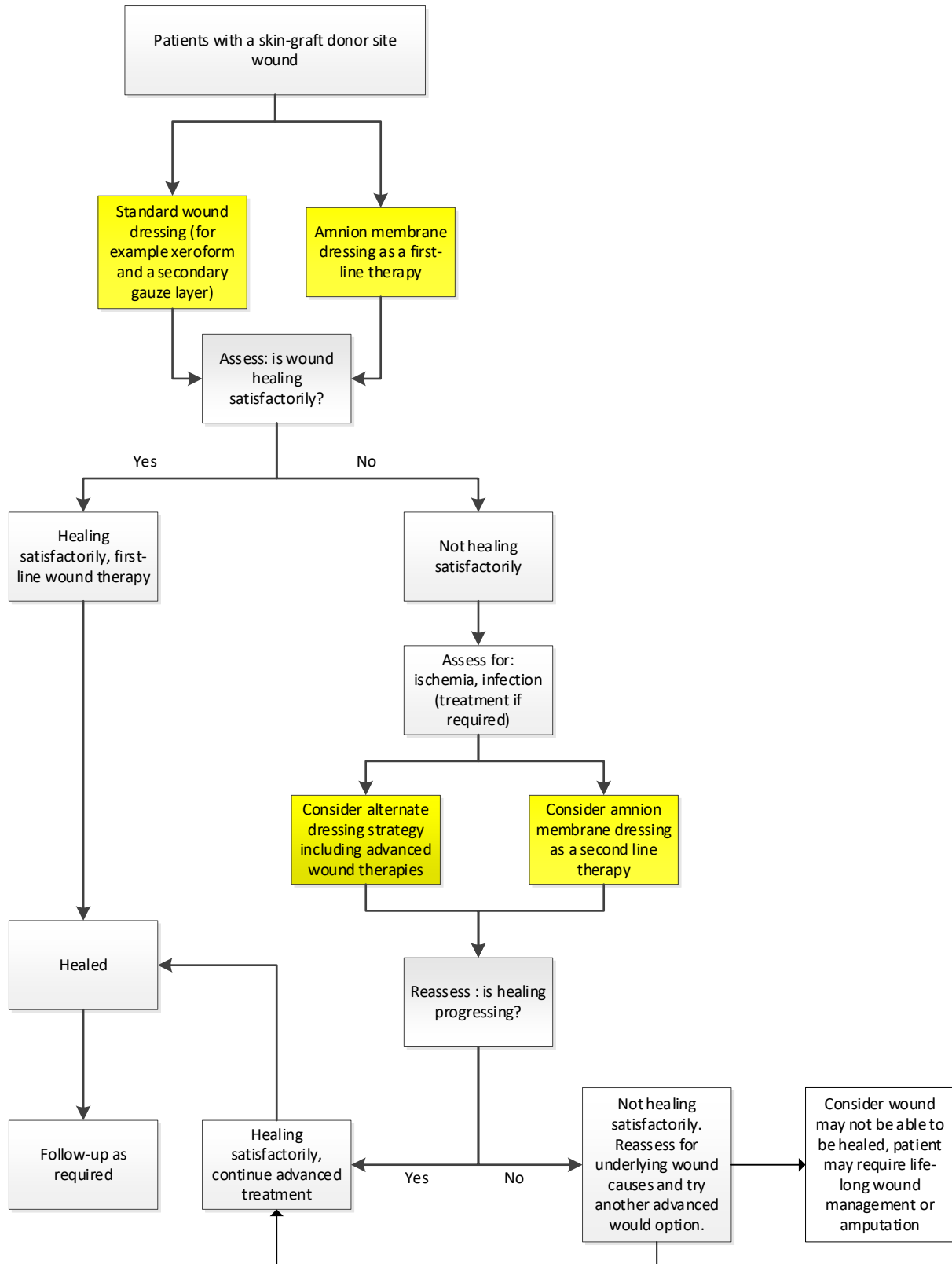


Source: Figure 6, p35 of the DCAR' Developed by the Assessment group based on expert advice and published literature (BRANZ 2019; Personal communication 2018; Personal communication, ps 2020; Victorian Adults Burns Service at the Alfred 2018)

Abbreviations: BTM = NovoSorb™ Biodegradable Temporising Matrix, TBSA = total body surface area.

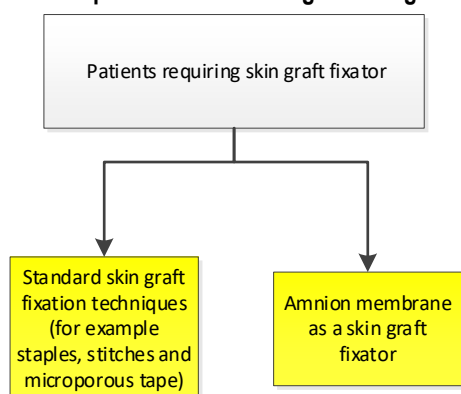
Notes: A: Some small but deep partial- and full-thickness burns may require a skin graft.

Figure 4 Proposed clinical management algorithm for Population 3b: patients with a skin graft donor site wound



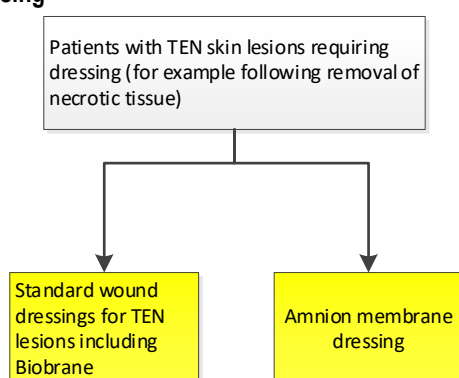
Source: Figure 8, p37 of the DCAR; Reproduced from the ratified PICO Confirmation (Department of Health 2020)

Figure 5 Proposed clinical management algorithm for Population 3c: patients requiring a skin graft fixator



Source: Figure 9, p38 of the DCAR; Reproduced from the ratified PICO Confirmation. (Department of Health 2020)

Figure 6 Proposed clinical management algorithm for Population 3d: patients with TEN skin lesions requiring dressing



Source: Figure 10, p38 of the DCAR; Reproduced from the ratified PICO Confirmation. (Department of Health 2020)
Abbreviations: TEN = toxic epidermal necrolysis.

9. Comparator

The primary comparator for AM across the three populations was described as SOC. However, due to the distinct disease characteristics and population profiles across the three populations, the content of SOC for each population and its subgroups has its own definition and context.

Population 1 – Ophthalmic conditions

For Population 1, best supportive care was nominated as the comparator for corneal wounds and entails a combination of topical steroids, topical cycloplegic agents, pain relief, oral tetracycline and tissue debridement. The exact combination of treatments and the frequency of application depends on the nature of the injury. However, specifically for pterygium surgery, a conjunctival autograft was explicitly considered as the comparator for AM.

Population 2 – Chronic skin wounds

For Population 2, two specific comparators were nominated for diabetic foot ulcers and venous insufficiency ulcers: UrgoStart dressing and split-thickness skin grafts. For arterial insufficiency ulcers, best supportive care was still referred to as the comparator where the critical component of care was improving vascularisation. It was noted in the PICO Confirmation that many other skin substitute products are available for treating chronic wounds. Expert advice indicated that these are not routinely used in Australia; therefore, these products have not been included as comparators.

Population 3 – Acute skin wounds

For Population 3, separate comparators are nominated for the four different subpopulations. For burns patients (subpopulation 3a), dermal substitutes are the most relevant comparator to AM. For patients with graft donor site wounds (subpopulation 3b), standard wound dressing was suggested as the most appropriate comparator. For patients requiring skin graft fixator (subpopulation 3c), traditional fixation techniques, including staples, stitches, and microporous tapes, are considered the appropriate comparator for AM. Lastly, for patients with toxic epidermal necrolysis (subpopulation 3d), Biobrane, a skin substitute used in Australia for superficial burn injuries, was considered the appropriate comparator.

10. Comparative safety

Population 1 – Ophthalmic conditions

Fifteen randomised controlled trials (RCT) were included for Population 1 which encompassed subpopulations of ocular burns (k = 3), pterygium (k = 7), and miscellaneous populations of SJS (k = 1), persistent epithelial defects (PEDs; k = 1), non-viral infectious keratitis (k = 1), and scleral and corneal thinning (k = 2). The DCAR considered there was a high level of heterogeneity across the 15 included RCTs in the context of patient population and SOC. Patient age, sex ratio, disease aetiology, and follow up time varied greatly across studies. SOC was also heterogeneous across studies ranging from topical treatments to various surgeries (e.g. tarsorrhaphy and conjunctival autograft).

The DCAR considered the evidence was limited within Population 1 due to the heterogeneity of the included studies. Varying populations and comparators caused challenges in making comparisons across studies. Furthermore, the studies usually had short follow up periods.

Adverse events and complications

In the 15 included studies, serious adverse events were rarely reported. Among trials where safety outcomes were investigated and reported, there were non-significant increases in reported adverse events in the AM group compared to the SOC group (Table 2). The most common safety concerns were mild, treatable, and generally resolved when the study concluded. Irrespective of the sub-group, most commonly reported safety concerns were corneal and conjunctival vascularisation or inflammation. Second to this was the development of symblepharon. Consistent with the RCTs, pain was considered a safety outcome for the purposes of the DCAR.

- In burns, pain was significantly reduced in patients with moderate burns who received AM compared to SOC; however, there was no difference in patients with severe burns.
- Two studies including patients with pterygium found increased inflammation in the AM transplant group; however, the increase was only significant in one of the studies. There was no difference in complications between groups of this subpopulation.
- Limbal damage was reported from patients who received a conjunctival autograft (SOC). No AM group patients experienced this adverse event. Thus, AM was suggested to be an alternative method for facilitating healing after pterygium surgery. Consequently, limbal damage can be prevented.
- In SJS cases, AM resulted in significantly less corneal and conjunctival vascularisation. Significantly reduced conjunctival congestion was also found for AM treated patients in this subpopulation.

Population 2 – Chronic skin wounds

Fourteen RCTs investigated chronic skin wounds treatment comparing AM (mainly dehydrated) with SOC. The 14 included studies encompassed subpopulations of diabetic foot ulcers (DFU; k = 9) and venous leg ulcers (VLU; k = 5). The DCAR considered that patient

baseline characteristics and treatments were homogenous across studies. No relevant studies were identified for arterial insufficiency ulcers, or used split thickness skin graft or UrgoStart dressing as comparators.

The DCAR considered that the evidence indicated that AM was at least as safe as SOC in DFU subpopulation, but uncertainty was found for VLU subpopulation. Across the included RCTs:

- Compared to SOC, AM was safer with reduced adverse events (AE) rates among DFU patients, reduced wound infections, non-life threatening AE, and pain among VLU subpopulation. Fewer withdrawals (attributable to non-healing wounds) were observed for patients receiving AM for both the DFU and VLU subpopulations compared to SOC.
- Equivalent safety for AM compared to SOC was observed in the DFU subpopulation for wound infection, cellulitis, osteomyelitis and withdrawal due to AE.
- Inferior safety of AM compared to SOC was observed in the VLU subpopulation for cellulitis, serious AE and withdrawals due to AE, based on limited evidence.
- Pain was improved in VLU subpopulation receiving AM compared with SOC, but only reported by three studies each using different outcome measures to measure pain.

Population 3 – Acute skin wounds

A total of eight studies were included that compared the effect of AM to SOC therapy in acute wound healing, including burns where patients required dermal substitute before skin grafting can take place (k = 3), patients with graft donor site wounds (k = 5), and patients who required a skin graft fixator (k = 1). A total of 547 patients with a mean age of 25 years participated in the eight studies. General eligibility criteria were patients with no history of cancer, diabetes, immunosuppressive, and cardiovascular conditions. The age range included was between 18 to 60 years with some variations between the RCTs.

Variability of the wounds, SOC, and population in the included RCTs made it difficult to draw a robust conclusion about the safety of AM. Therefore, comparison between the studies, in terms of safety was challenging. Furthermore, the high risk of bias among the eight studies included for this population also downgraded the quality of evidence, which limited the conclusion on safety of AM in acute wounds.

The DCAR considered that the evidence from the eight RCTs shows that:

- Superior safety of AM relevant to SOC therapy was demonstrated across the included trials for this population. Superiority was shown by less pain intensity and fewer wound infections among the AM group participants than those in the SOC group.
- Minor AEs, including loss of electrolytes, blood and serum albumin were reported in two RCTs. The rate of these AEs was higher in the SOC group .
- There were no mortalities associated with the use of AM across the eight studies included for this population. However, one study has reported mortality among participants in the SOC therapy group, which was not due to the treatment used in this study.

11. Comparative effectiveness

Population 1 – Ophthalmic conditions

A risk of bias assessment of the RCTs was performed for three effectiveness outcomes; visual acuity, wound healing, and disease recurrence. The risk of bias assessment determined a high risk of bias in 11 of the 12 trials that reported visual acuity outcomes. This bias risk was primarily due to poorly described methods on blinding and assessment of the outcome.

Among the ten studies that reported wound healing outcomes, six of them were found to have a high risk of bias and three others were deemed to have some concern. Only one RCT was considered low risk of bias. The cause for risk of bias varied between studies. The most common concerns of bias originated from the methods of measuring the outcome or selection of the reported results.

For RCTs reporting the disease recurrence outcome, five out of eight had a high risk of bias, and two of them were considered to have some concerns whereas only one study was assessed to have a low risk of bias. The inadequate allocation concealment during randomisation and blinding was considered the cause of the high risk of bias. There were also significant concerns regarding the impact of deviations from the intended treatment during the trial.

The DCAR considered that the effectiveness of an AM transplant in individuals with ophthalmic conditions was significantly different across the subpopulations. Generally, the included RCTs showed that AM and SOC had very similar effectiveness across all subpopulations. However, there were still some key differences.

- The included RCTs on burn and pterygium of eyes did not find statistically significant differences for visual acuity between the study arms. Visual acuity was significantly improved by AM treatment for patients with SJS in two studies.
- Both AM and SOC effectively treated corneal thinning; however, the SOC was more effective in restoring corneal thickness. SOC was favoured in patients with persistent epithelial defects for reducing healing time.
- Compared to SOC, AM treatment promoted early epithelialisation in moderate burns (two studies reported significant results).
- Across the seven RCTs which investigated the use of AM for pterygium surgeries compared to SOC, it was found that AM was associated with an increased recurrence of the pterygium (four out of seven studies reported recurrence and two were significant). Further, AM treatment was found not to effectively treat patients with scleral thinning after pterygium surgery with beta therapy.
- It was recommended in patients with non-viral infectious keratitis with cases of perforation, a procedure other than AM should be used.

The DCAR considered that based on the benefits and harms reported, it was suggested that, relative to SOC, AM safety and effectiveness are uncertain due to contradictory reported outcomes among the evidence base. All outcomes were found to have a high risk of bias and the quality of evidence was very low (Table 3).

Table 2 GRADE assessment of AM compared to SOC for ophthalmic conditions

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with SOC	Anticipated absolute effects Risk difference with AM
Effectiveness outcomes					
Visual acuity assessed with Snellen or logMAR chart	665 (12 RCTs)	⊕○○○ VERY LOW a,b,c,d,e	-	not pooled	not pooled
Wound healing assessed by re-epithelialisation time, change in defect size, wound healing rate, TBUT, Schirmer test time	603 (11 RCTs)	⊕○○○ VERY LOW c,d,e,f,g	-	not pooled	not pooled
Recurrence assessed with Prabhasawat et al. grading system (pterygium) or reappearance of disease (epithelial defects)	742 (8 RCTs)	⊕○○○ VERY LOW c,d,h	-	not pooled	not pooled
Safety outcomes					
Safety Adverse events assessed by ophthalmic examination	1,077 (15 RCTs)	⊕○○○ VERY LOW d,i,j,k	-	not pooled	not pooled
Safety Pain assessed by subjective patient reporting	159 (3 RCTs)	⊕○○○ VERY LOW d,l,m,n	-	not pooled	not pooled

Source: Table 41, p109 of the DCAR

Explanations:

- a. High risk of bias overall. Bias in the measurement of visual acuity as an outcome was the most consistent critical concern. The assessment of visual acuity was not well defined for most trials, outcome assessors were infrequently blinded to the intervention received, knowledge which could, and most likely would, impact the subjective comparative assessment of visual acuity.
- b. Although all studies reported the final value in logMAR units, some studies measured UCVA, some BCVA, and some didn't report which. Although most studies favoured neither intervention, some significantly favoured amnion membrane
- c. Some studies reported outcomes by eyes, some by participants, some by pterygia
- d. Based on definitions outlined by Pollock et al. 2016
- e. There were many time points where the outcome was measured, however results were not published.
- f. High risk of bias overall. There are significant concerns regarding how the amnion membrane as the intended treatment was undertaken during the trial. It is unclear how the breach of the blinding could impact on the comparative safety and effectiveness. Blinding during allocation, and of patients and outcome assessors was uncommon. However, the measurement of wound healing is generally objective, bias is introduced when blinding is not performed during data analysis
- g. Considered not serious, however, notable two of eleven studies assessed wound healing by the indirect methods tear film break up time and Schirmers test. Similar techniques were used for the remaining studies.
- h. High risk of bias overall. Reasons for potential bias were mixed across the trials. Reporting related to the concealment of allocation during the randomisation process and blinding of patients and the surgical team was frequently inadequate. Trials were not consistently registered, and pre-specified outcomes (particularly around time to follow up) were inconsistent
- i. Suspected high risk of bias. All other outcomes and most studies were concluded with a high risk of bias due to experimental design. Additionally, the outcome was usually measured by ophthalmic examination (unblinded)
- j. Most adverse events were not specified in methods but were discovered in follow up examinations. High level of heterogeneity in reported safety outcomes
- k. Considered not serious, however, notably here was usually no clear method of measurement. The reported outcome was based on statements from follow up examinations
- l. High risk of bias in study designs and outcome measures
- m. Non-consensus on favouring of intervention.
- n. Subjectively measured by patient reporting.

Population 2 – Chronic skin wounds

The three effectiveness outcomes were assessed for risk of bias: complete healing, time to complete healing and wound size reduction. For the outcome of complete healing, the risk of bias assessment determined a low to moderate risk of bias in nine out of the 14 trials. The main concerns of biases were associated with the inadequate blinding of outcome assessors

and deviation from the intended intervention. Time to heal, reported in seven studies, was considered to have some concerns in five studies and of high risk of bias in two. Wound size reduction was associated with some risk of bias in five out of seven studies. The remaining two studies were assessed as high risk due to insufficient information related to missing outcome data.

In general, the DCAR considered that the evidence indicated that AM was more effective than SOC for both DFU and VLU subpopulations.

- Superior effectiveness of AM compared to SOC was demonstrated for complete healing, time to heal, wound size reduction and partial healing in both subpopulations.
- Equivalent effectiveness for AM compared to SOC was shown for recurrence in the DFU subpopulation.
- Complete healing was the most reported outcome (11/14 studies), regardless of the subpopulation.

Based on the benefits and harms reported in the evidence base for DFU (Table 4) and VLU (Table 5), relative to SOC, the effectiveness outcomes favour AM for both subpopulations. In contrast, safety outcomes are uncertain for DFU and VLU subpopulations respectively - noting that there was only low quality of evidence available to support the conclusion on safety for VLU subpopulation.

Table 3 AM compared to SOC for DFU

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with SOC	Anticipated absolute effects Risk difference with AM
Effectiveness outcomes					
Complete healing Follow-up 6 to 16 weeks	457 (7 RCTs)	⊕⊕⊕⊖ MODERATE a,b,c,d,e	RR 1.99 (1.47 to 2.70)	306 per 1,000	306 more per 1,000 (145 more to 525 more)
Recurrence Follow-up 6 to 12 weeks	287 (3 RCTs)	⊕⊕⊖⊖ LOW b,c,f,g	RR 0.99 (0.22 to 4.46)	112 per 1,000	1 fewer per 1,000 (87 fewer to 387 more)
Partial healing Follow-up 4 to 6 weeks	154 (2 RCTs)	⊕⊕⊕⊖ MODERATE c,g,h	-	mean partial healing 0	0 (0 to 0)
Time to heal Follow-up 6 to 12 weeks	272 (4 RCTs)	⊕⊕⊖⊖ LOW a,b,g,k	-	mean time to heal 0	MD = -24.70 lower (-35.5 lower to -13.9 lower)
Wound size reduction Follow-up 6 to 12 weeks	65 (2 RCTs)	⊕⊕⊖⊖ LOW a,b	-	mean wound size reduction 0	MD = 60.28 higher (37.43 higher to 83.13 higher)
Safety outcomes					
Cellulitis Follow-up 6 to 12 weeks	284 (3 RCTs)	⊕⊕⊖⊖ LOW b,c,f,g	RR 0.80 (0.34 to 1.87)	76 per 1,000	15 fewer per 1,000 (50 fewer to 66 more)
Wound infection Follow-up 6 to 12 weeks	426 (4 RCTs)	⊕⊕⊖⊖ LOW b,c,f,g	RR 0.67 (0.35 to 1.30)	107 per 1,000	35 fewer per 1,000 (70 fewer to 32 more)
Osteomyelitis Follow-up 6 to 12 weeks	329 (3 RCTs)	⊕⊕⊖⊖ LOW b,c,f,g	RR 1.74 (0.36 to 8.43)	12 per 1,000	9 more per 1,000 (8 fewer to 89 more)
Non-life-threatening adverse events Follow-up 6 to 12 weeks	478 (8 RCTs)	⊕⊕⊖⊖ LOW a,b,i	-	mean non-life threatening adverse events 0	0 (0 to 0)
Serious adverse events Follow-up 12 weeks	287 (4 RCTs)	⊕⊕⊖⊖ LOW a,b,g,i,j	-	mean serious adverse events 0	0 (0 to 0)
Withdrawals due to adverse events Follow-up 6 to 12 weeks	219 (4 RCTs)	⊕⊕⊖⊖ LOW a,g,i	-	mean withdrawals due to adverse events 0	0 (0 to 0)
Withdrawals due to non-healed wound Follow-up 6 to 12 weeks	255 (5 RCTs)	⊕⊕⊕⊖ MODERATE a,b,c	-	mean withdrawals due to non-healed wound 0	0 (0 to 0)

Source: Table 42, p112 of the DCAR

Explanation

- a. no blinding: patients, personnel or outcome
- b. not all patients included in the analysis - withdrawal at mid-study period usually to seek alternative treatment or because of AE [more often in SOC group] - missing outcome data, could impact true value [especially in SOC group]
- c. comparator [SOC] maybe not the one that will be used all the time in real life [UrigoStart, in less extent skin graft]
- d. large effect size or CI
- e. one study at specific time point
- f. CI spans to benefit and harm - size effect
- g. few studies and, or low sample size
- h. no patient withdrawals at this point - occurred just after this outcome
- i. no definition or info on how it's measured
- j. significant p-value

Table 4 AM compared to SOC for VLU

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with SOC	Anticipated absolute effects Risk difference with AM
Effectiveness	outcomes				
Complete healing Follow-up 3 to 16 weeks	437 (4 RCTs)	⊕⊕⊕⊕ VERY LOW a,b,c	RR 1.60 (1.35 to 1.90)	403 per 1,000	242 more per 1,000 (262 fewer to 363 more)
Partial healing Follow-up 4 weeks	84 (1 RCT)	⊕⊕⊕⊕ LOW c,d,e	-	not pooled	not pooled
Time to heal follow-up 8 weeks	25 (1 RCT)	⊕⊕⊕⊕ VERY LOW a,c,d,e	-	not pooled	not pooled
Wound size reduction Follow-up 3 to 8 weeks	218 (3 RCTs)	⊕⊕⊕⊕ MODERATE ^e	-	not pooled	not pooled
Safety	outcomes				
Wound infection Follow-up 3 to 8 weeks	284 (2 RCTs)	⊕⊕⊕⊕ LOW a,c,e	RR 0.23 (0.12 to 0.44)	466 per 1,000	359 fewer per 1,000 (410 fewer to 261 fewer)
Cellulitis Follow-up 4 weeks	84 (1 RCT)	⊕⊕⊕⊕ LOW c,e	-	not pooled	not pooled
Non-life threatening adverse events Follow-up 3 to 12 weeks	393 (3 RCTs)	⊕⊕⊕⊕ VERY LOW a,c,e,f	not estimable	479 per 1,000	479 fewer per 1,000 (479 fewer to 479 fewer)
Serious adverse events Follow-up 12 weeks	109 (1 RCT)	⊕⊕⊕⊕ LOW a,c	not pooled	not pooled	not pooled
Withdrawals due to adverse events Follow-up 4 weeks	84 (1 RCT)	⊕⊕⊕⊕ LOW c,e	not pooled	not pooled	not pooled
Withdrawals due to non-healed wound Follow-up 12 weeks	109 (1 RCT)	⊕⊕⊕⊕ LOW c,e	not pooled	not pooled	not pooled
Pain Follow-up 3 to 8 weeks	(3 RCTs)	⊕⊕⊕⊕ LOW ^a	-	not pooled	not pooled

Source: Table 43, p113 of the DCAR

Explanations

- a. Missing outcomes, deviations from interventions and/or outcome measurement
- b. Non significant p-value, high I² and large effect size or CI
- c. Few studies, and or small sample size
- d. Comparator maybe not the one that will be used all the time in real life [UrgoStart, in less extent skin graft]
- e. No blinding: patients, personnel or outcome
- f. Studies didn't show the same type of results

Population 3 – Acute skin wounds

Assessment of the comparative efficacy of AM was challenging due to the variability of wounds, SOC, population and the way the included RCTs reported various wound healing parameters, including wound healing periods and time between AM and skin graft. Furthermore, the high risk of bias among the eight studies included for this population also downgraded the quality of evidence, which limited the conclusion on safety of AM in acute wounds.

The DCAR considered that the evidence from the eight RCTs, showed that:

- AM had superior effectiveness compared to SOC therapy. Superiority was demonstrated by accelerated wound healing and epithelialisation and reduced time to skin grafting.
- AM promoted a more rapid development of granulation tissue. Development of granulation tissue was a secondary intention that helps the wound healing process.
- AM reduced the length of hospital stay compared with the SOC group.

Overall, the DCAR considered that the quality of evidence supporting the effectiveness and safety of AM in the treatment of acute wounds was low (Table 6). Therefore, the confidence in the effect estimated was limited, and the true effect may be substantially different from the estimate of the effect. However, based on the benefits and harms reported in the evidence base summarised above, AM has superior safety and effectiveness compared with SOC.

Table 5 AM compared to SOC for acute wounds

Outcomes	No of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Risk with SOC	Anticipated absolute effects Risk difference with AM
Effectiveness outcomes					
Wound healing (time to heal) Assessed with time to wound healing and epithelisation, and wound size reduction	374 (6 RCTs)	⊕⊕⊖⊖ LOW ^{a,b,c}	-	not pooled	not pooled
Time for wounds to be ready for skin graft Assessed with growth of granulation tissue, wound starting to heal before skin graft could take place	443 (3 RCTs)	⊕⊕⊖⊖ LOW ^d	-	not pooled	not pooled
Safety outcomes					
Pain Assessed with pain score (0–10), pain scale (0–10)	456 (6 RCTs)	⊕⊕⊖⊖ LOW ^e	-	not pooled	not pooled
Infection Assessed with local signs of infection (oedema, redness, discharge, odour, irritation), systemic signs of infection (fever, tachycardia, blood leucocyte count)	128 (3 RCTs)	⊕⊕⊖⊖ LOW ^{f,g,h}	-	not pooled	not pooled

Source: Table 44, p115 of the DCAR

Explanations

- Bias arising from measurement of the outcome and selection of the reported results
- Some concerns relevant to randomisation process and bias due to deviations from intended intervention.
- Small sample sizes recruited across the RCTs
- High risk of bias arising from randomisation process, measurement of the outcome, and selection of the reported outcome.
- High risk of bias arising from randomisation process, measurement of the outcome, and selection of the reported outcome.
- High risk of bias arising from measurement of the outcome and selection of the reported outcome.
- Some concerns relevant to randomisation process, missing outcome data, and deviations from intended intervention.
- Small sample sizes recruited across the RCTs.

Clinical claim

The applicant made the following clinical claims about AM uses:

- Cryopreserved AM may have better efficacy than dehydrated.
- Cryopreserved AM is non-inferior to other forms of AM.
- For Population 1 and 2, compared to SOC, AM has superior for effectiveness and non-inferior for safety.
- For Population 3, compared to SOC, AM has non-inferior for effectiveness and non-inferior for safety.

The DCAR noted a lack of direct evidence comparing AM with the PICO defined comparator prevented the assessment of the first two clinical claims.

On the basis of the evidence profile (discussed above), it is suggested that, relative to SOC:

- for Population 1, AM safety and effectiveness are uncertain,
- for Population 2, AM has uncertain safety and superior effectiveness, and
- for Population 3, AM has superior safety and effectiveness compared with SOC.

12. Economic evaluation

The DCAR noted that AM can be applied to a wide range of indications across many different patient populations and subgroups of indications. Due the complexity and the heterogeneity in the subpopulations within each of the three populations and concerns regarding the limitations and poor quality of data in Population 1 and 3, it was not considered feasible to the cost-effectiveness of AM with its comparator for all three populations. Based on the clinical evidence reviewed and clinician advice that the use of AM to treat DFU (diabetic foot ulcers) as an area of considerable potential uptake in the event of PL listing, the DFU from Population 2 was considered the appropriate modelling target.

A cost-utility analysis (Table 7) was undertaken to compare AM to a SOC among DFU patients with failed treatment. Key economic assumptions, including transition from uncomplicated DFUs to no DFUs were derived from healing rates in the four RCTs⁴ with 12-week follow-up. Probabilities of infected DFUs transitioning to amputation and death were taken from the Australian DFU model developed by Cheng and colleagues (Cheng et al. 2017⁵).

⁴ Zelen et al. 2016, Lavery et al. 2014, DiDomenico et al. 2018 and Tettelbach et al. 2019

⁵ Cheng, Q et al. (2017) *International Wound Journal*. 14(4):616-28.

Table 6 Summary of the economic evaluation

Perspective	Health system
Intervention	Amnion membrane tissue grafts
Comparator	Standard of care
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RCTs for rates of healing, extrapolated analysis was based on the Cheng 2017 Australian DFU model
Time horizon	12 weeks trial, 260 weeks (5 years) extrapolated
Outcomes	QALYs
Methods used to generate results	Markov model
Health states	No DFU, uncomplicated DFU, complicated DFU with infection, post-minor amputation, infected post-minor amputation, post-major amputation, dead
Cycle length	1 week
Discount rate	5% used for base, 3.5% and 7% sensitivity analyses
Software packages used	Microsoft Excel 2010

Source: Table 4, p12 of the DCAR

Abbreviations: QALY = quality-adjusted life year; RCT = randomised controlled trial; DFU = diabetic foot ulcer

The DCAR estimated resource use for AM and SOC in the model following clinical input during the assessment and use of MBS and PBS costs for key items. Hospital costs were taken from the AR-DRG costs relating to minor and major amputation, along with complicated DFU treatment. Utility estimates for each health state were derived from a review of the literature. The incremental cost and the incremental effectiveness of AM compared to SOC are presented in Table 8.

Table 7 Incremental cost effectiveness ratio

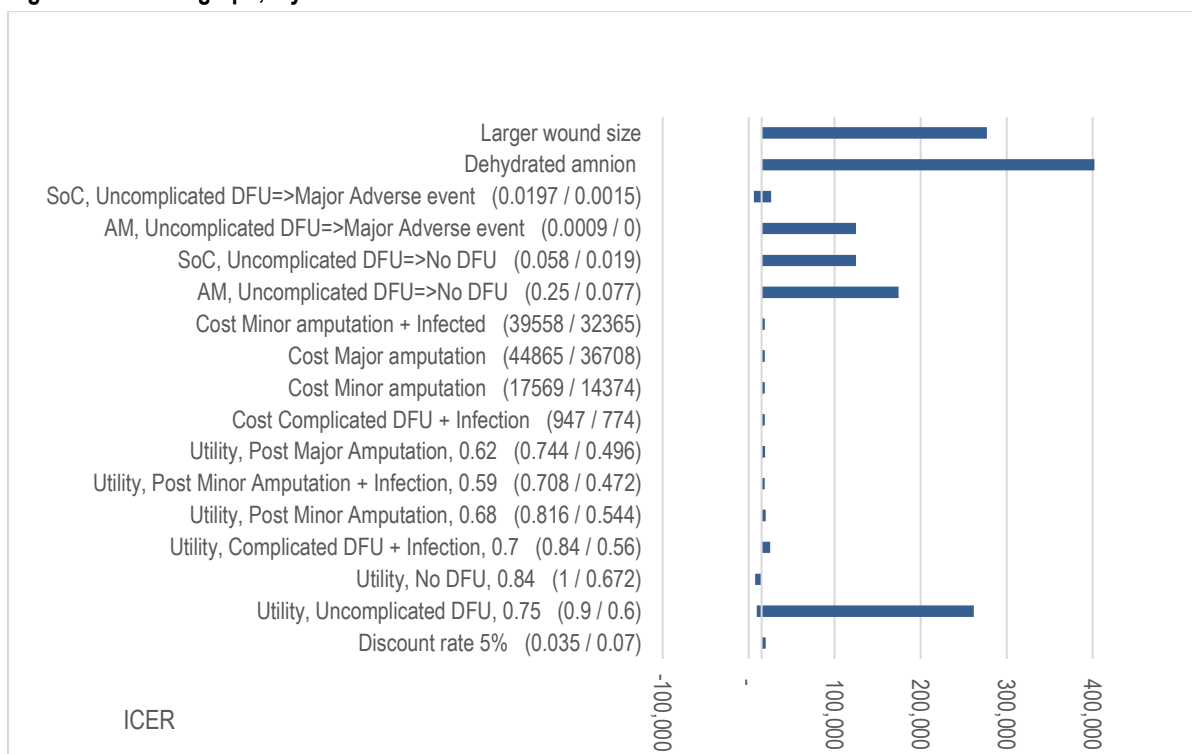
	Discounted cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
12 weeks					
Amnion membrane (AM)	6,290	2,882	0.20	0.01	511,045
Standard care (SOC)	3,408		0.19		
5 years (Base case)					
Amnion membrane (AM)	31,461	1,973	3.65	0.11	18,322
Standard care (SOC)	29,488		3.54		

Source: Table 5, p13 of the DCAR

Abbreviations: AM = amnion membrane, ICER = incremental cost effectiveness ratio, QALYs = quality-adjusted life years, SOC = standard of care

The DCAR performed univariate sensitivity analysis (see tornado diagram in Figure 7) to investigate uncertainties in the base-case model related to key assumptions such as healing rates in the longer term, utility for health states and unit costs.

Figure 7 Tornado graph, 5-year ICER

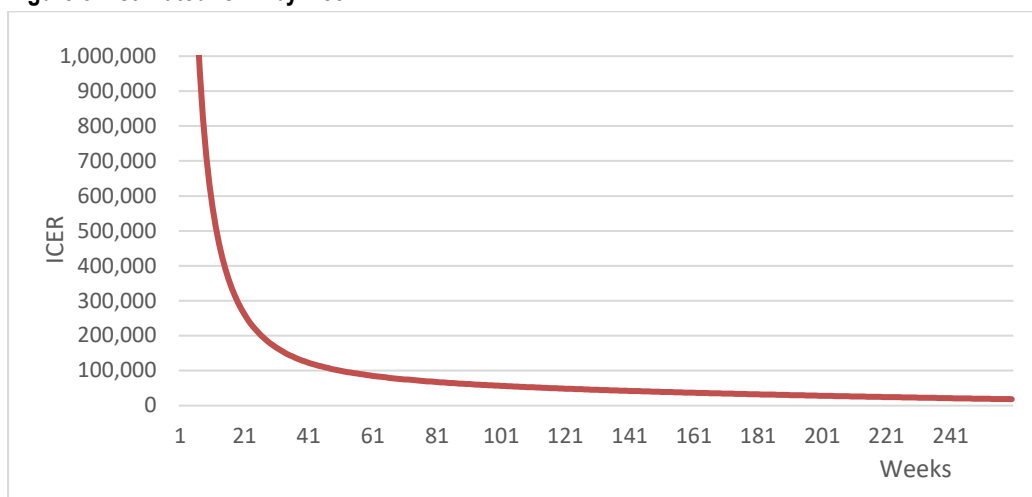


Source: Figure 40, p157 of the DCAR

Abbreviations: DFU = diabetic foot ulcer, ICER = incremental cost effectiveness ratio, QALYs = quality adjusted life years

The impact of the varying the model time horizon on the ICER is presented below in Figure 8. The trial analysis had an estimated ICER of \$511,045. This decreases to \$97,870 by the end of year one and \$18,322 by the end of year five.

Figure 8 Estimated ICER by week



Source: Figure 41, p156 of the DCAR

Abbreviations: ICER = incremental cost effectiveness ratio

Overall, the DCAR considered that the assumption regarding the unit price of AM, variation in healing rates across the key RCTs, timeframe for the model and utility for the uncomplicated DFU states have the largest impact on model results (Table 9).

Table 8 Key drivers of the economic model

Description	Method/Value	Impact
Cost of the AM product	AM was included in the model using the applicants proposed average cost of \$579 per 5cm circle. The cost of the dehydrated AM product (EpiFix) is three times this cost. When included in cost calculations, the ICER increased to four hundred thousand. Apligraf® was included as a comparator. It is more expensive and had lower healing rates when compared to AM in the Zelen trial. Correspondingly it is dominated.	The use of the dehydrated AM product price has the largest impact on the estimated ICER. The sensitivity analysis assumed no change in healing rate between the frozen and dried AM products due to a lack of data. Assumed wound size and size of AM used also have a large impact on the ICER given price sensitivity of results.
Healing rates across three major trials	Healing rates in major trials were averaged and included as base transition rates for AM and SOC. The selection of the highest and lowest values from these trials was used in a sensitivity analysis.	The inclusion of high and low values from the trials had a large impact on the calculated ICER. Lower and higher values were associated with specific trials, so comparing a high value from one trial with a low value from another may overlook contextual factors and overstate potential impacts
Utility assumed for no DFU and uncomplicated DFU	The model assumed utility values from one economic study. The utility for on DFU was 0.84 and uncomplicated DFU was 0.75. Given that data sources were limited, values were varied by twenty percent as part of sensitivity analysis to gauge model robustness to changes in this assumption.	The difference between the values assigned for these states has a large impact on the calculated ICER, as most patients reside in each of these states, and differences between AM and SC arms are driven by healing rates. Twenty percent variation did not have as large an impact as changes in AM product prices.
Limiting model projection over trial period of 12 weeks.	A stepped analysis was undertaken given that trial data was limited to 12 weeks. Extrapolation was undertaken using probabilities in the Australian Cheng DFU model.	There was a large difference between ICERS estimated at 12 weeks and 5-years. Given trial maximum follow-up was limited to 12 weeks, there is considerable uncertainty about the long-term clinical benefit of AM.

Source: Table 5, p13 of the DCAR

Abbreviations: AE = adverse event, AM = amnion membrane, ICER = incremental cost effectiveness ratio, QALYs = quality-adjusted life years, SOC = standard of care

13. Financial/budgetary impacts

The potential AM uptake in each subpopulation within three populations was estimated using an epidemiologic approach (Table 10). The projected adoptions are assumptions made by the assessment group on the potential uptake of amnion membrane for each subpopulation.

Table 9 Projected AM patients in Australia by subpopulation, 2021–25

With PL listing of AM	Row	2021	2022	2023	2024	2025	Source
Acute ophthalmic conditions							
Acute eye burns	A	65	66	67	68	69	25% projected adoption (Table 71) x estimated eligible patients (Table 70)
SJS and TEN	B	0	0	0	0	0	0% projected adoption (Table 71) x estimated eligible patients (Table 70)
Pterygium surgery	C	94	95	96	98	99	1% projected adoption (Table 71) x estimated eligible patients (Table 70)
Corneal transplants	D	78	79	80	81	82	5% projected adoption (Table 71) x estimated eligible patients (Table 70)
Eye wounds refractory to healing	E	28	28	29	29	30	5% projected adoption (Table 71) x estimated eligible patients (Table 70)
Chronic wounds							
Venous insufficiency ulcers	F	94	95	96	98	99	1% projected adoption (Table 71) x estimated eligible patients (Table 70)
Arterial insufficiency ulcers	G	8	8	9	9	9	1% projected adoption (Table 71) x estimated eligible patients (Table 70)
DFU	H	104	105	107	108	110	4% projected adoption (Table 71) x estimated eligible patients (Table 70)
Acute wounds							
Burns with dermal substitute	I	12	13	13	13	13	10% projected adoption (Table 71) x estimated eligible patients (Table 70)
Patients with a graft donor site wound	J	12	13	13	13	13	10% projected adoption (Table 71) x estimated eligible patients (Table 70)
Patients requiring skin graft fixators	K	12	13	13	13	13	10% projected adoption (Table 71) x estimated eligible patients (Table 70)
Total	L	508	515	522	530	537	
Without PL listing of AM							
Acute ophthalmic conditions							
Total	M	150	150	150	150	150	<i>Based on applicant advice that 150 grafts were released in 2019 for ophthalmic conditions</i>

Source: Table 72, p170 of the DCAR with adoption rates from Table 71, p170 of the DCAR.

Abbreviations: AM = amnion membrane, DFU = diabetic foot ulcers, PL = Prothesis List, TEN = toxic epidermal necrolysis, SJS = Stevens-Johnson Syndrome

The predicted financial impact of AM listing on the MBS and PL is shown in Table 11. The average price for cryopreserved AM proposed by the applicant was \$28.93 per cm². The DCAR noted this is less than that of dehydrated AM, where the price per cm² varies from \$313 to \$106 depending on product size. The base analysis assumed one AM was used per eye and per acute wound patients, and 2-5 AM was used per chronic wound patients.

Table 10 Combined budget impact of AM listing, 2021–2025

	2021	2022	2023	2024	2025
PL Costs					
Acute ophthalmic conditions ^a	\$153,266	\$155,411	\$157,587	\$159,793	\$162,030
Chronic wounds ^b	\$419,250	\$425,119	\$431,071	\$437,106	\$443,225
Acute wounds ^{a,c}	\$94,469	\$95,792	\$97,133	\$98,493	\$99,872
Subtotal	\$666,985	\$676,322	\$685,791	\$695,392	\$705,127
MBS Costs					
AM with listing†	-\$54,810	-\$55,577	-\$56,355	-\$57,144	-\$57,944
Total MBS and PL	\$612,175	\$620,745	\$629,436	\$638,248	\$647,183

Source: Table 7, p14 of the DCAR and footnotes added in by Department, informed from Table 73, pp171-172; Table 74, pp172-173; and Table 76, p175 of the DCAR

Abbreviation: PL = prosthesis list; MBS = Medicare Benefit Scheme; AM = amnion membrane

Note: † = the cost offsets to MBS with funding AM are due to less repeat dressings with AM (i.e. better wound healing)

^aBased on clinical feedback, the DCAR assumed 1 AM graft per patient for this population

^bBased on clinical feedback, the DCAR assumed 2 AM grafts per patient for venous ulcer and arterial ulcer subpopulations and 5 for diabetic foot ulcers (DFU) subpopulation from key DFU trial reported 3-6 grafts per healed DFU

^cThe DCAR also estimated there would be some substitution of AM for other dermal products (Novosorb with PL benefit of \$1,112) would occur

The DCAR sensitivity analyses indicated that results are most sensitive to the price of AM, estimated number of DFU patients, and grafts used per healed wound (Table 12).

Table 11 Net PL cost sensitivity analysis

	2021	2022	2023	2024	2025
Base Case PL	666,985	676,322	685,791	695,392	705,127
Burden of Disease					
Eye burns prevalence 7.5% increase	669,836	679,214	688,723	698,365	708,142
Pterygium prevalence 7.5% increase	672,067	681,476	691,017	700,691	710,501
DFU prevalence 7.5%	689,573	699,227	709,017	718,943	729,008
Burns dermal substitute prevalence 7.5%	668,652	678,013	687,505	697,131	706,890
Uptake					
Eye Burns (50%)	704,633	714,498	724,501	734,644	744,929
SJS and TEN (10%)	668,491	677,849	687,339	696,962	706,719
Pterygium (2%)	721,198	731,295	741,533	751,914	762,441
Corneal removal surgery (10%)	712,162	722,133	732,242	742,494	752,889
Refractory ophthalmic wound (10%)	683,211	692,776	702,475	712,309	722,282
Venous insufficiency ulcers (2%)	775,411	786,267	797,275	808,437	819,755
Arterial insufficiency ulcers (2%)	676,623	686,095	695,701	705,440	715,317
DFU (5%)	742,281	752,673	763,210	773,895	784,730
Burns dermal substitute (20%)	689,219	698,868	708,652	718,574	728,634
Graft donor site wound (20%)	703,102	712,945	722,926	733,047	743,310
Skin graft fixators (20%)	703,102	712,945	722,926	733,047	743,310
Cost of AM					
Epifix	4,071,321	4,128,319	4,186,115	4,244,721	4,304,147
Bigger wound	1,518,069	1,539,322	1,560,872	1,582,724	1,604,882
Grafts per wound					
Eye and acute, 2 per wound	914,719	927,525	940,511	953,678	967,029
DFU 3 per wound	546,510	554,162	561,920	569,787	577,764
DFU 6 per wound	727,222	737,403	747,726	758,195	768,809

Source: Table 78, p176 of the DCAR

Abbreviations: DFU = diabetic foot ulcer, TEN = toxic epidermal necrolysis, SJS = Stevens-Johnson Syndrome; PL = prosthesis list

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Certainty of evidence and risk of bias	The certainty of the clinical evidence using GRADE was very low for Population 1, up to moderate for Population 2 and low for Population 3. Risk of bias followed a similar pattern.
Heterogeneous patient populations/subpopulations and comparators where standard of care was defined differently	Difficulty comparing clinical results across different subpopulations prevented meta-analyses for some outcomes. This was particularly prominent in Population 1 and compounded AM's inconsistent effectiveness and safety for this population. Limited or absent clinical data meant that some subpopulations were not investigated.
Safety and effectiveness	Overall, AM treatment seems to be at least as safe as and more effective than standard of care as its comparator across the three populations. However, incremental clinical benefit size varies significantly across the three populations and between subpopulations.
Long-term safety	Patient follow-up across all the included trials was relatively short. The maximum length of follow-up for studies in Population 1 was up to 12 months, Population 2 up to 12 weeks, and Population 3 up to 3 weeks, depending on the characteristics of populations and wound types.
Cost of the product	Cost used in the model is \$579 for a 5 cm circle of AM. Use of larger AM grafts would increase the cost. Costs could be reduced by using smaller AM grafts for ophthalmic conditions.
Economic evidence	Economic evidence is provided for one indication only- AM for treating DFU (population 2). In this subpopulation, the ICER was high (\$97,870) at the more appropriate time horizon of 1 year. Furthermore, it is uncertain how cost-effective AM is in other settings.
Uptake	Uptake estimates are highly uncertain. The potential population is likely to be underestimated for ulcers and eye conditions.
Usage	PL benefits for AM will only apply if used as part of a hospital or hospital-substitute treatment which could have unintended consequences where patients are admitted to gain access to this treatment. Treatments are required weekly – diabetic foot ulcers require approximately 5 applications. These would not all be performed in the hospital setting. If not limited to hospitals, the types of professionals who are able to access AM should be considered with regard to equity and patient adherence with treatment.

ESC discussion

ESC noted that AM (cryopreserved or dehydrated) would be used under a range of existing Medicare Benefits Schedule (MBS) items, as determined by clinicians.

ESC noted that AM is proposed to treat wounds across three broad populations:

- Population 1 – first-line treatment for ophthalmic conditions where cells on the corneal surface are disrupted (e.g. pterygium, burns, Stevens–Johnson syndrome and toxic epidermal necrolysis [TEN]), and second-line treatment for other corneal wounds that have failed to heal
- Population 2 – chronic ulcers (unresponsive to treatment using standard care for at least 12 weeks; includes venous and arterial insufficiency ulcers, and diabetic foot ulcers)
- Population 3 – acute wounds such as burns, graft donor sites, wounds that require a skin graft fixator, and TEN.

ESC noted that the populations were complex with each population containing several subpopulations. Further, while standard of care (SOC) is the nominated comparator for all three populations, the definition and context for SOC differs for each population and subpopulation, further increasing the complexity. This resulted in 10 different clinical management algorithms. ESC noted a synthetic dermal cover developed in South Australia, could also have been included as a comparator for Population 3. ESC noted that AM delivery settings may also differ between populations or subpopulations, for example, AM treatment of chronic skin ulcers may occur in the community or in hospital.

ESC noted the consultation feedback from the Royal Australian and New Zealand College of Ophthalmologists, which supported the application and noted that AM products would also be beneficial in the community setting to avoid hospital admission. Consumer input questioned whether TEN should be included in the application, given the rarity of the condition and high mortality rate. ESC considered that TEN is usually an emergency condition and it would be appropriate for AM to be available as a treatment option.

ESC noted the application claimed that AM has non-inferior safety for all three populations compared to SOC, and that AM has superior efficacy (Population 1 & 2) / non-inferior efficacy (Population 3) compared to SOC. ESC noted that the application also made clinical claims regarding the efficacy of cryopreserved AM compared to dehydrated and other forms of AM. However, due to the lack of direct evidence, comparison of the relative efficacy of cryopreserved AM versus dehydrated AM, and whether cryopreserved AM is non-inferior to other forms of AM was not able to be assessed.

For Population 1, ESC noted the evidence consisted of 15 randomised clinical trials (RCT) that pertained to pterygium surgeries (k=7), ocular burns injuries (k=3) and other ophthalmic subpopulations (k=5). However, the quality of evidence was very low, with a high risk of bias and significant variations in study characteristics across the subpopulations. ESC agreed with PASC that the use of AM in acute ophthalmic conditions (e.g. trauma) should be considered separately to its use in chronic conditions. ESC noted that the evidence suggested that AM use in patients with ocular conditions is safe. In most cases, AM treatment was reported to be equally as effective as SOC however; ESC noted that effectiveness was highly dependent on the subpopulation of patients. Further, some studies reported that AM use was not appropriate or not recommended for certain ophthalmic conditions, including pterygium due to increased recurrence, scleral thinning after pterygium surgery with beta therapy, and patients with non-viral infectious keratitis with cases of perforation. ESC was unable to determine from the data whether AM should be indicated for all patients undergoing surgical corneal removal or only a subgroup undergoing extensive removal. Overall, ESC considered the safety and effectiveness data for Population 1 was inconsistent, and therefore ESC was uncertain whether AM has non-inferior safety and superior efficacy compared to SOC for all ophthalmic conditions included in Population 1. However, there may be subpopulation(s) within Population 1 where AM has non-inferior safety and superior efficacy compared to SOC.

For Population 2, ESC noted the evidence consisted of 14 RCTs that pertained to diabetic foot ulcers (DFU: k=9), venous leg ulcers (VLU; k=3) and other chronic ulcers (k=2). However, the quality of evidence was very low to moderate, with some risk of bias. ESC noted that only Population 2 had clinical data of sufficient quality for meta-analysis, and that the evidence suggested there were no major safety concerns for AM therapy in patients with DFUs or VLUs. The evidence suggested AM was more effective than SOC for patients with DFU or VLU for all reported outcomes, except for recurrence in the VLU subpopulation, for

which no evidence was found. ESC noted that, on average, patients with DFUs used five AM grafts, whereas patients with VLUs used one AM graft.

For Population 3, ESC noted the evidence consisted of eight RCTs that reported on the application of AM to graft site donor wounds (k=5), burns requiring dermal substitutes before skin grafting (k=3) and wounds requiring skin graft fixation (k=1). ESC noted the quality of evidence was low, with a high risk of bias. ESC noted no mortalities or severe adverse events were reported when using AM, and that the rate of safety issues was lower for AM compared to the comparator. The evidence suggested that AM is safe for treatment of acute wounds, including burns. Most RCTs claimed that AM is a superior dressing to its comparators, but some recommended further studies to evaluate the efficacy of AM for acute wound healing.

ESC noted the lack of long-term safety data for all populations. The maximum length of follow-up for studies in Population 1 was up to 12 months, Population 2 up to 12 weeks, and Population 3 up to 3 weeks, depending on the characteristics of populations and wound types. ESC considered that the long-term safety profile of AM should be monitored over time.

ESC noted that economic analysis was limited to a cost-utility analysis comparing AM with SOC in the DFU subpopulation (Population 2), as this was the subpopulation with the highest quality evidence and largest impact. ESC considered that it was difficult to assess the cost-effectiveness of AM when the economic modelling is limited to only one population. ESC suggested a cost-consequence analysis (CCA) for the other populations and subpopulations could provide MSAC with an indication of the economic impact for each population and subpopulation. The Department advises that a CCA will be provided for June ESC 2021 meeting.

ESC noted that the proposed cost of AM varies by the size of the product, based on a unit price of \$28.93/cm², and that the cost used in the model is \$579 for a 5 cm circle of AM. ESC noted that as AM is human tissue proposed for listing on Part B of the Prostheses List, it must comply with relevant State and Territory legislation regarding the sale of human tissue. This means that the benefit for a human tissue item is set at an amount that recovers the costs involved in supplying the human tissue to the patient (i.e. does not generate a profit). However, ESC queried the lack of breakdown for costs, in particular the costs for pathology testing (i.e. what tests and costs are included) and staffing. For transparency and clarity in how these costs were derived, ESC advised that, if possible, the applicant should provide MSAC with a breakdown for these along with confirmation of where the costs of cryopreservation and storage has been included. ESC noted that the smallest size of AM (5 cm diameter circle) may be too large for ophthalmic conditions, and wastage could be reduced if a smaller size were available. ESC also noted that [2 x 2 cm² AM grafts](#) are used for ophthalmic indications in the National Health System (NHS), UK.

ESC noted that the economic model comparing AM with SOC was based on a published Australian cost-effectiveness model (Cheng et al. 2017⁶) comparing optimal care with usual care for DFU patients. ESC considered that the model structure and variables were appropriate, and that translation issues were dealt with appropriately. ESC noted that the model outcomes were driven by the rate of healed ulcers (11% for AM compared with 4% for SOC) and serious adverse events (which were twice as high for SOC).

ESC noted that the incremental cost-effectiveness ratio (ICER) was \$511,045; however, this was based on a time horizon of 12 weeks (clinical trial data), which ESC did not consider to be long enough. The department contracted assessment report (DCAR) used a 5-year

⁶ Cheng, Q et al. (2017) *International Wound Journal*. 14(4):616-28.

timeframe (ICER = \$18,322) as the base case model, consistent with the Cheng et al. 2017 and to reflect the natural history of diabetes progression. However, due to the short trial follow-up, ESC considered that a 1-year timeframe would be more appropriate as the base case, noting that the ICER would be much higher at \$97, 870. Sensitivity analyses showed the ICER was sensitive to price and wound size (larger wounds require more AM grafts).

The application used an epidemiological approach for each subpopulation for the financial and budgetary impacts. ESC noted that uptake did not change over time, and considered that uptake of 1–4% for skin ulcers was likely to be underestimated. ESC considered the uptake estimates to be highly uncertain. ESC considered that the costs to the PL may be underestimated because the costs had only accounted for use of five AM grafts for diabetic foot ulcers based on average number of AM grafts used in a 12 week trial, but these wounds would require weekly dressing and in clinical practice may take months to heal and may relapse, potentially requiring many more AM grafts.

ESC noted concerns from the policy area that uptake of AM is likely to be considerable if the products are listed on the PL, and the lack of comparators on the PL will likely result in additional expenditure for private health insurers. ESC noted there is the potential for patients to be admitted to hospital in order for PL benefits for AM to be claimed, rather than being treated in the community where the patient would incur out-of-pocket costs for AM, and that this may have unintended consequences where patients are admitted to gain access to this treatment. In addition, ESC noted that AM is currently being used in Australia by optometrists, indicating that its use may be wider than in-hospital only. ESC considered that this raised equity issues, in that patients should not be treated differently for the same condition if they are inpatients or outpatients, nor should they be treated differently if they consult a general practitioner, specialist, optometrist, nurse or podiatrist for the same condition.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

The NSW Tissue Bank would like to take the opportunity to respond on the outcome:

- Large randomised controlled studies are yet to be conducted for the three (3) populations. In the studies presented, the controlled studies show equal to better improvement with AM compared to current treatments; no study shows a negative or worse outcome. The NSW Tissue Bank is keen to support clinical groups to perform studies in this area but often the patient populations such as Stevens-Johnsons Syndrome are rare and difficult to conduct.
- The committee is correct in the heterogeneity of patient subpopulations. This is very much a circumstance where AM is being used across a lot of chronic diseases as there are few other treatments with high efficacy, or the treatments available are much more expensive than AM. Further studies will be able to support this benefit, but we reiterate that the AM treatment is invariably equal to or better than current standards across all groups.
- There is a discrepancy in the key points and discussion section of the ESC minutes regarding the long-term safety data for all populations. AM is a biological dressing which breaks down to be replaced by a patient's own tissue after 12 weeks; AMT usually breaks down in 3 weeks. As such, studies have not focussed on long-term

effects and safety but on the primary outcome - usually wound healing. Given the biological mechanism of AM, long term safety issues are not scientifically expected except for transmission of infectious agents that is mitigated by donor screening (medical and social history assessment), safety testing (serology, nucleic acid testing, micro sampling) and tissue processing (bioburden reduction measures).

- Cost of product- a 5cm² AM disc is costed for \$578.57, the most common preparation for ocular use. The committee noted the NHS utilises a 2x2cm² graft. This would cover the cornea alone. Most surgeons prefer the larger size due to the ability to select the best section for the transplant and ability to double or triple the layering on the ocular surface. The medical directors (ophthalmic surgeons) of the NSW Tissue Bank recommend the larger size be retained as it increases the utility of the tissue, we are not limited by tissue supply and the cost benefit of a smaller piece will be minimal as the major cost is tissue preparation. AM is not wasted by surgeons but the excess trimmed after complete coverage achieved.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)