MSAC Application 1801

Autologous Skin Cell Suspension for the treatment of acute burn wounds in paediatric and adult patients

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:
The proposed health technology will be used for patients with severe burns covering greater than 20 percent total body surface area (% TBSA) who have sustained deep partial-thickness (DPT) and/or full-thickness (FT) burns wounds for which skin grafting is indicated. The proposed health technology is the preparation and application of autologous skin cell suspension (ASCS), at the point-of-care (PoC), for definitive closure of burn wounds. This treatment is prepared in a laboratory, or by an autologous cell harvesting device (ACHD), using the patient's own skin cells, promoting epidermal regeneration while reducing the amount of donor skin harvested for skin grafting needed for burn wound treatment.

The ASCS can be applied alone for DPT burns with confluent dermis, or as an adjunct to widely meshed split-thickness skin grafts (STSG) for FT burn wounds.

The treatment with ASCS is intended to be used for acute burn injuries of the skin, which occur when some or all the different layers of cells in the skin are destroyed by a hot liquid, a hot solid, or a flame (World Health Organisation 2023). The wound resulting from a burn injury is characterised by an inflammatory reaction leading initially to local oedema from increased vascular permeability, vasodilation and extravascular osmotic activity (Arturson 1980). It is caused by direct effect of the burn agent on microvasculature and resultant chemical inflammatory mediators (The Royal Children's Hospital Melbourne 2023). Burns are classified in three ways: depth, % TBSA affected and location on the body.

Estimating burn depth allows clinicians to plan treatment for patients to mitigate risk of scarring. Burn depths are categorised as superficial, superficial partial-thickness, deep partial-thickness (DPT) and full-thickness (FT) (Children's Health Queensland Hospital and Health Service 2021).

Deep partial thickness burns

DPT burns affect both the epidermis (outer layer of skin) and a significant portion of the dermis (reticular dermis) (Warby and Maani 2023). These burns are more severe than superficial partial-thickness burns but do not extend into the full thickness of the skin as FT burns do. In DPT burns, there is a marked decrease in blood flow making the wound very prone to conversion to a deeper injury and to infection.

DPT burns appear red or white with a waxy texture (NSW Statewide Burn Injury Service 2020). However, the appearance of the deep dermal burn changes dramatically over the next several days as the area of dermal necrosis along with surface coagulated protein turns the wound a white to yellow colour. These burns often result in scarring, and without proper care, there is a risk of developing contractures which is described as tightened skin that restricts movement. These wounds can convert to FT wounds if uncontrolled infection occurs or if blood flow to the tissues is compromised. A DPT burn injury of the hand, face, neck, or any joints can affect function.

These burns can heal on their own in typically over 3 to 9 weeks, however, will do so with severe scarring including contracture, and loss of function. If DPT burns are not anticipated to be healed by 3 weeks, surgical excision and skin grafting are commonly used to achieve definitive closure. This typically occurs no later than day 10 – 14 post injury.

Full-thickness burns

FT burn injuries destroy both the epidermis and dermis, producing irretrievable skin loss. Therefore, unless they are small in size (e.g., the size of a quarter or smaller), surgical intervention is necessary to restore the integrity of the skin (Warby and Maani 2023). A characteristic initial (pre-excision) appearance of the necrotic burn tissue is a waxy white colour. If the burn produces char or extends into the fat as with prolonged contact with a flame source, a leathery brown or black appearance can be seen along with surface coagulation veins. The burn wound is also painless (due to destruction of nerve endings) and has a coarse non-pliable texture to touch. FT burns cannot heal on their own and require surgical intervention (Burgess 2022). If left untreated, significant scarring, including contractures will occur.

Severe burns ≥ 20% total body surface area

Major burns are commonly defined as those affecting ≥20% TBSA and requiring surgical intervention for definitive closure. Severe large burns in this category often do not have uniform depth within the wound. This is often due to varying heat exposure to different parts of the body during the burn incident. Other factors affecting large burns are the anatomical differences as the thickness and composition of skin varies across different body parts. Additionally, protective factors such as clothing may leave some regions of the body more exposed during the incident.

Given the mixed depth nature of most large burns, the treatment approach often involves a combination of techniques. For the vast majority of ≥20% TBSA burns, ASCS is expected to be used in combination with STSGs. While less common, there may be cases where ASCS-only treatment is appropriate for certain areas of the burn, for DPT regions.

Based on the current clinical algorithm, the intended population for this application is adult and paediatric patients that are considered to require skin grafting for definitive closure of wounds sustained following a burn injury. ASCS treatment is intended to be used in conjunction with minimal STSGS on patients that present with DPT and/or FT burns. Additionally, the main characterisation for the intended population would also be for patients that have sustained major burns described as ≥20% TBSA who have mixed depth burns.

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Both DPT and FT burns are serious injuries that require urgent medical attention. They often necessitate specialised care in a burn unit, especially if large body surface areas are involved. Treatment typically involves careful wound management, pain control, and often surgical interventions like skin grafting to promote healing and minimise complications such as infection.

The proposed eligible patients are adults/paediatric patients with burns in ≥20% TBSA. The process for being considered eligible for surgical intervention using ASCS +/- STSGs involves initial assessment in the emergency department (ED), followed by referral to a burn unit. Here, burn depth and TBSA are evaluated. Where simpler methods of burn wound closure are insufficient, such as healing by secondary intention or use of negative pressure wound therapy (NPWT), a decision for surgical intervention is made. Early excision and grafting are considered to be the most appropriate management for severe burn injuries (Braza and Fahrenkopf 2023). This is for a multitude of reasons, including earlier wound closure and better aesthetic outcomes, in addition to reduced complications (Braza and Fahrenkopf 2023).

Emergency assessment and management of major burns

Burn injuries should be managed as a trauma case requiring primary and secondary survey (NSW Statewide Burn Injury Service 2019). Initial first aid is prompted to stop the burning process and cool the wound. Proper first aid will prevent further death of the zone of stasis. The approach to handling severe burns differs throughout the different States and Territories in Australia. Guidelines for patient management derived from the NSW Burn Injury Service, Children's Health Queensland Hospital, and The Royal Children's Hospital Melbourne are described here (NSW Statewide Burn Injury Service 2019, Children's Health Queensland Hospital and Health Service 2021, The Royal Children's Hospital Melbourne 2023).

The guidelines for emergency assessment and management of severe burns recommend using primary survey known as the ABCDE approach. This includes airway and cervical spine protection, breathing and ventilation, circulation and haemorrhage control, disability and neurological assessment, exposure and environmental control, fluid resuscitation, and management of pain relief (NSW Statewide Burn Injury Service 2019). All Australian Major Burn Units have formal referral processes for assessing, and if required, accepting referrals from other hospitals.

Assessment of Total Body Surface Area

The 'Rule of Nines' divides the body surface into areas of 9% or multiples of 9%, except for the perineum which is estimated at 1%. This allows the extent of the burn to be estimated with reproducible accuracy. Additionally small burns may be estimated by using the palmar surface (fingers and palm) of the patient's hand, which approximates to 1% body surface area (NSW Statewide Burn Injury Service 2019).

Assessment of burn depth

Burns are dynamic wounds, and it is difficult to accurately estimate the true depth and extent of the wound in the first 48-72 hours. Furthermore, most burn wounds are not a homogenous depth. However, to assess burn depth several aspects are assessed including capillary refill, consideration of prompt first aid, and source of injury. Table 1 summarises the appearance and assessment of the depth of the burn wound.

Table 1. Assessment of burn depth

Depth	Colour	Blisters	Capillary refill	Healing	Scarring
Partial-thickness/ Mid-dermal	Dark pink	Present	Sluggish >2 sec	2–3 weeks Grafting may be required	Yes (if healing >3wks)
Partial-thickness/ Deep dermal	Blotchy red / white	+/–	Sluggish >2 sec / absent	Grafting required	Yes
Full-thickness	White / brown / black (charred) / deep red	No	Absent	Grafting required	Yes

Source: NSW Statewide Burn Injury Service, 2019 (NSW Statewide Burn Injury Service 2019)

Difference between Paediatric and adult Patients

The principles of managing burns in children are similar to those for adults. Burn depth assessment in a child is often more difficult due to their thinner skin, and colour changes in burned skin are not always the same as in adults. Children require burns resuscitation fluid at a lesser TBSA percentage than adults (10% in children as opposed to 20% in adults) (Sharma and Parashar 2010). Small children are more likely to become hypoglycaemic, and maintenance fluids should incorporate glucose replacement in children <20kgs.

Operative management of patient is considered (eligibility of for proposed technology and skin grafting)

Each wound is assessed individually by surgeons to determine a wound closure solution that is ideally the simplest, the fastest, and with the best functional and aesthetic outcome. Split thickness skin grafts (STSGs) are indicated when simpler methods of wound closure will not suffice, such as healing by secondary intention or negative pressure wound therapy (Braza and Fahrenkopf 2023).

A skin graft is often required when a burn is either DPT or FT in depth (if the wound will not heal within two to three weeks) to improve mobility and long-term appearance of scar. Prerequisites of skin grafting are availability of donor sites and clean, well-vascularised (debrided) recipient sites (Braza and Fahrenkopf 2023).

Provide a rationale for the specifics of the eligible population:
The % TBSA burned and burn depth are the best predictors of morbidity and mortality and determine the treatment steps. Use of ASCS results in significantly less donor skin harvesting. Availability of donor skin is often a limitation for use of STSGs in large TBSA burn injuries, as repeated harvesting of the same donor site is required, leading to increased procedures and hospital length of stay (LOS). In paediatric patients, using skin grafts for wound coverage is especially limited by donor site availability for TBSA burns (Wala 2023). FT burns penetrate completely through the dermis and hypodermis. This layer is slow to heal without surgical intervention and necrotic tissue should be excised, which creates extensive scar formation that often requires reconstruction and surgery (Anyanwu and Cindass 2023).

Are there any prerequisite tests?
Yes/No

Are the prerequisite tests MBS funded?
Yes/No

Please provide details to fund the prerequisite tests:
The management of patient burn wounds is generally guided by specialist clinician decision or institutional preference. Hence specialist clinicians consider many different factors in their decision-making process to determine treatment selection prior to surgery.

Intervention

Name of the proposed health technology:
Use of ASCS for definitive closure of burn wounds ≥20% TBSA.

ASCS are dermal and epidermal cells, delivered as a suspension via spray or droplet form, to a wound. In the past four decades, ASCS have progressed remarkably from serial keratinocyte cultures to currently available commercial ASCS formulations (Bairagi 2021).

The RECELL® ACHD is the only commercially available technology for creating ASCS, however there are other methods to produce cell-based treatments for burns and wounds. That is through other enzymatic disaggregation protocols developed by research groups but performed in a laboratory (Esteban-Vives 2018). However, ASCS prepared by other methods in laboratories do not encompass the proposed service via the RECELL® ACHD as:

1) RECELL® ACHD is the only technology that can create ASCS to provide this service at PoC for patients. The service using the ACHD requires minimal specialised equipment compared to the laboratory setup needed for other protocols to create ASCS.

2) ASCS produced by RECELL® ACHD is suitable for both acute and delayed treatment phases, while ASCS produced in a laboratory are limited to delayed use due to production time; and

3) ASCS prepared by RECELL® ACHD has TGA and FDA approval and is supported by randomised clinical trials demonstrating its efficacy and safety. Other enzymatic disaggregation methods created by research groups lack regulatory approval and robust clinical evidence.

Describe the key components and clinical steps involved in delivering the proposed health technology:
The ASCS is prepared by the proprietary technology RECELL® ACHD, a single-use autograft-sparing device used in the operating room at the time of surgery and applied to wound site to achieve definitive closure of acute burn wounds. The ACHD enables a thin split-thickness skin sample to be processed to produce an ASCS for immediate delivery onto a prepared wound bed (AVITA Medical Americas 2024).

The ASCS prepared using this method contains a mixed population of cells, including keratinocytes, fibroblasts, and melanocytes, obtained by disaggregation of the skin sample. The preservation of melanocytes is important for restoring natural pigmentation to the recipient area. Additionally, sub-populations of keratinocytes critical for re-epithelialisation have been identified in the ASCS including basal keratinocytes, suprabasal keratinocytes, and activated keratinocytes (AVITA Medical Americas 2024).

The ACHD consists of a stand-alone, battery-operated unit, a proprietary enzyme solution, buffer solution, sterile surgical instruments, and spray applicators to be used at the PoC, with no culturing processes involved in the procedure (Holmes Iv 2018).

To optimise treatment, the ASCS should only be applied to a clean, vascularised wound bed with no remaining necrotic tissue, as would be the case for a conventional autologous skin graft. This can be achieved with either dermabrasion using a rotating diamond-head burr, sharp dissection or other alternative techniques, depending on the nature of the wound (AVITA Medical Americas 2024). The ASCS must not be used in the presence of infection, as initial re-epithelialisation and long-term viability are highly dependent on the absence of infection. Prophylactic antibiotics may be prescribed if the patient is at risk of contamination or infection. Wound swabs for up-to-date microbiology are recommended 48 hours prior to the planned surgery (AVITA Medical Americas

2024). Steps in preparing the ASCS by the ACHD are detailed in Attachment (Instructions for use document by Avita Medical) and outlined below (AVITA Medical Americas 2024).

Obtain skin sample

When a donor site is chosen, it is essential that the site is clean, of appropriate depth, and shows no evidence of surrounding cellulitis or infection. From the identified healthy donor site on the patient, a small, split thickness skin sample 0.15 to 0.20 millimetres (mm) in thickness can be harvested using a dermatome. The size of the skin sample required is based on the treatment area. When using the ACHD, a 1 cm^2 skin sample produces 1 mL of ASCS, which can treat up to 80 cm^2 (up to 1:80 expansion). Achieving skin closure in a burn wound typically requires a donor sample at or near a 1:1 ratio of STSG to the treatment site (recipient site). To minimise donor site requirements, STSGs may be meshed at a ratio of 3:1 recipient site to donor skin, however meshed grafts often result in poor cosmetic outcomes. Treatment with ASCS can help cover remaining areas of skin to counteract the mesh patterned appearance from use of meshed STSGs.

Prepare ASCS

After obtaining the skin sample, it is placed into a well in the ACHD which contains a proprietary formulation of enzyme heated to 37°C. The skin sample(s) is/are incubated for 15 to 20 minutes in the proprietary enzyme solution, during which the extracellular matrix is broken down and the intercellular bonds that constrain the skin cells are digested. Once the action of the enzyme has been achieved, the sample is removed and rinsed in buffer solution.

To begin mechanical disaggregation, one sample at a time is placed on the tray. A small amount of clean buffer solution is placed on the skin sample and the sample is mechanically scraped to further disaggregate the cells. Once mechanical disaggregation is complete, as indicated by the epidermal layer being fully scraped away into suspension and the dermis nearly disintegrated, the cells are suspended in a predefined volume of buffer solution and then filtered into the cell strainer. The filtered cell suspension is then aspirated into the applicator syringe.

Apply ASCS

The ASCS can be applied directly to DPT wounds or in combination with meshed autografts for FT wounds. The ASCS can also be sprayed onto the donor site to increase healing in the area.

The ASCS can be sprayed or dripped onto the wound bed dependent on the volume of cell suspension to be applied and size of wound bed (spray application can only be used for ≥2 ml of cell suspension in the syringe). After application of the ASCS, the wound is covered with a non-adherent, non-absorbent, small pore dressing. Secondary dressings that are moderately absorbent, minimally adherent, low shear, and readily removable (e.g., petrolatum gauze) should be placed over the primary dressing. Additional absorbent gauze for padding, as well as a crepe or compression bandages, may be used (AVITA Medical Americas 2024).

Identify how the proposed technology achieves the intended patient outcomes:
A donor site, where surgeons harvest skin for grafting, can cause significant physical and psychological distress to patients, especially in cases of extensive burns requiring STSGs. Patients often report more pain, pruritus, and discomfort at the donor site than at the grafted area, yet this morbidity is frequently underestimated (Asuku 2021). There's a lack of comprehensive research on donor site outcomes and their impact on patients' overall well-being and quality of life. Understanding the true burden of donor sites necessitates shift in burn care to include innovative treatments that would reduce the use of STSGs and address the associated morbidities (Asuku 2021).

Treatment using ASCS achieves intended patient outcomes by minimising donor skin requirements during the acute treatment phase and definitive closure of the burn wound. Quality of life following burn injuries is profoundly affected by pain and scarring at both the donor and recipient sites and is also influenced by treatment variables such as time to wound closure. Early intervention decreases scarring, pain, and the risk of infection in burn wounds. Requiring less donor skin not only shortens the waiting period for obtaining healthy skin from patients but also reduces the need for subsequent procedures to harvest donor skin in large TBSA burns.

To achieve definitive closure of wound, application of ASCS prepared from patient skin using the ACHD during acute treatment phase occurs. The ASCS has been shown to contain viable cells including the following phenotypes essential for epidermal regeneration and pigmentation (Tenenhaus and Rennekampff 2012, Wood 2012b). Those specifically are:

- Keratinocytes – The main cell of the epidermis, keratinocytes are responsible for providing the barrier function of skin. During healing, keratinocyte migration is limited to the edge of the wound, and is driven by multiple factors including the absence of neighbour cells, local release of growth factors, and upregulation of cellular receptors (Ter Horst 2018) (Gushiken 2021).
- Fibroblasts – Dermal fibroblasts deposit new extracellular matrix proteins and are stimulated by keratinocytes to synthesise growth factors, which in turn stimulate keratinocyte migration and proliferation (Ter Horst 2018) (Werner 2007).
- Melanocytes – Melanocytes produce melanin which is responsible for normal pigmentation (Ter Horst 2018).

The keratinocytes migrate into the wound bed and behind the migrating tongue, keratinocytes begin to proliferate to ensure an adequate supply of cells for wound closure (Gushiken 2021). Fibroblasts at the margin migrate into the wound bed and synthesise and deposit extracellular proteins necessary for connective tissue formation to support cellular ingrowth (Rittié 2016) (Martin 1997). The crosstalk between keratinocytes, fibroblasts, endothelial, and immune cells are critical for wound healing. Stimuli for the migration and proliferation of cells during re-epithelialisation are orchestrated by growth factors, chemokines, and cytokines produced by these cell types (Rittié 2016). Furthermore, the absence of neighbouring cells at the wound margin also introduces signals that regulate and promote the sequence of healing (Rittié 2016).

Essentially, once the ASCS is applied to the wound bed, those cells provide signalling and multiply and spread throughout the wound to assist in definitive closure, resulting in quicker healing time, better repigmentation of wound and less scarring. Definitive closure is achieved with reduced donor site requirements, resulting in less donor site pain and scarring.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes/No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
AVITA Medical was granted trademark protection for use of the term RECELL® for the ACHD. The device has a proprietary enzyme component that is specialised for preparation of the ASCS. It is also possible to produce similar ASCS in a laboratory setting or delayed manner, however laboratory produced ASCS does not have pivotal clinical trial evidence demonstrating efficacy or the benefits from PoC treatment as demonstrated with use of the ACHD.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes/No

Provide details and explain:
Maximum coverage for one device is up to 1920 cm^2 from up to four skin sample sizes that are 6cm^2 each (24cm^2 in total). If applicable, multiple ACHDs may be required for larger TBSA burns, to cover the full surface of the wound.

If applicable, advise which health professionals will be needed to provide the proposed health technology:
The preparation of ASCS using the ACHD is to be done by an appropriately licensed and trained healthcare professional (AVITA Medical Americas 2024). Surgeons that would facilitate the use of ACHD would be burns and plastic surgeons, general surgeons and paediatric surgeons in burns units.

Harvesting of a thin sample of donor skin is carried out by the lead surgeon or delegated to another trained healthcare professional. Subsequently, the surgeon, or any adequately trained HCP in RECELL® ACHD can handle the enzymatic processing and mechanical disaggregation of skin cells. The application of ASCS is then administered by the surgeon or delegated to another trained healthcare professional.

Furthermore, the PoC nature of the device allows for the whole process to be carried out by clinicians, without input from specialised laboratory staff.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
Delivery of ASCS prepared using the ACHD should be applied under the supervision of the surgeon, with delegation of preparation/application steps to appropriately trained personnel.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
N/A

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes/No

Provide details and explain:
Health care professionals receive standardised training in the use of ACHD to administer ASCS.

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☐ Consulting rooms
☒ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☐ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes/No

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:
The appropriate comparator to achieve definitive wound closure is the use of autologous split-thickness skin grafts (STSGs) in the immediate or delayed treatment setting.

Immediate definitive wound closure

When surgical procedures are necessary to close a burn wound, STSGs are used for definitive closure for DPT and FT burn wounds. STSGs are a thin shaving of skin harvested from patients' own skin known as the donor site which includes the epidermal and dermal tissue and are performed in an operating theatre with the patient anaesthetised (NSW Statewide Burn Injury Service 2020). The donor skin (healthy skin) will be placed over the recipient site and will be joined up to the surrounding skin. In large % TBSA burns, multiple grafting procedures can be needed to harvest donor skin from the same site to completely cover the recipient site. For subsequent skin grafting procedures, waiting times for re-harvesting of donor skin is typically two weeks to let the original donor site heal. However, re-harvesting from donor sites is not ideal as there is a potential risk of donor site complication as dermis becomes thinner with each harvest (Kadam 2016). In all burn injuries, donor sites are frequently troublesome for patients and these wounds are a source of significant pain and are at a risk for infection, discoloration, and scarring.

When STSGs are used to close a smaller wound, sheet grafts are used, which require a 1:1 ratio of donor skin to graft site. However, techniques to expand the donor skin are used to reduce donor site requirements such as sheet, meshed and meek STSGs. Meshed STSGs are used in larger TBSA burns and are stretched using a device that perforates (slits) the harvested skin to be extended (~2-3 times). However, larger meshing ratios results in poor cosmetic results at the treatment site.

Meek STSGs allows for harvesting and transferring of autologous tissue in which small portions of skin can be harvested and expanded to treat larger areas.

Overall, in the immediate treatment phase setting, STSGs are limited by the availability of healthy donor skin and can result in non-uniform cosmetic results where expansion techniques are used (Biswas 2010, Kadam 2016).

Delayed wound closure

Based on clinician judgement, skin substitute products are used in wound closure surgery prior to skin grafting to allow for regeneration of new tissue after debridement (Personal communications with A/Prof Warwick Teague and Professor Roy Kimble, 2023).

Failure of engraftment is typically the result of inadequate recipient site excision, shear stress or wound infection. Definitive coverage following large burns rapidly exhausts available donor skin and must, therefore, be performed in stages. When the excised burned area exceeds the available donor skin, 'temporary coverage' is needed to both permit donor site re-epithelialisation in anticipation of re-harvest and to avoid the complications of open excisions (Jeschke 2020). Temporary closure using skin substitutes are also indicated for rapid wound coverage in cases of less vascularised wound bed. They provide an increase in the dermal component of healed wound, reduce or remove inhibitory factors of wound healing, and can reduce inflammatory response and subsequent scarring. Hence skin substitutes provide temporary physiological closure usually for FT wounds after excision while awaiting autografting (Halim 2010).

Temporary skin substitutes include NovoSorb biodegradable temporising matrix (BTM), Biobrane and MatriDerm.

Definitive wound closure using skin autografting is typically performed as a subsequent procedure after optimal tissue regeneration has been achieved with skin substitutes. Therefore, STSGs are used in the delayed setting commonly for either:

1. Re-grafting following initial skin grafting: In cases where the initial skin grafting procedure was unsuccessful or insufficient, a second autografting procedure may be necessary to achieve complete wound closure.
2. Delayed closure after temporary skin substitute use: When temporary skin substitutes have been applied to manage the wound initially, a follow-up procedure using STSGs is performed to provide definitive wound closure.

Currently, in some burn units in Australia, the service to create ASCS by the ACHD is performed in clinical practice to supplement traditional methods of treating acute DPT and FT burn wounds (Personal communications with Dr Suzanne Rea, 2023).

List any existing MBS item numbers that are relevant for the nominated comparators:

The MBS items relevant for nominated comparators are 46117, 46118, 46119, 46120, 46121, 46122 and 46123. These outline wound closure that require autologous skin grafting for definitive wound closure and other skin substitute products for temporising in the immediate treatment setting. Multiple MBS items are identified as they are defined based on TBSA of the burn wound. The selected MBS items specify burn wound TBSA from 20% to >80%. Table 2 outlines the various codes used and their description for TBSA ≥ 20%.

Table 2 Immediate definitive burn wound closure items for burn wounds ≥20% TBSA

Current items	Item Description	*TBSA	Fee
46117	Excised burn wound closure, if the defect area is *TBSA of total body surface and if the service: (a) is performed at the same time as the procedure for the primary burn wound excision; and (b) involves: (i) autologous skin grafting for definitive closure; or (ii) allogenic skin grafting, or biosynthetic skin substitutes, to temporize the excised wound; excluding aftercare, other than a service associated with a service to which item 46100 applies (H)	20% ≤ TBSA < 30%	$1,373.65 Benefit: 75% = $1,030.25
46118		30% ≤ TBSA < 40%	$1,726.50 Benefit: 75% = $1,294.90
46119		40% ≤ TBSA < 50%	$2,078.75 Benefit: 75% = $1,559.10
46120		50% ≤ TBSA < 60%	$2,430.40 Benefit: 75% = $1,822.80
46121		60% ≤ TBSA < 70%	$2,782.70 Benefit: 75% = $2,087.05
46122		70% ≤ TBSA < 80%	$3,170.50 Benefit: 75% = $2,377.90
46123		TBSA ≥ 80%	$3,550.75 Benefit: 75% = $2,663.10

Additionally, MBS items 46134 and 46135 is relevant for specifying the use of skin grafting (split skin graft or other autologous tissue) during delayed definitive closure procedures where use of temporary skin closure products were placed in a previous procedure. The described MBS items specify burn wound TBSA from 20% and greater and are shown in Table 3

Table 3 Delayed definitive burn wound closure items for burn wounds ≥20% TBSA

Current items	Item Description	*TBSA	Fee
46134	Definitive burn wound closure, or closure of skin defect secondary to necrotising fasciitis, if the defect area involves *TBSA of total body surface, using autologous tissue (split skin graft or other) following previous procedure using non-autologous temporary wound closure, excluding aftercare (H)	20% ≤ TBSA < 30%	$2,260.45 Benefit: 75% = $1,695.35
46135		TBSA ≥ 30%	$3,550.75 Benefit: 75% = $2,663.10

Please provide a rationale for why this is a comparator:

STSGs (sheet, meshed or meek) are standard clinical practice for definitive wound closure of extensive FT and DPT burn wounds that otherwise would leave a disfiguring scar if left to heal by secondary intention. This approach requires harvesting large areas of donor skin from unaffected areas of the patient's body, particularly when treating large burn wounds. Donor sites from STSGs lead to additional complications including pain, prolonged healing times and further scarring.

Clinical evidence and expert opinion confirm that use of ASCS will reduce donor skin requirements for definitive burn wound closure. Therefore, addressing an unmet clinic need by reducing donor site morbidity, waiting times and hospital LOS. Additionally, the use of ASCS prepared by the ACHD would also improve the appearance of using meshed STSGs by filling in their interstices (Personal communications with A/Prof Warwick Teague and Professor Roy Kimble, 2023).

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☐ None *(used with the comparator)*
☒ Displaced *(comparator will likely be used following the proposed technology in some patients)*
☐ Partial *(in some cases, the proposed technology will replace the use of the comparator, but not in all cases)*
☐ Full *(subjects who receive the proposed intervention will not receive the comparator)*

Please outline and explain the extent to which the current comparator is expected to be substituted:

In mixed depth burns with limited donor skin availability, treatment with ASCS is expected to supplement the use of STSGs to reduce the amount of autografting required to close the wound. Therefore, the current comparator is expected to be partially displaced by use of ASCS.

Given the mixed depth nature of most large burns ≥20% TBSA, the treatment approach will involve a combination of techniques across the wound. For most burn wounds ≥20% TBSA, some areas of the wound would receive STSG + ASCS and some areas just ASCS. This allows for treatment of varying burn depths within the same wound and optimisation of limited donor sites in major burn cases. Therefore, some use of STSGs would be displaced by ASCS.

Outcomes

(Please copy the below questions and complete for each outcome)

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator): (please select your response)

☒ Health benefits
☒ Health harms
☒ Resources
☐ Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

<u>Efficacy outcomes</u>

- Recipient site healing
- Donor site size and healing

<u>Safety outcomes</u>

- Adverse events (AEs) and serious adverse events (SAEs)
- Device-related AEs
- Graft loss
- Infection
- Scar formation
- Delayed healing/wound assessment
- Allergic response to trypsin

<u>Patient relative outcomes</u>

- Pain and visual appearance in recipient site and donor site

The two pivotal trials (CTP001-5 and CTP001-6) investigated the safety and effectiveness of RECELL® device when used alone and in conjunction with widely meshed STSGs.

A Comparative Study of RECELL® device and Autologous Split thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries (DPT Burns) (Holmes Iv 2018)

The co-primary effectiveness endpoints were (1) non-inferiority of the incidence of RECELL® ACHD treated recipient site (burn injury) wound closure (≥95% re-epithelialisation) at 4 weeks compared to that observed in conventional skin grafting treated (Control) recipient sites and (2) superiority of donor site healing (100% re-epithelialisation) at 1 week was demonstrated for RECELL® ACHD versus Control. Safety assessments included evaluation of delayed healing, infection, allergic response to trypsin, wound durability, scarring outcomes, device-related AEs, and SAEs. This involved scar ratings of both the treatment site and donor site (for both ASCS or STSG procedures) through 52 weeks post treatment.

RECELL® Combined with Meshed Skin Graft for Treatment of Acute Burn Injuries (Full-thickness and Mixed-Depth Burns)(Holmes 2019)

The first co-primary endpoint was non-inferiority of the incidence of complete wound closure for RECELL® ACHD treated burn wounds (treated with the combination of ASCS and widely meshed autografts) compared to that observed in Control-treated burn wounds (conventional autograft) by 8 weeks after treatment, as assessed by a blinded evaluator. Complete wound closure was defined as complete skin re-epithelialisation without drainage, confirmed at 2 consecutive study visits at least 2 weeks apart. The second co-primary end was superiority in donor skin expansion (and therefore relative reduction in donor area requirements for RECELL® versus Control treatment), as assessed by the Geometric Mean Ratio (GMR) of the RECELL®:Control autograft expansion ratios. Acute healing and pain outcomes were evaluated through 12 weeks. Pain, healing, durability, and scar outcomes were evaluated in the longer-term follow-up visits conducted at 24, 36, and 52 weeks.

Other hospital related outcomes and considerations

Additional outcomes are retrospectively reviewed in Compassionate Use cohort (CTP004) and Continued Access (CTP001-7/CTP001-8)

- Hospital length of stay
- Number of autograft procedures

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):
RECELL® ACHD is currently utilised in the two burns units in Western Australia and is funded via State Health Department budgets (Personal communications with Dr Helen Douglas and Dr Suzanne Rea, 2023).

Outside of Western Australia and burns indications, RECELL® ACHD is also utilised in scar and pigmentation cases typically in private practice of dermatologists or plastic surgeons. These procedures are paid out of pocket by the patient.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

The proposed item and descriptor below are an amendment to item 46117. This same amendment will be carried over to the items 46118 – 46123 for the.

MBS item number (where used as a template for the proposed item)	Items 46117 to 46123 is used as a template for the proposed item descriptor
Category number	Category 3
Category description	Therapeutic Procedures
Proposed item descriptor	Excised burn wound closure, if the defect area is 20% ≤ TBSA < 30% of total body surface and if the service: (a) is performed at the same time as the procedure for the primary burn wound excision; and (b) involves: (i) Autologous skin grafting with or without autologous skin cell suspension for definitive closure; or (ii) Autologous skin cell suspension for definitive closure; or (iii) allogenic skin grafting, or biosynthetic skin substitutes, to temporize the excised wound; excluding aftercare (H)
Proposed MBS fee	$1,373.65 Benefit: 75% = $1,030.25
Indicate the overall cost per patient of providing the proposed health technology	$1,373.65 Benefit: 75% = $1,030.25
Please specify any anticipated out of pocket expenses	Purchasing of the RECELL autologous cell harvesting device
Provide any further details and explain	The device itself is not funded on the prescribed list, hence its use will be dependent on the purchasing of the device through the States health department budgets.

Additionally, amendments to delayed definitive closure procedure is outlined below for item 4613. The same changes will be made for the proposed item descriptor in item 46135.

MBS item number (where used as a template for the proposed item)	Items 46134 and 46135 is used as a template for the proposed item descriptor
Category number	Category 3
Category description	Therapeutic Procedures
Proposed item descriptor	Definitive burn wound closure, or closure of skin defect secondary to necrotising fasciitis, if the defect area involves 20% ≤ TBSA < 30% of total body surface, using autologous tissue (split skin graft or autologous skin cell suspension or other) following previous procedure using non-autologous temporary wound closure, excluding aftercare (H)
Proposed MBS fee	$2,260.45 Benefit: 75% = $1,695.35
Indicate the overall cost per patient of providing the proposed health technology	$2,260.45 Benefit: 75% = $1,695.35
Please specify any anticipated out of pocket expenses	Purchasing of the RECELL autologous cell harvesting device
Provide any further details and explain	The device itself is not funded on the prescribed list, hence its use will be dependent on the purchasing of the device through the States health department budgets.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
Due to the heterogenous nature of burn injuries, the clinical management algorithm can vary significantly between patients. Furthermore, across Australia the burn management algorithm is individualised across each burn unit.

In general, burn injuries are managed as trauma cases requiring primary and secondary survey to identify immediate life threats (NSW Statewide Burn Injury Service 2019). That is assessing patient's airway, breathing, circulation, signs of disability and then exposure. To assess the extent of burns, TBSA (via Lund & Browder Chart) and burn depth are evaluated. Since burns are dynamic wounds, it is difficult to accurately estimate the true depths and extent in the first 48-72 hours. Appropriate first aid given within the first 3-hour time frame from initial burn and fluid management is essential for TBSA ≥10% in paediatric patients or TBSA ≥20% in adults (NSW Statewide Burn Injury Service 2019, Children's Health Queensland Hospital and Health Service 2021, The Royal Children's Hospital Melbourne 2023).

For major burns, key laboratory assessments that may be conducted are evaluation of haemoglobin, electrolytes, blood glucose levels, group and hold and venous blood gas.

Analgesia is required for pain management, especially during the assessment, cooling, dressing and mobilisation phase (The Royal Children's Hospital Melbourne 2023). Appropriate initial choice includes intranasal fentanyl or IV morphine (The Royal Children's Hospital Melbourne 2023).

The burns wounds are then cleaned and debrided of any clear loose/blistered skin. Dressing products are highly individualised dependant on burn unit, depth of wound, and the expected duration required before removal or wound review. Surgical intervention and skin grafting is considered where it is highly unlikely for burn wounds to heal on its own in an appropriate time frame (NSW Statewide Burn Injury Service 2020).

Surgical intervention can include debridement, placing temporary skin substitutes and skin autografting. Firstly, debridement and cleaning of recipient site from necrotising tissue is done in theatre. ACHD would then be considered for use given donor site availability for immediate wound closure procedures.

In some cases, temporary wound closure products such as skin substitutes are employed before skin autografting for extensive burns to facilitate the growth of the neo dermis.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

Yes/No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
Prior to surgical intervention, clinicians will assess burn wounds individually and consider the most appropriate burn wound management pathway despite the technology used in theatre. If considered clinically appropriate, ASCS will be used to reduce donor site requirements in conjunction with or without meshed STSGs based on depth of burn.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
Meshed STSGs are used in conjunction with ASCS for definitive closure of FT burns.

Explain what other healthcare resources are used in conjunction with the comparator health technology:
The same set of healthcare resources are used for both ASCS or STSGs.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
A reduction in utilisation of healthcare resources is expected with the use of ASCS in conjunction with or without STSGs. Reduced donor site harvesting minimises time to recovery, inpatient resource use, and number of subsequent autografting procedures and dressing changes (Kowal 2019, Foster 2021).

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
The clinical management algorithm is not expected to materially change after the use of the proposed health technology.

Initial dressings post-surgery

After applying ASCS, the wound is required to be covered with a non-adherent, non-absorbent, small pore dressing. The dressing may be fixed to the wound with surgical glue, sutures, or staples, as necessary. Use of known cytotoxic medication (for instance, silver sulfadiazine) is contraindicated for areas treated using ASCS. Secondary dressings that are moderately absorbent, minimally adherent, low shear, and readily removable (e.g., petrolatum gauze) should be placed over the primary dressing. Additional absorbent gauze for padding, as well as a crepe or compression bandages, may be used.

Subsequent dressings

The outer dressings and compression bandages may need to be changed if exudate levels are high; however, the primary dressing should remain in place for 6-8 days, or as clinically indicated. The primary dressing will loosen and lift as new epidermis is formed and should not be removed from areas to which it is still adhered.

Once the primary dressing has been removed, an appropriate protective dressing should be applied to protect the wound surface. Use of a sterile greasy or paraffin gauze dressing are necessary until any blistering or open areas resolve to prevent newly regenerated epidermis adhering to dressing and causing injury upon dressing removal.

Any signs or symptoms of infection or impaired healing at this stage should be recorded and addressed.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
After use of the comparator health technology, secondary dressings are removed to observe skin graft progress and to provide appropriate management for level of healing. Usually this is done 3 to 7 days post operation. Clinicians will reassess the wound and plan whether regrafting is required. Sometimes regrafting is required when the initial graft fails or there is insufficient for skin during the initial surgery to cover all burn areas.

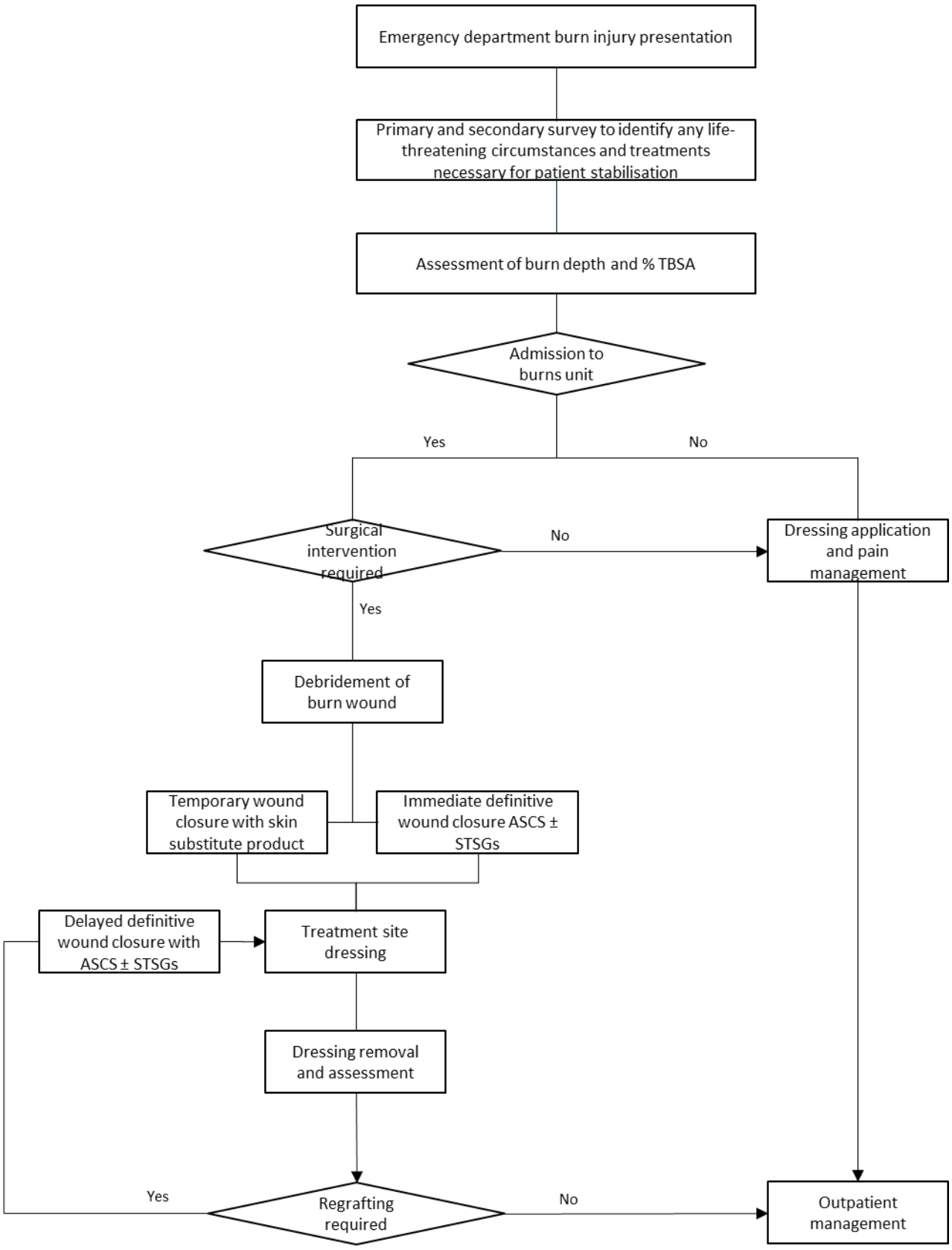
If subsequent procedures are not necessary, the graft site should be redressed for moist wound healing to any open areas. Depending on the size and depth of burn wound, time to healing can vary quite significantly and will require several dressing changes with sedation. Once graft is healed and there are no signs of moist areas, outpatient scar management is considered.

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
ASCS +/- STSGs will result in a reduction of healthcare resources after treatment. Depending on the severity of the burn injury and the duration of healing, the post-surgery care can vary considerably. Treatment with ASCS is expected to lead to a reduction in hospital LOS by reducing the number of subsequent autografting procedures required to close extensive burn wounds (Kowal 2019). With less operations required this can also result in a reduction of the amount of dressing changes required. Additionally, post-scar management (i.e., the use of lasers and other scar management therapy) can be reduced (Wood 2012a).

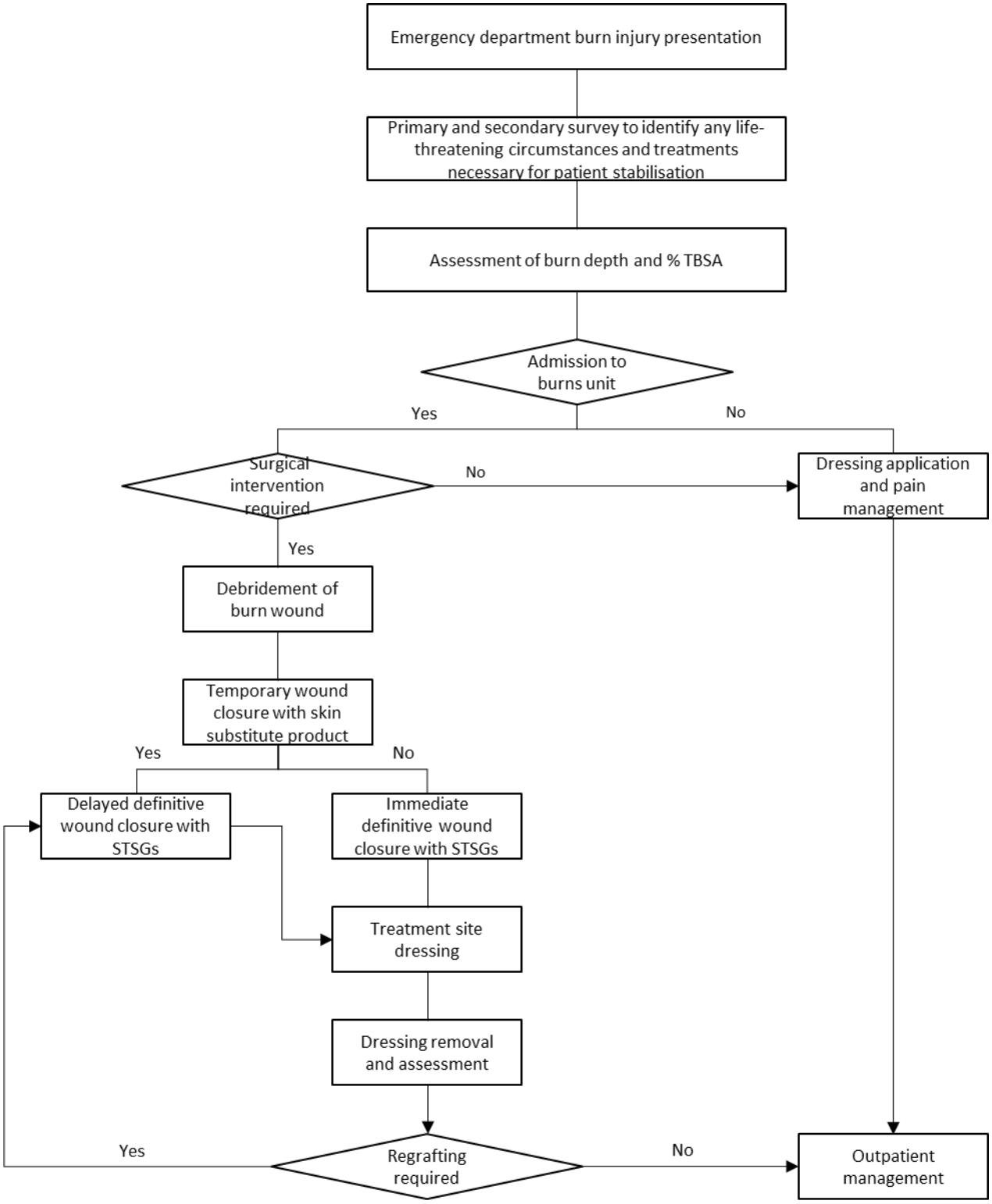
Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

Please ensure that the diagrams provided do not contain information under copyright.

With proposed health technology



Without proposed health technology



Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Overall, use of ASCS ± STSGs for treatment of burn wounds ≥ 20% TBSA is superior in reducing donor site requirements vs STSGs alone.

Specifically, use of ASCS + STSGs for treatment of burn wounds is superior in reducing donor site requirements vs STSGs alone in FT burn sites. Additionally, treatment of burn wounds is superior in reducing donor site requirements using ASCS vs STSGs alone in DPT burn sites.

Treatment using ASCS + STSGs is non inferior to STSG for recipient site healing and scar outcomes in FT burns. Treatment using ASCS alone is non inferior to STSG for recipient site healing and scar outcomes in DPT burns.

Therefore, ASCS is beneficial in facilitating definitive closure of burn wounds by reducing donor site morbidity without compromising important clinical outcomes associated with wound healing and long-term scar appearance.

The overall claim is supported by two prospective multi-centre, randomised clinical studies which were conducted in the US under an investigational device exemption (IDE) in a total of 131 subjects. Both studies evaluated the safety and effectiveness of RECELL® ACHD for treatment of acute burn wounds. In both studies (CTP001-5 and CTP001-6), use of ASCS prepared by the ACHD significantly minimised the amount of donor skin required, by 97% for DPT burns and 32% for mixed depth burns (inclusive of FT) when used in combination with STSG. The incidence of complete wound healing at week 4 was 97.6% in the RECELL® ACHD treated sites and 100% in the control autografting sites with no major differences observed in the healing process for DPT burns. Confirmed recipient site closure by week 8 was 92.3% for ASCS vs 84.6% for the STSG recipient sites in FT burns.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
The proposed technology would be utilised where the requestor would seek to reduce burden of autologous skin harvesting associated with conventional skin grafting alone.

Identify how the proposed technology achieves the intended patient outcomes:
ASCS for the treatment of burn wounds achieves intended patient outcomes of through improvement of patient outcomes by reducing the amount of donor skin needed to definitively close the burn wound without compromising on healing and scarring outcomes. Therefore, use of the ASCS through the intrinsic regenerative capacity of isolated cells also improved the pain and morbidity associated with donor sites in traditional STSGs.

For some people, compared with the comparator(s), does the test information result in:
A change in clinical management? Yes/No

A change in health outcome? Yes/No

Other benefits? Yes/No

Please provide a rationale, and information on other benefits if relevant:
Treatment with ASCS results in a change in clinical management, health outcomes and additional benefits. Other benefits have been investigated in multiple observational studies and economic models (Wood 2012a, Lim 2014, Bairagi 2019, Kowal 2019, Foster 2021, Carter 2022, Carson 2023). Outcomes examined include hospital LOS and number of autografting procedures required for definitive closure. These outcomes also influence other hospital resource allocations, such as the incidence of infectious complications, blood product usage, analgesic costs, need for pressure garments and likelihood of graft loss (Lim 2014). Moreover, early intervention with ASCS for definitive wound closure can reduce outpatient procedural costs such as the need for costly scar wound management and rehabilitation services (Wood 2012a).

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator? (please select your response)
☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
Treatment with ASCS is done at PoC using the ACHD. Use of the ACHD does not impact procedural time. This is because harvesting of the skin sample and enzymatic processing of the cells is done simultaneously to wound debridement or other skin autografting that is required.

However, purchasing of the ACHD which is a single use device will increase the resource costs during a single index procedure.

When comparing ASCS +/- STSG vs STSG alone over the course of an entire hospitalisation of a patient with severe burns, the use of the ASCS treatment will reduce hospital LOS and resources needed for definitive burn wound closure (Kowal 2019). This will be demonstrated in the cost effectiveness model through number of subsequent procedures required to treat the burn wound with the addition of ASCS.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	Multicentre randomised clinical trial Standard of care controlled and within-subject controlled No masking of treatment. The participant and blinded evaluator were not told which treatment area received which procedure (RECELL® or Control).	Study CTP001-5 NCT02380612 A Comparative Study of the ReCell® Device and Autologous Split Thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries	A prospective study was conducted to evaluate the clinical performance of RECELL® vs 2:1 meshed STSG (control). Number of subjects was 101, between 18 and 65 years of age with 1% to 20% TBSA acute, DPT thermal burn that required autografting for definitive closure.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6097595/#CIT0006	24 May 2018
2.	Multicentre randomised clinical trial Standard of care controlled and within-subject controlled No masking of treatment. The participant and blinded evaluator were not told which treatment area received which procedure (RECELL® + STSG or Control).	Study CTP001-6 NCT02380612 Demonstration of the safety and effectiveness of the RECELL® System combined with split thickness meshed autografts for the reduction of donor skin to treat mixed depth burn injuries	A prospective clinical trial was conducted with 30 subjects ≥ 5 years of age with 5-50% TBSA to evaluate RECELL® in conjunction with a skin graft meshed more widely than the control (ACHD + 3:1 STSG vs a 2:1 STSG, or ACHD + 4:1 STSG vs 3:1 STSG, or ACHD + 2:1 STSG vs 1:1 STSG) for the treatment of mixed-depth burns, including FT.	https://www.sciencedirect.com/science/article/pii/S0305417918308830?via%3Dihub	19 Dec 2018
3.	Prospective, interventional, study	Study CTP004 NCT02992249 Prospective Evaluation of the ReCell® Autologous Cell Harvesting Device For Specific Compassionate Use Cases	This study initiated a self-managed Expanded Access program for AVITA Medical and RECELL®. Compassionate use was for patients (n = 100) who did not qualify for pivotal trials (CTP001-5 and CTP001-6) who had life-threatening wounds requiring grafting for closure.	N/A	N/A

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
4.	Multicentre randomised clinical trial Standard of care controlled and within-subject controlled	CTP001-7 NCT02994654 CONTINUED ACCESS PROTOCOL: Demonstration of the Safety and Effectiveness of ReCell® Combined With Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries	The purpose of this is study to provide continued access to RECELL® following completion of protocol CTP001-6 in patients ≥ 5 years with a TBSA burn injury between 5 and 50% (inclusive). (n = 12)	N/A	N/A
5.	Prospective, multicentre, single-arm interventional study	CTP001-8 NCT03333941 Continued Access to the RECELL® Device for Treatment of Acute Burn Injuries	CTP001-8 was an amendment to the protocol CTP001-7. The change from the previous continued access protocol (CTP001-7) to this version is that this protocol is a single-armed observational study allowing for all eligible burn areas requiring autografting to be treated with ASCS as an adjunct to more widely meshed grafts. (n = 76)	N/A	N/A
6.	Retrospective analyses of compassionate use (CTP004) and continued access studies (CTP001-7, CTP001-8)	509 Evaluation of Autologous Skin Cell Suspension for Definitive Closure of Extensive Burn Injuries in Adult Population	The purpose of this study is to present preliminary data on the outcomes for patients ≥18 years with life threatening, >50% TBSA, burn injuries treated with the combination of meshed STSGs and ASCS (n = 22).	https://doi.org/10.1093/jbcr/irz013.401	8 Mar 2019

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
7.	Retrospective analyses of compassionate use (CTP004) and continued access studies (CTP001-7, CTP001-8)	T3 Evaluation of Paediatric Population Treated for Burn Injuries Using an Autologous Skin Cell Suspension	The purpose of this study is to present preliminary clinical outcomes obtained for paediatric patients with acute thermal burn injuries treated with ASCS. Patients (n = 33) were treated with ASCS ranging from 0.8 to 14.2 years of age. The mean TBSA was 46% (range 20–90%).	https://doi.org/10.1093/jbcr/irz013.002	8 Mar 2019
8.	Retrospective analyses of compassionate use (CTP004) and continued access studies (CTP001-7, CTP001-8)	339 The Use of an Autologous Cell Harvesting and Processing Device in Two Burn Patients at an Urban Paediatric Burn Centre	Two paediatric patients that sustained life threatening burns (32% and 21% TBSA) were treated with ASCS and analysed for reducing surgical procedure and expedited healing.	https://doi.org/10.1093/jbcr/irz013.250	8 Mar 2019
9.	Retrospective analyses of compassionate use (CTP004) and continued access studies (CTP001-7, CTP001-8)	Use of Autologous Cell Harvesting Device Reduces Number of Autografting Procedures Required for Treatment of Paediatric Full-thickness Burn Injuries	Patients < 18 years old treated with ASCS were compared to a cohort of matched patients from version 8.0 of the American Burn Association's National Burn Repository (NBR) who received SOC.	https://pediatrictraumasociety.org/meeting/program/2022/1.cgi	2-5 Nov 2022
10.	Retrospective analyses of compassionate use (CTP004) and continued access studies (CTP001-7, CTP001-8)	104 This is How We Do It: Rehabilitation Following the Use of an Autologous Cell Harvesting Device	Functional outcomes were assessed in the treatment of life-threatening burns in patients (n = 26) who lacked adequate STSG donor sites. Functional outcomes were assessed. More aggressive early physical and occupational therapy was assessed on patients treated with ASCS.	https://doi.org/10.1093/jbcr/irz013.105	8 Mar 2019

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
11.	Retrospective analyses of compassionate use (CTP004) and continued access studies (CTP001-7, CTP001-8)	109 Evaluation of Autologous Skin Cell Suspension for Healing of Burn Injuries of the Hand	Adult and paediatric patients (n = 30) who had mixed-depth or FT burns to the hands treated with ASCS in combination with meshed STSG. Outcomes including percent re-epithelialization, subjective cosmetic parameters, and adverse events were analysed.	https://doi.org/10.1093/jbcr/irz013.110	8 Mar 2019
12.	Prospective, within-patient, pilot randomised clinical trial (CTP001-4)	Sood et al. (2015) A comparative study of spray keratinocytes and autologous meshed split thickness skin graft in the treatment of acute burn injuries	This study compares RECELL vs meshed STSGs in adult patients (N=10) with DPT burns 4%-25% TBSA. Clinical endpoints assessed were donor site requirements, appearance, and pain. Results showed reduced donor site size and similar appearance ratings between RECELL®, and graft treated sites.	https://pubmed.ncbi.nlm.nih.gov/25785905/	Feb 2015
13.	Prospective RCT	Gravante et al. (2007) A randomised trial comparing RECELL® System of epidermal cells delivery versus classic skin grafts for the treatment of DPT burns	This study compares the RECELL System and traditional skin grafting for DPT burns. Over two years, 82 patients were enrolled with controlled sampling. Primary endpoints included time for complete epithelisation and aesthetic/functionality quality. Skin grafting was faster, but ReCell showed smaller donor site areas and reduced postoperative pain.	https://www.sciencedirect.com/science/article/abs/pii/S0305417907001209?via%3Dihub	29 Sep 2007

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
14.	Single-centre, three-arm, randomised trial	Bairagi et al. (2019) Comparative effectiveness of Biobrane®, RECELL® Autologous skin Cell suspension and Silver dressings in partial-thickness paediatric burns: BRACS randomised trial protocol	The BRACS trial focuses on finding the most effective wound management for mixed PT injuries in children. In this study children under 16 with burns ≥5% TBSA were included. The primary outcome is re-epithelialisation time, with secondary outcomes including pain, itch, scar severity, and healthcare resource use.	https://academic.oup.com/burnstrauma/article/doi/10.1186/s41038-019-0165-0/5685908?login=false	31 Oct 2019
15.	Retrospective study	Lim et al. (2014) Is the length of time in acute burn surgery associated with poorer outcomes?	This study included adult subjects (N = 753, ≥15 yrs), with 91% of patients presenting with minor and major burns. This study investigated acute burn surgery duration and short-term outcomes. Using RECELL® alone predicted a 24.4% reduction in LOS compared to STSG alone, and a 20.9% decrease in surgery duration (p<0.001).	https://pubmed.ncbi.nlm.nih.gov/23876784/	19 Jul 2013
16.	Prospective study	Dunne and Rawlins (2014) Early paediatric scald surgery--a cost effective dermal preserving surgical protocol for all childhood scalds	This study included paediatric patients (N=40) with scald burns >5% TBSA, treated 24-48 hours after scald injury. The study compared Biobrane alone vs RECELL® + Biobrane vs STSGs alone. The endpoints examined were requirement for subsequent STSG for definitive closure and scarring outcomes.	https://pubmed.ncbi.nlm.nih.gov/24333011/	13 Dec 2013

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
17.	Prospective randomised clinical pilot study	Wood et al. (2012) A prospective randomised clinical pilot study to compare the effectiveness of Biobrane® synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries	Paediatric patients (N=13) with PT scald injury were clinically assessed for burns of 2% TBSA or more and deemed not to heal within 10 days. The primary outcome was surgery performed after 10 days; secondary outcomes were rates of healing, pain experienced, and scar outcomes.	https://www.sciencedirect.com/science/article/abs/pii/S0305417912000095?via%3Dihub	Sep 2012
18.	Observational Study	Carter et al. (2022) LOS and Costs with Autologous Skin Cell Suspension Versus STSGs: Burn Care Data from US Centres	This study analysed patients with DPT or FT burns >50% TBSA and compared RECELL® + STSGs vs STSGs alone. Outcomes measured were patient LOS and hospital costs. LOS using RECELL was 21.7 days, while LOS with STSG alone was 25.0 days, resulting in a 3.3-day (13.2%) reduction.	https://link.springer.com/article/10.1007/s12325-022-02306-y	14 Sep 2022
19.	Observational Study	Carson et al. (2023) Analysis of real-world length of stay data and costs associated with use of autologous skin cell suspension for the treatment of small burns in US centres	Projections using the Burn Effectiveness Assessment Cost Outcomes Nexus (BEACON) model suggest that among patients with small burns (TBSA<20 %), use of ASCS± STSG leads to a shorter hospital LOS and cost savings compared with use of STSG alone. This study evaluated whether data from real-world clinical practice corroborate these findings.	https://www.sciencedirect.com/science/article/pii/S0305417922002996?via%3Dihub	May 2023

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
20.	Economic modelling	Kowal et al. (2019) Cost-Effectiveness of the Use of Autologous Cell Harvesting Device Compared to Standard of Care for Treatment of Severe Burns in the United States	The model focuses on adults with severe burns of TBSA ≥ 10% receiving inpatient care. This study examined patient LOS, number and duration of definitive closure procedures and inpatient resource use.	https://link.springer.com/article/10.1007/s12325-019-00961-2	7 May 2019
21.	Retrospective health economic evaluation of real-world data	Foster et al. (2021) Evaluating Health Economic Outcomes of Autologous Skin Cell Suspension for Definitive Closure in US Burn Care Using Contemporary Real-World Burn Centre Data	This model analysed patients with DPT or FT burns >10% TBSA and compared RECELL® vs STSGs alone. Outcomes examined were number of autograft procedures, total surgical time for graft and donor site, frequency of dressing changes, LOS for contracture surgery.	https://cmro.in/index.php/jcmro/article/view/458	10 Sep 2021

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*
***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

**** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

Identify yet to be published research that may have results available in the near future (that could be relevant to your application).

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1.	**N/A**				

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

**** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

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